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Analyzing the relationship between dietary patterns, health outcomes and individual food choices

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Analyzing the relationship between dietary patterns, health outcomes and individual food choices

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Table of contents

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EDITORIAL
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Editorial: Analyzing the Relationship Between Dietary Patterns, Health Outcomes, and Individual Food Choices

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Keywords: diet, obesity, Mediterranean diet, inflammation, personalized nutrition

Editorial on the Research Topic

Analyzing the Relationship Between Dietary Patterns, Health Outcomes, and Individual Food Choices

Diet is a major contributor to human health and proper food choices can greatly improve prognosis (1). The mechanisms of action underlying the effects of selected food items are still under active investigation. This is why it is important to collect epidemiological, experimental, and biochemical data on individual food choices and health outcomes. One example (but there are many other ones) is that of the Mediterranean diet, where a collection of ample epidemiological evidence (2) coupled with literally hundreds of biochemical studies elucidating the cellular actions of selected components such as olive oil (3) or legumes (4), and at least one large clinical trial, i.e., the PREDIMED (5), built the basis for its election as one of the healthiest diets worldwide.

In this issue of Frontiers in Nutrition, we compiled 22 articles spanning the whole area of human nutrition, from, e.g., restricted time feeding to the metabolic differences between refined and whole grains. Low-grade, chronic inflammation plays an important role in the development or prevention of degenerative diseases such as atherosclerosis, cardiovascular disease, neurodegeneration, and cancer (6). The diet inflammatory index is one way to estimate the link between the pro- or anti-inflammatory potential of the food we eat and the health outcomes associated with it. Future investigations should, indeed, take this and other parameters into account in addition to the mere calorie intake and/or macronutrient profiles.

Thanks to the progresses made by food technology, modern diets are—on average—more nutritious and affordable than the ancient ones. One issue that is gaining traction is that of the so-called ultra-processed foods (7). Even though this notion is highly debated because of the complete lack of biological plausibility (8), data are accumulating that show how (based on current classifications) high consumption of this food category might be associated with poorer prognosis in various areas, including the psychiatric one. This is certainly an issue worth exploring more in depth, leaving ideology aside.

In summary, this Research Topic of Frontiers in Nutrition contributes to increasing our knowledge of how dietary choices affect our health and will help shape informed public health policies. In the future, the use of artificial intelligence, machine learning, and appropriate analysis of big data will further improve our dietary profiles, leading to personalized nutrition

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based on an individual's genetic background (9). We envision a strong acceleration of nutrigenomics, nutrigenetics, and epigenetics to implement solid guidelines in the developed and developing worlds.

AUTHOR CONTRIBUTIONS

FV and FS wrote the article. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Lichtenstein H, Appel LJ, Vadiveloo M, Hu FB, Kris-Etherton PM, Rebholz CM, et al. 2021 dietary guidance to improve cardiovascular health: a scientific statement from the American heart association. *Circulation*. (2021) 144:e472–7. doi: 10.1161/CIR.0000000000001031
2. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *Eur J Clin Nutr*. (2018) 72:30–43. doi: 10.1038/ejcn.2017.58
3. Visioli F, Franco M, Toledo E, Luchsinger J, Willett WC, Hu FB, et al. Olive oil and prevention of chronic diseases: summary of an international conference. *Nutr Metab Cardiovasc Dis*. (2018) 28:649–56. doi: 10.1016/j.numecd.2018.04.004
4. Herforth A, Arimond M, Alvarez-Sanchez C, Coates J, Christianson K, Muehlhoff E. A global review of food-based dietary guidelines. *Adv Nutr*. (2019) 10:590–605. doi: 10.1093/advances/nmy130
5. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. (2018) 378:e34. doi: 10.1056/NEJMoa1800389
6. Calder PC, Bosco N, Bourdet-Sicard R, Capuron L, Delzenne N, Dore J, et al. Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. *Ageing Res Rev*. (2017) 40:95–119. doi: 10.1016/j.arr.2017.09.001
7. Martinez-Perez C, San-Cristobal R, Guallar-Castillon P, Martinez-Gonzalez MA, Salas-Salvado J, Corella D, et al. Use of different food classification systems to assess the association between ultra-processed food consumption and cardiometabolic health in an elderly population with metabolic syndrome (PREDIMED-plus cohort). *Nutrients*. (2021) 13:2471. doi: 10.3390/nu13072471
8. Gibney MJ, Forde CG, Mullally D, Gibney RE. Ultra-processed foods in human health: a critical appraisal. *Am J Clin Nutr*. (2017) 106:717–24. doi: 10.3945/ajcn.117.160440
9. Jinnette R, Narita A, Manning B, McNaughton SA, Mathers JC, Livingstone MK. Does personalized nutrition advice improve dietary intake in healthy adults? A systematic review of randomized controlled trials. *Adv Nutr*. (2021) 12:657–69. doi: 10.1093/advances/nmaa144

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Stunting in the Context of Plenty: Unprecedented Magnitudes Among Children of Peasant's Households in Bukombe, Tanzania

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Background: It is perceived that children living in peasants' households are protected from undernutrition owing to a relative better food availability. However, evidence suggests an increased vulnerability that is not conforming to such norm and varies from one region to another. To address this research gap, we examined the magnitude and factors associated with stunting among under-5 children from peasant's households and compared them with children of other households in a rural district in Tanzania.

Methods: This cross-sectional study was conducted in Bukombe district, Tanzania, among the randomly selected 358 under-5 child-caregiver pairs. We collected data through face-to-face interviews and took anthropometric measurements, which were converted to height for age Z-score. Data were analyzed using both descriptive and logistic regression methods to compare the nutrition status of children in two contexts and determine other factors associated with stunting among children in Bukombe district.

Results: Under-5 children in Bukombe district succumbed to a higher magnitude of stunting (52.8%) compared to the national average. In comparison to the children from the other households, those residing in peasant households succumbed to even higher burden of stunting (46 vs. 56%). Poor feeding practices were common in these communities and more pronounced among peasant communities. About 71% of children in peasants' households had lower dietary diversity compared to 55% of other households ($p = 0.003$). Other factors associated with stunting included older age (AOR = 2.74, $p = 0.003$), severe food insecurity (AOR = 3.34, $p = 0.002$), and birth weight (AOR = 0.31, $p = 0.02$).

Conclusion: Children of peasants' households in Bukombe district are at a higher risk of stunting compared to households with other occupations despite their engagement in farming. In addressing this persistent challenge in rural Tanzania and areas with similar context, efforts should be streamlined to address poor feeding practices, food insecurity, and the interventions tailored for maternal nutrition to ameliorate low birth weight.

Keywords: stunting, feeding practices, peasant, dietary diversity, food security

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INTRODUCTION

Undernutrition among children under-5 is a major public health concern in developing countries (1–3). It results in far-reaching consequences later in life (4) as it affects growth and cognitive development. Undernutrition remains a factor to more than one third child mortality globally (5, 6) and consequently the most important risk factor for the burden of disease in developing countries (7). The first 1,000 days are crucial in development, and efforts to address risk factors during this period have the potential to ameliorate undernutrition and the long-term consequences resulting from such conditions (5, 8–10). The burden of undernutrition is higher in low- and middle-income countries, and Tanzania is no exception. Tanzania is among 10 countries with the highest burden of stunting. Efforts to address this burden have resulted into a decline from about 50% in 1990s to 34% in 2015 (1, 3). The remaining burden is still high and risking the nation's development agenda.

Food insecurity is one of the underlying causes of undernutrition. However, contrary to the global trend, the magnitude of stunting in Tanzania remains persistently higher in high food-producing regions (2, 11). Such regions known as "food basket regions" of Tanzania include Ruvuma, Iringa, Njombe, and Rukwa. These and others with relatively higher food productivity including Geita and Kagera regions succumb to unprecedented prevalence of stunting above 40% (1, 2). Evidence generated from some of these regions suggested that women involvement in farming increases the risk of undernutrition (3). These primary caregivers use most of their daytime in farms, an occupation that deprives child caring including breastfeeding. Children in these areas are weaned much earlier than recommended to allow their caregivers return to their farming activities (3, 12).

Notwithstanding their engagement in farming and therefore food productivity, peasants' households may face food insecurity owing to including seasonal food insecurity, post-harvest losses, poverty, poor nutritional knowledge, and extended cycle of demographical disadvantages. Most of these peasants grow only one or two types of food products, subjecting them into low dietary diversity and therefore insecurity. To a larger extent, such challenges may contribute to a higher burden of stunting. To ameliorate it, tailored nutrition sensitive and specific interventions are needed to address the risk factors. So far, determinants of stunting among children in peasant families have not been studied widely, and there is a dearth of information on how stunting is associated with the occupation in which the household is engaged. We therefore sought to examine the magnitude of stunting among under-5 children in peasant households and compared to that of children from families engaging in other economic activities. We also assessed the other local determinants of stunting among children in rural Bukombe district.

Abbreviations: AOR, adjusted odd ratio; CI, confidence interval; EBF, exclusive breast feeding; FANTA, Food and Nutrition Technical Assistance; HAZ, height-for-age Z-score; HFIAS, Household Food Insecurity Access Scale; HH, households; MOHCDGEC, Ministry of Health, Community Development, Gender, Elderly and Children; OR, odd ratio; SD, standard deviation; SPSS, Statistical Package for Social Science; TDHS-MIS, Tanzania Demographic and Health Survey and Malaria Indicator Survey; TFNC, Tanzania Food and Nutrition Centre; WAZ, weight-for-Age Z-score; WB, World Bank; WHA, World Health Assembly; WHZ, weight-for-height Z-score.

METHODS

Study Design and Setting

This cross-sectional study examined the magnitude of stunting, feeding practices, and other factors associated with stunting among children under-5 in peasant families in rural Bukombe district, Tanzania. We also assessed magnitudes of other nutrition status including underweight and wasting stratified by occupation status of the household. Bukombe district is one of six districts in Geita region in the Northern Tanzania. Stunting is prevalent to 41% of children under-5 (2). The major economic activity of residents in this district is small-scale farming. Others engage in petty trade, small-scale mining, formal/skilled employment, and self-employment through different unskilled manual works (13). Data were collected in July and August 2018, coinciding a post-harvest season in the area.

Participants

We recruited a total of 358 under-5 children-caregiver pairs. We randomly sampled four out of the 17 wards. We selected four villages from each ward and sampled 22 or 23 households per village to give 358 study households through a systematic random sampling. In case a selected household had more than one child under the target group, a simple random sample using paper numbers was used to select one child. In case a sampled household had no child under the study target age group, the nearest house was used to replace the household.

Measurements

The outcome variable was stunting status defined as children below minus two standard deviations (−2SD) of the height for age Z-score (HAZ) in the reference population. Other undernutrition measures were wasting and underweight. Children below −2SD of the standard population's weight for height Z-score (WHZ) were regarded wasted while those below −2SD of the standard population's weight for age Z-score (WAZ) were considered underweight (14). We used the 2011 WHO Anthro software version 3.2.2 to calculate HAZ, WHZ, and WAZ.

Independent variables included child feeding practices measured through feeding frequency and dietary diversity. Assessment of the feeding frequency was through a question to the caregiver on a number of times they fed their children in the previous 24 h (12). Responses of below four times per day were categorized as low feeding frequency. To assess dietary diversity, caregivers were asked to identify the food type the children were fed in the previous 24 h. A list of common food in Bukombe was prepared in line with the nationally representative survey questionnaire. A list of eight food groups provided by Food and Nutrition Technical Assistance (FANTA) tool (15) was used to form the child dietary diversity score (DDS). Minimum dietary diversity was referenced from the nationally representative survey 2015–2016, that is, feeding from at least four out of the following eight food groups: grains, roots, and tubers; legumes and nuts; dairy products (milk, yogurt, and cheese); flesh foods (meat, fish, poultry, and liver/organ meat); eggs; Vitamin A-rich fruits and vegetables; other fruits and vegetables, and food cooked in oils/fats. Consumption of food from at least four food groups means that the child has a high likelihood of consuming at least one animal source of food and at least one fruit or vegetable in addition to a staple food (grains, roots, or tubers) (2).

Household food insecurity was assessed using Household Food Insecurity Access Scale (HFIAS) in the past 1 month basing on the nine-item questionnaire provided by FANTA (16, 17). In this study, the HFIAS had a Cronbach's alpha of 0.89 and an item-to-rest correlation ranging from 0.87 to 0.9. The scores were grouped into food secure, mildly insecure, moderately insecure, and severely food insecure (16, 17) like in another study conducted in Tanzania (12).

We assessed illness episodes by asking caregivers to recall whether their children had disease conditions. They included malaria, fever, skin diseases, acute respiratory infections, pneumonia, vomiting, or diarrhea in the past 1 month. We measured birth intervals for children who had siblings at the time of the study by asking the caregivers to recall the time when the sibling was born. Responses were categorized into below 24 months or above 24 months (18).

To assess antenatal visit, caretakers were asked to recall the number of antenatal clinics the mother had during pregnancy of the child. The responses were categorized into three or less visits as low number of visits, and four and above as the required number of visits as recommended by the WHO and the Tanzania Ministry of Health and Community Development, Gender, Elderly and Children (MOHCDGEC) guidelines as also applied in national surveys (2). To assess post-natal health checks for newborns, we based on the TDHS-MIS 2015/16 questionnaire as having received any health facility post-natal health checks. We measured child immunization status (19) defined as full immunized or not completed vaccination as per the recommended schedule by the MOHCDGEC available and applied in the TDHS-MIS 2015/16 (2). Completion of Penta-3 vaccine was the indicator for completion of vaccines (2).

To assess birth weight, we obtained information in the child's Reproductive and Child Health (RCH) card number 4 used to monitor child growth, immunization, and clinic attendance. As recommended by the WHO categories for birth weight were below 2.5 kg as low birth weight, between 2.5 and 3.5 kg as normal, or above 3.5 kg as high birth weight as also applied in the national survey (2). We defined place of delivery as applied in the national survey (2), categorized that as health facility delivery or home/way delivery.

We categorized caregiver education level according to Tanzania education systems as also applied in another study (12) and categorized into no formal education, having a primary level education, or having above primary level. We measured family economic activities by asking caretakers to self-report the main occupation of the household. Responses were based on the main economic activities common in the area that included farming, petty trade, food seller, bodaboda (a public transport system using motorcycle), small mining scale, formal employment (in the government or other annual contracted jobs in registered organizations), informal employment (unskilled labor) or unregistered example day workers. In analysis, five categories of occupations (farming, employees, businessman/woman, small mining, and unskilled manual labor) were maintained.

The weighted wealth index was calculated using household's ownership of household items; housing characteristics such as source of drinking water, toilet facilities, and flooring materials; and food availability. These dichotomized variables were adopted from the household's questionnaire of the TDHS-MIS 2015/16 (2). The dichotomized variables were reduced using principal component analysis (PCA) from 52 initial variables to 19 that loaded as the first output component with 45% of the variation that may closely measure economic status. Factor loadings were summed and categorized into five equal wealth quintiles as poorest, poor, middle, rich, and wealthiest.

Data Collection

We collected anthropometric data using SEGA digital scale for measuring child weight as recommended by the WHO (20) and like in other studies (2, 3). For the weighing of very young children who could not stand alone on the scale, the mother or caretaker was weighed first, then the mother or caretaker was weighed again while holding the child after taping the mother-baby button (tarred weighing); the child weight showed on the screen and recorded in kilograms. Height was measured in centimeters using a wooden length measuring board. Younger children below 24 months and who could not stand were measured lying down beside the board (recumbent length), while standing height was measured for older children (2, 3).

A pretested and translated questionnaire from English to Swahili language was used to collect data from caregivers. We recruited research assistants from community health workers with data collection experience. They had primary level education or above and were working in the same district on health-related projects. We conducted training for 2 days to familiarize them with the aims of the study, the tools and interpretation of questions, ethical consideration, and use them to conduct the pretesting of the tool. Of the 2 days, the first day training was conducted in the class, while the second day was field practical training.

Data Analysis

Data was analyzed using both descriptive and regression analyses. For descriptive analyses, we examined the characteristics of the study population including the demographic characteristics, feeding practices, burden of illnesses, and the nutrition status. We used chi-square test to compare such characteristics as sex, nutrition status, feeding practices, and occupation of the households. Bivariate and multiple logistics regression analyses were conducted to examine factors associated with stunting. Associations that reached $p < 0.2$ at bivariate analysis were included into the multiple logistics regression analysis.

TABLE 1 | Descriptive characteristics of children age 6–59 months recruited for the study in Bukombe, June 2018 (N = 358).

Variable	Total		Male		Female		*P* Value
	N	%	*N*	%	*N*	%	
Age of child (months)							
6–11	74	20.7	36	20.9	38	20.4	
12–23	64	17.8	27	15.7	37	19.9	
24+	220	61.5	109	63.4	111	59.7	0.580
Household head's main occupation							
Peasant	242	67.6	117	68	125	67.2	0.094
Unskilled manual labor	38	10.6	23	13.4	15	8.1	
Employee	17	4.7	7	4.1	10	5.4	
Businessman/ woman	16	4.5	10	5.8	6	3.2	
Small mining activities	45	12.6	15	8.7	30	16.1	
Main source of food							
Purchasing	112	31.3	52	30.2	60	32.3	0.367
Own crop harvest	241	67.3	116	67.4	125	67.2	
Supplies from relatives	5	1.4	4	2.3	1	0.5	

TABLE 2 | Household occupation distribution of feeding practices and nutrition status among children age 6–59 months recruited for the study in Bukombe, June 2018.

Child feeding practices	Peasants		Other occupations		Total		*P* value
	N	%	*N*	%	*N*	%	
Complementary food initiation time							
<6 months	64	26.9	39	34.8	103	29.4	
6 months	134	56.3	57	50.9	191	54.6	
≥7 months	40	16.8	16	14.3	56	16	0.311
Child feeding frequency in 24 h							
≤3 times	168	70.6	88	78.6	256	73.1	
≥4 times	70	29.4	24	21.4	94	26.9	0.116
Dietary diversity score (DDS)							
≤3 scores	168	70.6	61	54.5	229	65.4	
≥4 scores	70	29.4	51	45.5	121	34.6	0.003
Stunting (<-2.0SD)							
Stunted	136	56.2	53	45.7	189	52.8	
Normal	106	43.8	63	54.3	169	47.2	0.062
Underweight (<-2.0SD)							
Underweight	27	11.2	6	5.2	33	9.2	
Normal	215	88.8	110	94.8	325	90.8	0.067
Wasting (<-2.0SD)							
Wasted	8	3.3	0	0	8	2.2	
Normal	233	96.7	116	100	350	97.8	
Household food security							
Food secure	115	79.9	29	20.1	144	40.2	
Mild insecurity	55	66.3	28	33.7	83	23.2	
Moderate insecurity	43	46.2	50	53.8	93	26	
Severe insecurity	29	76.3	9	23.7	38	10.6	<0.001
Household main source of food							
Own crop harvest	119	82.6	42	17.4	241	67.3	
Purchasing	43	36.8	74	63.2	117	32.7	<0.001

RESULTS

Sociodemographic Characteristics of Children

The mean age in the study population was 29 months (SD 15.34). Four in 10 children were from a caregiver with no formal education, and more than half of the children were from households engaging in farming as the main occupation. Above half of the children were from households that obtain food from their own farming harvests (**Table 1**).

Feeding Practices and Nutrition Status Among Children

About three in every four under-5 children on complementary feeding had low feeding frequency, while 65.4% had low DDS. More children with low DDS were from peasant families (70.6%) compared to (54.5%) children from families in other occupations (p = 0.003) (**Table 2**). More than half of the children in this study (56.2%) were stunted. Magnitude of stunting was higher (56.2%) among children from peasant families compared to (45.7%) children from families engaged with other occupations (p = 0.062) (**Table 2**).

Factors Associated With Stunting

Children from a food insecure household were more likely to be stunted [adjusted odds ratio (AOR) = 3.34, 95% CI =1.11–10.02, p = 0.032]. Children aged 24–59 months were more likely to be stunted compared to younger children (AOR = 2.74, 95% CI =1.47–5.13, p = 0.003). Moreover, children born with normal weight (2.5–3.5 kg) were less likely to be stunted compared to children with underweight (AOR = 0.31, 95% CI = 0.12–0.83, p = 0.02). Children from peasantry households had two times higher risk of stunting compared to children from households engaged with other occupations (AOR = 1.96, 95% CI = 0.96–3.91, p = 0.063); however, the association did not reach a statistically significant level (**Table 3**).

DISCUSSION

Magnitude of stunting was higher in this rural peasantry community compared to the national average (2). Moreover, evidence generated from this nationally representative survey suggests that children of peasants' households suffered the greater brunt of undernutrition compared to other occupations. Such high burden of undernutrition could be a result of poor feeding practices that were predominant in this context.

TABLE 3 | Logistic regression; factors associated with stunting (HAZ <-2.0SD) among children age 6–59 months in Bukombe, June 2018.

Variable	Bivariate logistic regression			Multiple logistic regression		
	OR	95% CI (OR)	P	AOR	95% CI (AOR)	P
Age (months)						
6–11	1.0			1.0		
12–23	1.46	0.83–2.56	0.185	1.59	0.86–2.91	0.14
24–59	2.37	1.36–4.12	0.002	2.74	1.47–5.13	0.003
Sex of child						
Female	1.0			1.0		
Male	1.38	0.91–2.09	0.128	1.47	0.94–2.3	0.09
Household occupation						
Other occupations	1.0			1.0		
Peasants	1.52	0.98–2.38	0.055	1.94	0.96–3.91	0.063
Care taker level of education						
No education	1.0			1.0		
Primary school	0.93	0.59–1.45	0.755	1.02	0.54–1.92	0.949
Post-primary school	0.58	0.29–1.16	0.126	0.53	0.19–1.46	0.220
Weighted wealth index						
Poorest	1.0			1.0		
Poor	1.06	0.55–2.03	0.868	1.07	0.44–2.58	0.881
Middle	1.09	0.57–2.07	0.808	0.87	0.36–2.12	0.757
Rich	1.18	0.61–2.31	0.609	0.96	0.39–2.37	0.937
Richest	1.72	0.89–3.35	0.109	2.39	0.97–5.90	0.059
Breast feeding initiation time						
Within an hour	1.0			1.0		
After 1 h	1.18	0.71–1.81	0.465	1.82	0.97–3.43	0.064
Exclusive breast feeding						
EBF	1.0			1.0		
Non-EBF	1.02	0.67–1.55	0.930	0.94	0.53–1.66	0.826
Breast feeding duration						
<24 months	1.0			1.0		
≥24 months	1.13	0.65–1.95	0.666	0.91	0.47–1.75	0.775
Feeding frequency						
≤3 times	1.0			1.0		
≥4 times	0.74	0.47–1.23	0.269	0.59	1.29–1.19	0.142
Dietary diversity score						
≤3 scores	1.0			1.0		
≥4 scores	0.98	0.63–1.53	0.930	0.73	0.39–1.34	0.306
Food insecurity						
Food secure	1.0			1.0		
Mild insecurity	0.94	0.55–1.61	0.809	0.87	0.41–1.87	0.722
Moderate insecurity	0.72	0.43–1.21	0.212	0.82	0.40–1.69	0.600
Severe insecurity	2.14	0.99–4.63	0.055	3.34	1.11–10.02	0.032
Child illness						
Absent	1.0					
Present	1.58	0.7–3.53	0.269			
Malaria						
No episode	1.0					
Having episode	0.97	0.62–1.53	0.900			
Diarrhea						
No episode	1.0					
Having episode	1.29	0.21–7.86	0.781			
Fever						
No episode	1.0			1.0		
Having episode	1.41	0.93–2.15	0.106	1.79	0.98–3.27	0.056
Antenatal care						
≤3 times	1.0					
≥4 times	0.97	0.64–1.48	0.902			
Post-natal care						
Yes	1.0					
No	1.19	0.78–1.84	0.419			
Vaccination						
Completed	1.0					
Not completed	1.08	0.61–1.88	0.800			
Low birth weight						
≤2.5 kg	1.0			1.0		
2.5–3.5 kg	0.36	0.14–0.91	0.031	0.31	0.12–0.83	0.02
>3.5 kg	0.44	0.17–1.13	0.089	0.34	0.13–0.93	0.04
Place of delivery						
Health facility	1.0					
Home/way	1.04	0.68–1.6	0.845			

OR, odds ratio (crude); AOR, adjusted odds ratio; EBF, exclusive breast fed.

Among children recruited for the study, 73.1% had low feeding frequency, and 65.4% had low DDSs. This is similar to 70% low feeding frequency reported among children in Geita region (2) and not very different from 53.5% reported in another rural district of southern highlands of Tanzania (3).

Low feeding frequency might be explained by caretakers' involvement in farming, taking most of their day and thus affecting child care including breastfeeding and complementary feeding (3). It may also be explained by the seasonal household's food insecurity in farming communities reported elsewhere (12). Dietary diversity was low and might be explained by the sources of food of the household. Most of such households engage in monoculture farming. Under such contexts, they may predominantly have access to a limited number of food products and mostly cereal-based food. This can be related to evidence from this study that majority of peasant households depend on food on their own crop harvests compared to households on other occupations that acquire food through purchasing. Thus, children from peasant households were likely to be fed only what is available in the harvest stocks. In the context of Bukombe, such foods are corn, millet, potatoes, and cassava, all of which provide carbohydrates and not adequate proteins among other nutrients. Children from households in other occupations were more likely to be fed what was mainly purchased, which might be of a variety of food groups.

Children in predominant peasant households were more likely to be stunted compared to their counterparts from families in other occupations. Evidence suggests that the higher likelihood of undernutrition among children in peasant households may be due to poor maternal health, poor parental care, and poor child feeding practices associated with women's long time involvement in farming activities (3, 12). Low dietary diversity was more likely among children in peasant households compared to others in this study. Lack of adequate caring time for their children may also subject them to poor health seeking behavior and access to clean water and poor sanitation, all leading to poor health and undernutrition. Stunting among children from a food insecure household was higher compared to food secure households. Household food insecurity is associated with poor child feeding practices in other contexts (12).

Low birth weight increased the likelihood of stunting. Stunting was rarer among children under normal birth weight compared to children with lower birth weight. Similarly, findings have been reported in rural districts of Tanzania (21, 22) and Kenya (23). This might reflect poor maternal nutrition and development of chronic undernutrition through transgenerational effect of *in utero* effects (2, 5, 10). Earlier studies documented that maternal nutrition is a strong factor for birth outcomes and later health status of the child (5, 21, 24). Mother's poor nutritional status before conception, short stature, and poor nutrition during pregnancy, poor feeding, and weight gain during pregnancy have higher chances of low birth weight and stunted children (5, 21, 24). In the context of this study, poor maternal nutrition and low birth weight outcomes might be explained by the household occupation. In this predominant peasant community, women are more likely to succumb to poor maternal health due to spending more time in farms with consumption of low food diversity, which is available for them. Poor health seeking behavior, inadequate nutritional care, and lack of resting time may put pregnancy at higher risk.

Older under-5 children were more likely to be stunted compared to younger ones like in previous studies (12, 18, 23). Like in other studies, stunting starts to manifest after exclusive breastfeeding period owing to introduction of low dietary diversity and frequency. Moreover, food insecurity, which is predominantly among farming communities, further subjects these children to a narrow range of potentially nutritional food substrates capable of ameliorating undernutrition and particularly stunting. In peasant households, caregivers are more likely to reduce their care time to older children in prioritizing farming activities. At age 2 years, children are expected to remain at home while mothers/caretakers go to farms, affecting parental care and child feeding practices (3).

Potential Study Limitations and Mitigation

We used tools that required recall for as long as 1 month post-event. This might have led to loss of accuracy in information. This limitation was kept minimal by taking time with the participant and giving them time to remember events. For DDS and child feeding frequency, the recall was 24 h, illness episodes among children recall was 30 day, household food insecurity recall was 30 days as recommended by FANTA (16, 17). This study was a cross sectional in design, and evidence cannot provide causality. However, in addition to other evidence, it provides associations that can be used to provide recommendations. Lack of generalizability is another potential limitation. However, we can generalize our findings to areas with similar contexts in Tanzania and beyond.

CONCLUSIONS AND RECOMMENDATIONS

Magnitude of undernutrition was high in Bukombe district. Chronic form of undernutrition was prevalent in among 52.8% of all under-5 children sampled in this study. Stunting was more prevalent among children in peasant population compared to children in other occupations due to poor feeding practices. Majority of children were fed at a low feeding frequency and dietary diversity. Stunting was also significantly associated with age, household food insecurity, and low birth weight.

In addressing undernutrition among children in Bukombe district and others with similar contexts, tailored interventions should target the first 1,000 days, households with food insecurity, and children born with low birth weight. To ameliorate undernutrition among children of peasant households, interventions are needed to improve maternal nutrition emphasizing pre- and during and post-pregnancy periods, access to and attendance to antenatal and post-natal periods, and providing adequate care and time for children under-5. Knowledge in feeding practices and access to nutritional adequate food remain of paramount importance.

DATA AVAILABILITY STATEMENT

The data sets used and analyzed during the current study are available and still under analysis for subsequent publications but will be available upon request from authors.

ETHICS STATEMENT

Ethical clearance was provided by the Muhimbili University of Health and Allied Sciences (MUHAS) Ethical Committee, issued on May 29, 2018. Permission to conduct the study at the field was requested and provided by the Bukombe district medical officer. Written informed consents were obtained from parents/guardians of children after being informed on the operation and application of the study findings. Confidentiality of the respondents was ensured at all stages of the study.

AUTHOR'S NOTE

LS was a postgraduate student pursuing MPH under the supervision of BS senior lecturer and the Director of Research and Publications at Muhimbili University of Health and Allied Sciences, Tanzania.

AUTHOR CONTRIBUTIONS

LS designed the study, conducted data collection, did data analysis and interpretation of findings, wrote and approved the manuscript. BS provided technical inputs to improve designing the study, supported data analysis, read, improved, and approved the final manuscript write-up.

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REFERENCES

1. Tanzania Food and Nutrition Centre. *Ministry of Health and Social Welfare Tanzania National Nutrition Survey* (2014).
2. Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC) [Tanzania Mainland], Ministry of Health (MoH) [Zanzibar], National Bureau of Statistics (NBS), Office of the Chief Government Statistician (OCGS), and ICF. *Tanzania Demographic and Health Survey and Malaria Indicator Survey (TDHS-MIS) 2015-16.* Dar es Salaam; Rockville, MD: MoHCDGEC, MoH, NBS, OCGS, and ICF (2016).
3. Nordang S, Shoo T, Holmboe-Ottesen G, Kinabo J, Wandel M. Women's work in farming, child feeding practices and nutritional status among under-five children in rural Rukwa, Tanzania. *Br J Nutr*. (2015) 114:1594–603. doi: 10.1017/S0007114515003116
4. UNICEF, WHO, Group WB. *Levels and Trends in Child Malnutrition. Joint Child Malnutrition Estimates Edition*. (2012). Available online at: http://www.who.int/nutgrowthdb/jme_brochoure2017.pdf
5. Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries. *Paediatr Int Child Health*. (2014) 34:250–65. doi: 10.1179/2046905514Y.0000000158
6. Kramer CV, Allen S. Malnutrition in developing countries. *Paediatr Child Health*. (2015) 25:422–7. doi: 10.1016/j.paed.2015.04.002
7. Müller O, Krawinkel M. Malnutrition and health in developing countries. *CMAJ*. (2005) 173:279–86. doi: 10.1503/cmaj.050342
8. World Health Organization. *Global Nutrition Targets 2025 Stunting Policy Brief*. WHO/NMH/NHD/14.3. WHO Int (2014). p. 1–10.
9. de Onis M, Branca F. Childhood stunting: a global perspective. *Mater Child Nutr*. (2016) 12:12–26. doi: 10.1111/mcn.12231
10. Bhutta ZA. Early nutrition and adult outcomes: pieces of the puzzle. *Lancet*. (2013) 382:486–7. doi: 10.1016/S0140-6736(13)60716-3
11. Leach, V. *C. Children and vulnerability in Tanzania: a brief synthesis*. Special Paper 07.25. Dar es Salaam: REPOA (2007).
12. Wandel M, Holmboe Ottesen G. Maternal work, child feeding, and nutrition in rural Tanzania. *Food Nutr Bull*. (1992) 14:49–54. doi: 10.1177/156482659201400102
13. *The United Republic Of Tanzania Prime Minister's Office Regional Administration and Local Government*. Geita Investment Profile. (2013).
14. WHO. *Nutrition Landscape Information System (Nlis) Country Profile Indicators: Interpretation Guide*. (2010).
15. Bilinsky P, Swindale A. *Household Dietary Diversity Score (HDDS) for Measurement of Household Food Access : Indicator Guide Version 2 Anne Swindale Household Dietary Diversity Score (HDDS) for Measurement of Household Food Access : Indicator Guide VERSION 2*. (2006).
16. World Health Organization. *Infant and Young Child Feeding; A Too for Assesing National Practice, Policies and Programs*. Geneva: WHO Libr Cat Data. (2003).
17. Coates J, Swindale A, Bilinsky P. *Household Food Insecurity Access Scale (Hfias) for Measurement of Food Access: Indicator Guide*. Version 3. Washington, DC: Food and Nutrition Technical Assistance (2007).
18. Sunguya BF, Poudel KC, Mlunde LB, Urassa DP, Yasuoka J, Jimba M. Poor nutrition status and associated feeding practices among HIV-positive children in a food secure region in tanzania: a call for tailored nutrition training. *PLoS ONE*. (2014) 9:e98308. doi: 10.1371/journal.pone.0098308
19. Masanyiwa Z, Lwelamira J. *Prevalence and Factors Associated with Child Malnutrition in Nzega District, Rural Tanzania*. (2016).
20. World Health Organization. *Training Course on Child Growth Assessment*. WS 103. Geneva (2008). p. 1–116.
21. Roberfroid D. Feeding Practices and factors contributing to wasting, stunting, and iron-deficiency anaemia among 3-23-month old children in Kilosa. *J Health Popul Nutr*. (2005) 23:222–30. doi: 10.3945/ajcn.114.090175
22. Chirande L, Charwe D, Mbwana H, Victor R, Kimboka S, Issaka AI, et al. Determinants of stunting and severe stunting among under-fives in Tanzania: Evidence from the 2010 cross-sectional household survey. *BMC Pediatr*. (2015) 15:165. doi: 10.1186/s12887-015-0482-9
23. Altare C, Delbiso TD, Mutwiri GM, Kopplow R, Guha-sapir D. Factors associated with stunting among pre-school children in Southern Highlands of Tanzania. *J Trop Pediatr*. (2016) 62:390–408. doi: 10.1093/tropej/fmw024
24. Higgins-Steele A, Mustaphi P, Varkey S, Ludin H, Safi N, Bhutta ZA. Stop stunting: situation and way forward to improve maternal, child and adolescent nutrition in Afghanistan. *Matern Child Nutr*. (2016) 12:237–41. doi: 10.1111/mcn.12288

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Association Between Dietary Patterns and Fluorosis in Guizhou, China

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Objective: Many studies have explored the effects of individual foods or nutrients on fluorosis, but no studies have focused on dietary patterns. This study examined the relationship between dietary patterns and coal-burning fluorosis in Guizhou, China.

Methods: This 1:1 matched case-control study was conducted in Zhijin County of Guizhou province with a sample size of 200 cases of fluorosis and 200 age and gender matched controls. Habitual dietary intake was assessed by face-to-face interviews, using a validated 75-item food frequency questionnaire (FFQ) and various covariates using structured questionnaires. The dietary patterns were identified by factor analysis.

Results: The factor analysis identified three major dietary patterns which were labeled healthy, easy-to-roast and high protein. After adjusting for various confounding factors, a decreased risk for fluorosis was observed in the highest tertile of the healthy dietary pattern relative to the lowest tertile (OR = 0.47, 95% CI = 0.27–0.84, P-trend = 0.003) and a positive association was observed between the easy-to-roast dietary pattern and fluorosis risk (OR = 2.05, 95% CI = 1.15–3.66), with a significant linear trend ($P = 0.017$). We did not find an association between fluorosis risk and the high protein dietary pattern. The relationships remained significant when the analyses were stratified by gender and fluorosis subtypes.

Conclusion: The healthy dietary pattern may lower coal-burning fluorosis risk; in contrast, the easy-to-roast dietary pattern significantly increases the risk of coal-burning fluorosis.

Keywords: dietary pattern, factor analysis, fluorosis, coal burning, case-control and matched study

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INTRODUCTION

Endemic fluorosis is a disease affecting mainly the bones and teeth, caused by exposure to high levels of fluorine in the environment. Over 70 million people may be affected globally, including China, India, Africa and South America. Reports predicted that over 26 million people in China suffer from fluorosis due to fluoride contamination in their drinking-water. A further 16.5 million people burn fluoride-rich coal indoors for heating and cooking, a process which is termed coal-burning fluorosis (CBF) (1). The most severe CBF case was located in Guizhou, China; 43% of its districts and counties had fluorosis incidents (2). Although CBF cases have been recently reduced through the use of improved stoves and awareness education, the incidence rate of fluorosis remains high (3, 4). This disease seriously restricts economic development and reduces quality of life. Therefore, further strategies are needed to prevent and control fluorosis.

Nutrition may play an important role in the development of fluorosis. Studies have not been successful at establishing a consistent association between CBF risk and specific foods and nutrients [e.g., corn (5, 6) chili (6), sour soup (7), vitamins (8–11), and calcium (12, 13)]. The inconsistent results linking foods and fluorosis may, in part, reflect the difficulty of disentangling the high degree of correlation among dietary constituents. To address this problem, Schwerin et al. proposed using dietary patterns to examine diet-disease relationships (14). Dietary patterns incorporate food interactions in the diet and consider the overall diet, reflecting more closely real-world food intakes, and are therefore more useful to predict disease risk than individual foods or nutrients (15). Factor analysis is a variable consolidation technique that can be applied to dietary data to identify underlying dietary patterns based on the inter-correlations of food groups. To our knowledge, there have been no studies on the association between dietary patterns and fluorosis. Therefore, we conducted this 1:1 matched case–control study to identify major dietary patterns among Chinese residents of Guizhou province and to examine the associations of these dietary patterns with the risk of fluorosis.

SUBJECTS AND METHODS

Study Subjects

This 1:1 matched case-control study was conducted between July and August 2015 in Zhijin County, Guizhou Province, China, where coal-burning fluorosis is endemic. All of the CBF cases were diagnosed by the Zhijin County Disease Control and Prevention Center according to the Chinese Diagnostic Criteria of Dental Fluorosis (WS/T208-2011, China) and the Chinese Diagnostic Criteria of Endemic Skeletal Fluorosis (WS/T 192-2008, China). Cases were identified by one professional doctor in Zhijin Center for Disease Control and Prevention, and eligible cases, aged 18–75 years old, were recruited through village doctors. Subjects in the following situations were excluded: (1) pathological fractures or fractures from car accidents, falls and other fractures caused by violence; (2) patients with tetracycline stained teeth and dental cavities; (3) patients previously diagnosed with cancer, coronary heart disease, stroke, gout, or kidney disease; (4) patients who self-reported substantial changes in dietary habit within the previous 5 years. For each CBF case, a control participant was selected from residents living in the same county and within the same sex and age group (±3 years). Control participants were required to be at least 18 years old, to have lived in Zhijin County for at least the previous 10 years and were selected according to the same exclusion criteria as CBF patients. The study sample consisted of 200 CBF patients and 200 controls. All of the study participants signed informed consent forms prior to the interview and the Medical Ethics Committee of Zunyi Medical University approved the project (No. 2014-1-003).

Data Collection

The following information was collected by trained interviewers through face-to-face interviews using a structured questionnaire. The questionnaire included (1) socio-demographic characteristics (age, gender, education level); (2) lifestyle habits (alcohol drinking, tea drinking, smoking status, domestic fuel type, use of improved stoves, consumption of roasted food); (3) dietary habits in the year before the interview; and (4) relevant diseases (hypertension, diabetes, gout, kidney disease, cancer, heart-related diseases, and stroke). Tea drinkers were defined as individuals who drank tea at least twice weekly; Likely, smokers are the participants who smoked at least five packs of cigarettes a year and those who drank alcohol at least once a week continuously for at least 6 months were considered alcohol drinkers. CBF patients and controls were required to respond to the same questionnaire.

Dietary Assessment

The participants were instructed to recall their usual dietary consumption using a validated 75-items food frequency questionnaire (FFQ) (16). Foods consumption was estimated in terms of the frequency of use per day, per week, per month, or per year. To help the participants quantify the amounts, they were provided with color pictures of foods with approximate proportion sizes. The selected value for each food was then converted to reflect the daily intake. Energy and nutrient intakes were computed based on the China Food Composition database (17).

Food Grouping and Identification of Dietary Patterns

To reduce the complexity of the data, 75 food items from the FFQ were categorized into 25 predefined food groups according to similarities in their nutrient profiles or processing methods. Dietary factor patterns were then identified by principal component analysis. A varimax (orthogonal) rotation was performed to improve interpretability and minimize the correlation. Factors were retained based on eigenvalues (>1.3 cut-off), scree plots and factor interpretability (18). Factor loadings for each food group were calculated and factor scores per pattern were calculated for each subject by summing the total intake of each food group, weighted by their factor loadings. High scores represented a high intake of food items resulting in a positive loading on the corresponding dietary pattern, whereas low scores represented a low intake of those items. Food groups with absolute values >0.25 are presented in **Table 1**. Based on the analysis, three categories were selected.

Urinary Fluoride Detection

A 10 ml urine sample was collected from each participant. Urinary fluoride concentration was analyzed by a standardized method (WS/T 89-2015, China). Briefly, 1 ml of urine was mixed with 24 ml of deionized water, one pill of fluoride adjustment buffer powder was added to each 25 ml mixture. Then, the

TABLE 1 | Characteristics of fluorosis cases and controls.

Variables	Case (*n* = 200)	Control (*n* = 200)	*P*-value
Age, years (Mean ± SD)	49.8 ± 13.4	49.7 ± 13.5	0.916
Body mass index, kg/m^2 (Mean ± SD)	23.8 ± 3.9	23.6 ± 3.9	0.253
Urine fluoride, mg/L (Mean ± SD)	1.62 ± 1.0	1.28 ± 0.6	<0.001
Duration of residence, years (Mean ± SD)	39.7 ± 18.1	39.717.1	0.951
Dental fluorosis	193	193	
Skeletal fluorosis	87	87	
Female (%)	115 (57.5)	115 (57.5)	0.923
Ethnic (%)			0.313
Han	118 (59.0)	108 (54.0)	
Others	82 (41.0)	92 (46.0)	
Marital status (%)			0.584
Married or cohabitation	172 (86.0)	168 (84.0)	
Divorce or widowed	18 (9.0)	17 (8.5)	
Unmarried	10 (5.0)	15 (7.5)	
Education level, years (%)			0.008
≤6	162 (81.0)	141 (70.5)	
6–9	32 (16.0)	39 (19.5)	
≥10	6 (3.0)	20 (10.0)	
Household income, Yuan/month (%)			0.049
<500	23 (11.5)	11 (5.5)	
500–2,000	55 (27.5)	64 (32.0)	
2,000–6,000	94 (47.0)	86 (43.0)	
≥6,000	28 (14.0)	39 (19.5)	
Fuel type (%)			0.053
Raw coal	116 (58.0)	127 (63.5)	
Mixed coal	44 (22.0)	33 (16.5)	
Firewood	40 (20.0)	40 (20.0)	
Smoker‡ (%)	74 (37.0)	72 (36.0)	0.835
Alcohol drinker§ (%)	66 (33.0)	61 (30.5)	0.568
Tea drinker‖ (%)	83 (41.5)	74 (37.0)	0.357
Like roasting food# (%)	118 (59.0)	100 (50.0)	0.070
Improved stove use¶ (%)	149 (74.5)	171 (85.5)	0.006

‡*Smokers were defined as having smoked at least one cigarette daily for at least 6 consecutive months.*

§*Alcohol drinker was defined as having had wine (beer, white wine and red wine) at least once per week for at least 6 consecutive months.*

‖*Tea drinkers were defined having drank tea at least twice weekly.*

¶*Improving the kitchen stove to exclude the fluoride out of the room to decrease the pollution of the air indoors.*

#*A habit of roasting food with indoor burning of fluoride-rich coal.*

concentration of urine fluoride in the mixture was measured by a HQ40d portable meter and the concentration of fluorine in the urine of the subjects was calculated according to the corresponding proportion. The coefficient of variation for the urinary fluoride was 2.29%. The urine fluoride concentrations for all participants were categorized into either the normal category (<1.6 mg/L) or the abnormal category (more than 1.6 mg/L), according to national criteria (WS/T 256-2005).

Statistical Analysis

The data were tabulated as mean and SDs for continuous variables, or by proportions for categorical variables. To achieve an approximately normal distribution for statistical analysis, a logarithmic transformation and a square root transformation were performed for intake of energy and dietary nutrients, respectively. Dietary nutrient intake data were controlled for total energy intake by the regression residual method (19). The chi-square test and *t*-test were used to test the differences in socio-demographics and nutrient intakes of the fluorosis cases and controls. The factor scores were categorized into tertiles. T1, T2, and T3 represented a low, medium and high food intake patterns, respectively.

Conditional logistic regression analysis models were constructed to obtain odd ratios (ORs) and corresponding 95% confidence intervals (95% CIs) as estimates of relative risk, which are shown for the second and third tertiles, with the lowest tertile group as the reference category. We estimated the risk of fluorosis associated with each of the three dietary patterns separately. In the multivariate models, the relationships between dietary patterns and the risk of fluorosis were further examined after adjusting for various potential confounding variables such as duration of residence in Zhijin, ethnicity, marital status, education level, household income, body mass index (BMI), urinary fluoride level, smoking, alcohol drinking, tea drinking, domestic fuel type, and use of improved stove, whether, or not like roasting food. We further examined the association between dietary pattern and CBF across different subgroups stratified by gender (man/women) and whether or not like roasting food (Yes/No). To test the *p*-value of the trends, the ordinal values of the tertile of each factor score were entered as continuous variables in a logistic regression analysis model. In this study, SPSS 18.0 was used for the statistical analysis, all of the *P*-values were two sided and statistical significance was determined at the $p < 0.05$ level.

RESULTS

The characteristics of the CBF cases and controls are presented in **Table 1**. Of the 200 CBF patient–control pairs, 193 patient pairs had dental fluorosis and 85 patient pairs had skeletal fluorosis. The average age was 49.8 years in the CBF patients and 49.7 years in the control group. The CBF group had lower education levels, household incomes, higher urinary fluoride levels, and were less likely to use an improved stove. No significant differences were found between the CBF cases and control in marital status, BMI, duration of residence in Zhijin, smoking status, alcohol, or tea drinking.

We identified three major dietary patterns using the factor analysis procedure, presented in **Table 2**. The first pattern, named the high protein dietary pattern, was characterized by a high intake of beef, seafood, poultry, fish and pork. The second pattern, named the healthy dietary pattern, was characterized by a high intake of fruit, dairy, legume, nuts, and fungus. The third pattern was characterized by a high intake of squash, potatoes, corn, dried chili and cured meat. This last group was labeled as the easy-to-roast dietary pattern, because Zhijin County residents commonly roast this last group of foods before consumption. Dietary patterns 1, 2, and 3 accounted for 7.9, 7.1, and 5.7% of

TABLE 2 | Factor-loading matrix for the three major dietary patterns*.

Food items	High protein pattern (Factor 1)	Healthy pattern (Factor 2)	Easy-to-roast food pattern (Factor 3)
Beef	0.690	–	–
Sea food	0.665	–	–
Pork	0.521	–	–
Poultry	0.622	–	–
Fish	0.551	–	–
Dairy	–	0.558	–
Legume	0.336	0.557	–
Sour soup	–	0.496	–
Dark-colored fruits	–	0.565	0.284
Light-colored fruits	–	0.573	–
Nut	–	0.440	–
Mushroom and algae	–	0.408	–
Gourds	0.258		0.562
Corn	–		0.496
Dried chili	–		0.474
Potato	–		0.555
Cured meat	–		0.465
Dark-colored vegetables	0.287		–
Light-colored vegetables	–		0.270
Houttuynia cordate	0.316		–
Eggs	0.271		–
Cooking oil	–	0.296	–
Root vegetables	–	0.259	–
Cereals	–		0.322
snacks	–	0.306	–

Absolute values <0.25 were excluded for simplicity.

TABLE 3 | Odds ratios (ORs) and 95% confidence intervals (95% CIs) of fluorosis according to tertiles of factor scores for each dietary pattern.

	Tertiles of factor scores for dietary pattern			*P*-trend
	Tertile 1[§]	Tertile 2	Tertile 3	
High protein pattern				
Case/control	57/65	83/67	60/68	
OR (95% CI)[1]	1	1.44 (0.88, 2.34)	1.02 (0.59, 1.74)	0.944
OR (95% CI)[2]	1	1.62 (0.94, 2.76)	1.47 (0.81, 2.65)	0.205
Healthy pattern				
Case/control	112/66	48/66	40/68	
OR (95% CI)[1]	1	0.42 (0.25, 0.69)*	0.33 (0.19, 0.57)**	<0.001
OR (95% CI)[2]	1	0.42 (0.24, 0.71)*	0.47 (0.27, 0.84)*	0.003
Easy-to-roast pattern				
Case/control	37/65	70/66	93/69	
OR (95% CI)[1]	1	1.91 (1.12, 3.25)**	2.49 (1.45, 4.30)**	0.001
OR (95% CI)[2]	1	1.75 (0.99, 3.09)	2.05 (1.15, 3.66)*	0.017

OR, odds ratio; CI, confidence interval.
*[§]Tertile1 was the reference tertile. [1]Model 1 Crude adjusted ORs were obtained without further adjustment of covariates. [2]Model 2 adjusted for duration of residence in Zhijin, ethnic, marital status, education level, body mass index, urinary fluoride level, household income, smoking, alcohol drinking, tea drinking, daily energy intake, supplement use, fuel type, improved stove use, like roasting food, *$P < 0.05$, **$P < 0.01$.*

the variability, respectively, and 26.7% of the variance in food intake overall.

As shown in **Table 3**, univariate analyses showed CBF was inversely associated with the healthy dietary pattern ($p < 0.001$) but positively associated with the easy-to-roast dietary pattern. A significant relationship remained even after adjustments were made for duration of residence in Zhijin, ethnicity, marital status, education level, household income, smoking status, alcohol drinking, tea drinking, daily energy intake, dietary supplement usage, domestic fuel type, use of improved stoves, and whether or not like roasting food. The risk of CBF decreased by approximately 53% in the highest tertile of the healthy dietary pattern group, compared with the reference lowest tertile (OR = 0.47, 95% CI = 0.27–0.84, $p = 0.003$). Significant relationships were observed between CBF risk and the healthy dietary pattern (T3 vs. T1: OR 2.05, 95% CI 1.15–3.66, $p = 0.017$). In addition, there was no association between the high protein diet pattern and CBF.

The results of dental and skeletal fluorosis sub-type analyses are shown in **Table 4**. We observed a similar dental fluorosis incidence in the healthy diet group as in the easy-to-roast diet group. Skeletal fluorosis was negatively associated with the healthy diet group ($p = 0.025$), but marginally positively associated with the easy-to-roast diet group after adjustment ($p = 0.089$). Stratified analyses showed a negative association between the healthy dietary pattern and CBF in women but not in men, and a positive association between the easy-to-roast dietary pattern and CBF (**Supplementary Table 1**).

DISCUSSION

To our knowledge, this matched case-control study was the first to use factor analysis to evaluate the associations between dietary patterns and CBF risk in a population living in a coal-burning fluorosis area. We extracted three distinct dietary patterns, which are high protein, healthy and easy-to-roast. We found that the healthy dietary pattern had a significant protective effect against CBF, whereas the easy-to-roast dietary pattern was related to an increased risk of CBF.

In present study, we found that a healthy dietary pattern, typified by a high intake of fruit, dairy, legumes, nuts and fungus, was associated with a decreased risk of CBF. Although no studies specifically reported the association between bone damage and CBF, there were many studies that explored the relationship between dietary pattern and bone health. A similar pattern was observed in a matched case-control study of hip fractures in a Chinese population, where a healthy dietary pattern of nuts, fungus, soy and milk were found to be beneficial to bone health (20). Recently, two meta-analyses assessed the relationship between dietary patterns, bone mineral density and the risk of fracture and suggested a healthy diet reduced risk of low BMD in different age groups. The studies also

TABLE 4 | Odds ratios (ORs) and 95% confidence intervals (95% CIs) of dental and skeletal fluorosis according to tertiles of factor scores for each dietary pattern.

	Tertiles of factor scores for dietary pattern			*P*-trend
	Tertile 1[§]	Tertile 2	Tertile 3	
DENTAL FLUOROSIS				
High protein pattern				
Case/control	65/63	71/64	57/66	
OR (95% CI)[1]	1	1.40 (0.85, 2.31)	0.95 (0.55, 1.62)	0.821
OR (95% CI)[2]	1	1.49 (0.85, 2.63)	1.30 (0.70, 2.42)	0.428
Healthy pattern				
Case/control	110/64	47/64	36/65	
OR (95% CI)[1]	1	0.42 (0.25, 0.70)*	0.32 (0.18, 0.55)**	<0.001
OR (95% CI)[2]	1	0.45 (0.25, 0.81)*	0.46 (0.25, 0.84)*	0.001
Easy-to-roast pattern				
Case/control	38/63	68/65	87/65	
OR (95% CI)[1]	1	1.89 (1.09, 3.06)**	2.45 (1.39, 4.28)**	0.002
OR (95% CI)[2]	1	1.70 (0.92, 3.12)	2.03 (1.11, 3.72)*	0.023
SKELETAL FLUOROSIS				
High protein pattern				
Case/control	29/29	31/26	27/32	
OR (95% CI)[1]	1	1.00 (0.41, 2.42)	0.65 (0.27, 1.56)	0.326
OR (95% CI)[2]	1	1.38 (0.63, 3.02)	1.19 (0.51, 2.80)	0.646
Healthy pattern				
Case/control	50/32	21/29	16/26	
OR (95% CI)[1]	1	0.49 (0.23, 1.07)	0.34 (0.14, 0.84)*	0.007
OR (95% CI)[2]	1	0.51 (0.24, 1.08)*	0.41 (0.18, 0.93)*	0.021
Easy-to-roast pattern				
Case/control	15/30	32/26	40/31	
OR (95% CI)[1]	1	2.31 (0.99, 5.39)	2.59 (1.09, 6.17)	0.039
OR (95% CI)[2]	1	2.36 (1.01, 5.50)*	2.29 (1.01, 5.19)*	0.036

OR, odds ratio; CI, confidence interval.
*[§]Tertile1 was the reference tertile. [1]Model 1 Crude adjusted ORs were obtained without further adjustment of covariates. [2]Model 2 adjusted for duration of residence in Zhijin, ethnic, marital status, education level, body mass index, urinary fluoride level, household income, smoking, alcohol drinking, tea drinking, fuel type, improved stove use, like roasting food, *P < 0.05, **P < 0.01.*

compared the risk of fracture between high and low food intake categories of healthy diet patients (OR = 0.81; 95% CI: 0.69, 0.95; $p = 0.01$) (21, 22). The studies indicated a healthy diet was characterized by "Calcium foods," "Dairy and whole grains," "Fruit, milk, and whole grains," "Milk and root vegetables," "Vegetable-fruit-soy," and "Dairy-fruit" (21, 22). In the present study, we found similar components to these healthy dietary patterns. Therefore, healthy diet had a beneficial effect on CBF in the present study and may be attributed to its protective role in bone health. The observed healthy dietary pattern has a balanced food composition, which may explain its beneficial effect against CBF. Additionally, Food choices may be influenced by educational level of participant. Participants with higher education were more likely to follow a healthy diet because they had access to healthy food items. No epidemiological studies have explored the association between nuts, mushrooms, and fluorosis, although a few studies have found that dairy and fruit have protective effects against fluorosis (23–25). Patients who adhered to a healthy dietary pattern had a high intake of calcium, magnesium, carotenoids, vitamin C, vitamin E, and isoflavones. Experimental studies have demonstrated that dietary calcium intake promotes the formation of a high bone formation and adequate dietary calcium or calcium supplements may contribute to a lower risk of fluorosis as calcium antagonizes the effects of fluoride (26, 27). Additionally, oxidative stress is a prime contributing mechanism in CDF and antioxidative nutrients may play important role in preventing CDF (28). It was reported that lycopene combated NaF-induced apoptosis of ameloblast cells and dental fluorosis by improving oxidative stress and down-regulating the caspase pathway (29). Furthermore, vitamin E and lycopene have been shown to prevent fluorosis-induced spermatogenic cell apoptosis through the suppression of oxidative stress-mediated JNK and ERK signaling pathways (30). Several studies suggested isoflavones from legumes and vitamin C may prevent fluorosis by antagonizing the oxidative stress damage caused by fluorine (31, 32). Therefore, we speculate that the antioxidant effects and effect of calcium on bone metabolism may partly explain the protective effects of healthy diets.

This analysis noted a positive association between the easy-to-roast food dietary pattern and CBF risk. We compared the factor scores of easy-to-roast dietary patterns between two groups and found high scoring individuals had a preference for roasted foods. The stratified analysis showed that the positive association between the easy-to-roast foods and fluorosis only existed in subjects who like roasting food. These results indicated the cooking method itself may be an actual risk factor for developing CBF. We conducted this case-control study in Zhijin County, where the moist climate requires residents to burn stoves with mixed fluoride-rich coal and clay. Residents were used to roasting foodstuff over it, such as corns, potato, squash and red chili. Cured meat is also a roasted food and residents commonly hang it for more than 2 months in a house polluted by fluoride dust in Zhijin County. Thus, this dietary pattern involved foods which were easy to roast before consumption. The combustion process released fluoride from the coal and fluorine content significantly increases on the roasted foodstuffs. Previous studies reported fluoride contents of roasted chili, corn, squash, potatoes and cured meat reached 419.8 mg/kg (33), 39.5 mg/kg (33), 121.8 mg/kg (34), 134.6 mg/kg (35), and 182.2 mg/kg (36), respectively. Corn and potatoes are the primary foods consumed by residents of Zhijin and daily mean fluoride intake (per person) from corn was 37.6 and 3.5 mg from potatoes (37). Previous studies demonstrated that particular roasted foods, such as corn, chilli, and potatoes, were the primary pathological cause of coal-burning fluorosis, because of the fluorine pollution coming from the coal briquettes and binder clay (6, 37, 38). Therefore, the present study suggests that the easy-to-roast dietary pattern in our study was positively associated with a risk of fluorosis not because the foods themselves were a source of fluorine, but rather roasting food over coal stoves caused the fluorine pollution.

In subgroup analysis, we observed a protective effect of the healthy dietary pattern against fluorosis in women but not in men. The gender difference in the association between dietary pattern and fluorosis has not been clearly explained. Diet might influence fluorosis between men and women differently due to sex hormones, or sex-specific genes, which are related to the control of fluorosis. Additionally, one of the main foods in this healthy dietary pattern were legumes, which contain the phytoestrogen isoflavone. Meta-analysis and randomized controlled trials demonstrated soy isoflavones have potential bone-specific effects in women (39, 40). The matrix of soy protein-enriched soy isoflavones may improve their bioavailability and biologic efficacy, improving tibia bone architecture (41). Thus, the negative association between the healthy dietary pattern and CBF in women may be attributed to estrogen's effect on isoflavones. Further studies are needed to clarify underlying mechanisms of this process.

The present study had several limitations. First, given the case-control design, we were unable to evaluate the causal associations between dietary patterns and the risk of fluorosis, which need to be confirmed in future studies. Second, it is known that FFQs have measurement error to some extent, although the FFQ used in this study has been validated (16). Third, the factor analysis requires many subjective decisions related to the selection of food groups, including decisions about the number of factors extracted, the type of rotation, and the interpretation and labeling of the factors. Although, this 1:1 matched case-control study was based on community populations, fluorosis and control were not randomly selected, which limited the generalization of findings. Finally, although we adjusted many factors for the statistical analysis, residual confounding was still unavoidable due to potential measurement errors and missing adjustments for some unmeasured factors.

In summary, the present study identified that a healthy dietary pattern has a protective effect against CBF, and that an easy-to-roast dietary pattern was significantly associated with an increased risk of CBF. Our findings suggest that a high consumption of fruit, dairy, legumes, nuts, mushrooms, and a low consumption of roasted corn, potatoes, chillis, and squash may protect against CBF in populations living in coal-burning fluorosis areas.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Zunyi Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JL designed the study, and conducted the study, and revised the manuscript. SY and ML was responsible for the data management, analysis, and wrote the first draft of the manuscript. XM critically revised the manuscript. NT, XZ, and TC assisted in conducting the research and data collection. DW developed the idea and proofread the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2019.00189/full#supplementary-material

REFERENCES

1. Fawell J, Bailey K, Chilton J, Dahi E, Fewtrell L, Magara Y. *Fluoride in Drinking-Water*. Zunyi: WHO Press (2006). 6–45 p.
2. Jha SK, Mishra VK, Sharma DK, Damodaran T. Fluoride in the environment and its metabolism in humans. *Rev Environ Contam Toxicol*. (2011) 211:121–42. doi: 10.1007/978-1-4419-8011-3_4
3. Guan ZZ, Wu CX, Qi XL. Evaluation of health status of coal-burning fluorosis areas in Guizhou province after comprehensive management. *J Guizhou Med Univ*. (2018) 43:1124–28.
4. Liu YL, M P, Luo KL, Li L. The state and trend of endemic fluorosis from 1991 to 2012 in China. *J Chongqing Norm Univ*. (2016) 33:142–51. doi: 10.11721/cqnuj20160228
5. Zhou YX, Mo SL, Wang RH, Liu WF, Liu JC, Wang JQ, et al. Corn baked by burning coal triggered overexpression of osteopontin in hepatocytes of rats following fluorosis. *Toxicol Ind Health*. (2012) 28:195–202. doi: 10.1177/0748233711410905
6. Luo KL, Li L, Zhang SX. Coal-burning roasted corn and chili as the cause of dental fluorosis for children in Southwestern China. *J Hazard Mater*. (2011) 185:1340–7. doi: 10.1016/j.jhazmat.2010.10.052
7. Liu J, Luo MJ, Zhao X, Yang S, Zhang YM, Zhou D. Study on relationship between edible sour soup and coal-burning fluorosis. *Chongqing Med J*. (2019) 48:156–60. doi: 10.3969/j.issn.1671-8348.2019.04.024
8. Liu J, Yang S, Luo MJ, Zhao X, Zhang YM, Tao N. Analysis on the correlation between dietary vitamin C intake and coal-burning fluorosis. *J Mod Med Health*. (2018) 34:2119–21. doi: 10.3969/j.issn.1009-5519.2018.14.004
9. Yang S, Luo MJ, Tao N, Zhang YM, Zhao X, Liu J. Relationship between dietary intake of vitamin A and coal burning fluorosis. *Shandong Med J*. (2018) 58:28–31. doi: 10.3969/j.issn.1002-266X.2018.06.007
10. Yang S, Luo MJ, Tao N, Zhang YM, Zhao X, Liu J. Association between dietary intake of vitamin E and coal-burning fluorosis. *Guangdong Med J*. (2018) 39:2054–57. doi: 10.13820/j.cnki.gdyx.2018.13.018
11. Liu J, Yang S, Luo MJ, Zhao X, Zhang YM, Luo Y. Association of dietary carotenoids intake with skeletal fluorosis in the coal-burning

fluorosis area of Guizhou province. *Biomed Environ Sci.* (2018) 31:438–47. doi: 10.3967/bes2018.057

12. Patel PP, Patel PA, Zulf MM, Yagnik B, Kajale N, Mandlik R, et al. Association of dental and skeletal fluorosis with calcium intake and serum vitamin D concentration in adolescents from a region endemic for fluorosis. *Indian J Endocrinol Metab.* (2017) 21:190–5. doi: 10.4103/2230-8210.196013
13. Simon MJ, Beil FT, Ruther W, Busse B, Koehne T, Steiner M, et al. High fluoride and low calcium levels in drinking water is associated with low bone mass, reduced bone quality and fragility fractures in sheep. *Osteoporos Int.* (2014) 25:1891–903. doi: 10.1007/s00198-014-2707-4
14. Schwerin HS, Stanton JL, Smith JL, Riley AMJ, Brett BE. Food, eating habits, and health: a further examination of the relationship between food eating patterns and nutritional health. *Am J Clin Nutr.* (1982) 35:1319–25. doi: 10.1093/ajcn/35.5.1319
15. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol.* (2002) 13:3–9. doi: 10.1097/00041433-200202000-00002
16. Zhang CX, Ho SC. Validity and reproducibility of a food frequency Questionnaire among Chinese women in Guangdong province. *Asia Pac J Clin Nutr.* (2009) 18:240–50. doi: 10.6133/apjcn.2009.18.2.13
17. Yang YX, Wang GY, Pan XC. *China Food Composition*. 2nd ed. Beijing: University Medical Publishing House (2009).
18. Varraso R, Garcia-Aymerich J, Monier F, Moual NL, Batlle JD, Miranda J, et al. Assessment of dietary patterns in nutritional epidemiology: principal component analysis compared with confirmatory factor analysis. *Am J Clin Nutr.* (2012) 96:1079–92. doi: 10.3945/ajcn.112.038109
19. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr.* (1997) 65:1220S—8S. doi: 10.1093/ajcn/65.4.1220S
20. Zeng FF, Wu BH, Fan F, Xie HL, Xue WQ, Zhu HL, et al. Dietary patterns and the risk of hip fractures in elderly Chinese: a matched case-control study. *J Clin Endocrinol Metab.* (2013) 98:2347–55. doi: 10.1210/jc.2013-1190
21. Denova-Gutierrez E, Mendez-Sanchez L, Munoz-Aguirre P, Tucker, KL, Clark P. Dietary patterns, bone mineral density, and risk of fractures: a systematic review and meta-analysis. *Nutrients.* (2018) 10:E1922. doi: 10.3390/nu10121922
22. Fabiani R, Naldini G, Chiavarini M. Dietary patterns in relation to low bone mineral density and fracture risk: a systematic review and meta-analysis. *Adv Nutr.* (2019) 10:219–36. doi: 10.1093/advances/nmy073
23. Liu GJ, Ye QF, Chen W, Zhao ZJ, Li L, Lin P. Study of the relationship between the lifestyle of residents residing in fluorosis endemic areas and adult skeletal fluorosis. *Environ Toxicol Pharmacol.* (2015) 40:326–32. doi: 10.1016/j.etap.2015.06.022
24. Susheela AK, Mondal NK, Tripathi N, Gupta R. Early diagnosis and complete recovery from fluorosis through practice of interventions. *J Assoc Physicians India.* (2014) 62:572–9.
25. Hussain J, Hussain I, Sharma KC. Fluoride and health hazards: community perception in a fluorotic area of central Rajasthan (India): an arid environment. *Environ Monit Assess.* (2010) 162:1–14. doi: 10.1007/s10661-009-0771-6
26. Li GS, Ren LQ. Effects of excess fluoride on bone turnover under conditions of diet with different calcium contents. *Zhonghua Bing Li Xue Za Zhi.* (1997) 26:277–80. doi: 10.1111/j.1439-0264.1997.tb00136.x
27. Xu H, Liu QY, Zhang JM, Zhang H, Li GS. Elevation of PTH and PTHrp induced by excessive fluoride in rats on a calcium-deficient diet. *Biol Trace Elem Res.* (2010) 137:79–87. doi: 10.1007/s12011-009-8561-0
28. Suzuki M, Bandoski C, Bartlett JD. Fluoride induces oxidative damage and SIRT1/autophagy through ROS-mediated JNK signaling. *Free Radic Biol Med.* (2015) 89:369–78. doi: 10.1016/j.freeradbiomed.2015.08.015
29. Li WS, Jiang BH, Cao XL, Xie YJ, Huang T. Protective effect of lycopene on fluoride-induced ameloblasts apoptosis and dental fluorosis through oxidative stress-mediated Caspase pathways. *Chem Biol Interact.* (2017) 261:27–34. doi: 10.1016/j.cbi.2016.11.021
30. Tian Y, Xiao YH, Wang BL, Sun C, Tang KF, Sun F. Vitamin E and lycopene reduce coal burning fluorosis-induced spermatogenic cell apoptosis via oxidative stress-mediated JNK and ERK signaling pathways. *Biosci Rep.* (2018) 38:1–4. doi: 10.1042/BSR20171003
31. Peng W, Xu SR, Zhang J, Zhang Y. Vitamin C attenuates sodium fluoride-induced mitochondrial oxidative stress and apoptosis via Sirt1-SOD2 pathway in F9 cells. *Biol Trace Elem Res.* (2019) 191:189–98. doi: 10.1007/s12011-018-1599-0
32. Zhu JZ, Liu JH, Zhao WT, Zhang HF. Protective effects of soy isoflavones on liver and kidney damage in rats with fluorosis. *Chin J Contr Endem Dis.* (2016) 31:527.
33. Li DS, Wang SQ, Li P, Duan RX, He GY, Hu XQ, et al. Analysis of 7 years' monitoring on coal-burning pollution endemic fluorosis in the state test spot in Zhijin County of Guizhou province. *Chin J Endemiol.* (1999) 18:349–51.
34. Xie L, Wei X, Pan NS, Zeng CS, Zhang XQ, Wu XY, et al. Detection of Fluoride in gourd and eggplant in coal area of Zunyi city. *For All Health.* (2015) 303–4. doi: 10.3969/j.issn.1009-6019.2015.03.393
35. Xie L, Wei X, Pan NS, Zeng CS, Zhang XQ, Wu XY, et al. Detection of fluoride sweet potato and potato in coal area of Zunyi city. *Chin Baby.* (2015) 354–5.
36. Zeng GH, Long XJ, Hu DF, X QW, Zhang B, Wang QS, et al. Investigation on current prevalence of endemic fluorosis in Loudi city, Hunan province. *Chin J Endemiol.* (2004) 23:240–1. doi: 10.3760/cma.j.issn.1000-4955.2004.03.018
37. Qin X, Wang S, Yu M, Zhang L, Li X, Zuo Z, et al. Child skeletal fluorosis from indoor burning of coal in southwestern China. *J Environ Public Health.* (2009) 2009:969764. doi: 10.1155/2009/969764
38. Li L, Luo KL, Tang YG, Liu YL. The daily fluorine and arsenic intake for residents with different dietaries and fluorosis risk in coal-burning fluorosis area, Yunnan, Southwest China. *Environ Sci Pollut Res Int.* (2015) 22:2031–40. doi: 10.1007/s11356-014-3485-4
39. Zhang X, Liu Y, Xu Q, Zhang Y, Liu L, Li H, et al. The effect of soy isoflavone combined with calcium on bone mineral density in perimenopausal Chinese women: a 6-month randomised double-blind placebo-controlled study. *Int J Food Sci Nutr.* (2019) 4:1–9. doi: 10.1080/09637486.2019.1673703
40. Akhlaghi M, Ghasemi Nasab M, Riasatian M. Soy isoflavones prevent bone resorption and loss, a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr.* (2019) 10:1–15. doi: 10.1080/10408398.2019.1635078
41. Zheng X, Lee SK, Chun OK. Soy Isoflavones and osteoporotic bone loss: a review with an emphasis on modulation of bone remodeling. *J Med Food.* (2016)19:1–14. doi: 10.1089/jmf.2015.0045

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Consumption of Vitamin K and Vitamin A Are Associated With Reduced Risk of Developing Emphysema: NHANES 2007–2016

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Chronic obstructive pulmonary disease (COPD) comprising of emphysema and chronic bronchitis are the most common chronic respiratory diseases that impart a huge economic and clinical burden. Factors other than smoking and air pollutants can cause inflammation and emphysematous changes in the lung airspaces or alveoli have been understudied. Using a cross-sectional study design, we assessed the association of dark green vegetables, vitamin K and Vitamin A with emphysema status among adults at U.S. These nutrients have a role in lung biology. A complete case NHANES data ($n = 17{,}681$) was used. After adjusting for modifiable and non-modifiable confounders, consumption of recommended amounts of vitamin K was associated with 39% decrease in odds (Odds Ratio: 0.61; 95% CI: 0.40–0.92, *P*-val: 0.02) of emphysema. Similarly consumption of recommended amounts vitamin A dose was associated with 33% decrease in odds (Odds Ratio: 0.67; 95% CI: 0.44–1.00, *P*-val: 0.05) of emphysema. Vitamin K shows an inverse association suggesting that it may be important in slowing the emphysematous process. Vitamin A is important in maintaining the anti-inflammatory process. Together vitamin K and vitamin A are important in the lung health.

Keywords: COPD, emphysema, lung disease, green vegetable, NHANES data

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and asthma are the most common chronic respiratory diseases that imparts a huge economic and clinical burden in the health sectors (1, 2). In the US, COPD costs $30 billion in direct health care expenditures and $20 billion in indirect expenditure (1). COPD is the first leading cause of disability and 3rd leading cause of death in the U.S (3, 4). COPD comprises of two heterogeneous subtypes: emphysema and chronic bronchitis (5). Emphysema is associated with structural changes, including abnormal and permanent enlargement or damage of the airspaces distal to the terminal bronchioles, while chronic bronchitis results from inflammation of the lining of the bronchial tubes (6). Reported risk factors associated with the emphysematous changes such as gender, tobacco smoke, obesity, and exposure to air pollutants (7, 8) do not completely explain development of emphysema.

Even though smoking is a key risk factor for the development and progression of the COPD, many patients with this obstructive lung function are never-smokers. Along these lines, recent studies have shown that lack or excess of specific nutrition may also play a role in developing lung diseases. Some of these studies provide evidence that vegetable intake may have potential benefits in the biology of the lung diseases (9–26). However, data is still limited with regards to specific constituents or micronutrients in vegetables that are either risk factors for or have beneficial roles on the development of the COPD phenotypes and more specifically emphysema. Trace elements have also been linked to harmful effects on lung function (27). For example cadmium in tobacco smoke may contribute to the development of pulmonary emphysema. However, there is poor understanding of the mechanisms behind the pathogenic role of cadmium in lung diseases.

Studies have shown that inflammation plays a role in the exacerbation of COPD (28), and chronic inflammation can cause damage to the lung airways and tissues (29), resulting to irreversible emphysematous changes in the lung alveoli (30, 31). Reports have shown that micronutrients such as vitamins E and C play a role in strengthening the immune system (32, 33). A meta-analysis has shown that high vitamin C intake levels have a significant protective effect against lung diseases e.g., lung cancer (34, 35). Although vegetables have been shown to have beneficial nutrients that can aid healthy lung structure (34, 36, 37), more research is warranted to link specific nutrients in the greens that can help protect the alveoli from developing emphysematous lung injuries. Since vitamin K is mostly obtained from dark green vegetable, it is highly likely that it may have an impact on the biology of lung airway or alveoli structure (38, 39). Low intake of vitamin A also from dark green vegetables has been associated with COPD in different populations (40–42) and a few studies have shown the potential role of vitamin A in maintaining the integrity of the lung epithelium, non-emphysematous state and exerts anti-inflammatory effects (43, 44). Therefore, we hypothesize that dark green vegetables including vitamin K and vitamin A consumptions may be associated with emphysema.

Thus, the objective of this study is to (separately) examine the association between dark green vegetables, and risk of emphysema; and the association between both vitamins K and A with the risk of developing emphysema.

METHODS

Study Design and Population

A cross-sectional design was used in this study. Data was acquired from the National Health and Nutrition Examination Survey (NHANES), which is a program designed to assess the health and nutritional status of adults and children in the United States (45). Data for the current analysis are from the 2007–2016 survey cycles. The sample for the survey was selected to represent the U.S. population of all ages which included adults aged ≥20 in U.S who completed the questionnaire. The questionnaire collected information on demographics (gender, age, race, education, household income, and marital status), behavioral factors (smoking status and heavy drinking), BMI, medical conditions, and 24 h food recall. About 12,000 persons every 2-year cycle were asked to participate, and the average response rate was 87.5% (45). Of the 12,000 NHANES respondents, subsamples were randomly selected to participate in a variety of survey components (e.g., dietary survey, laboratory examination) according to the NHANES protocol. From 2007 to 2012, one-half of the total respondents were sampled to complete the survey components of interest in our study; from 2013 to 2016, one-third of total respondents were sampled.

TABLE 1 | Subtypes of vegetables.

Vegetable
(1) White potatoes and Puerto Rican starchy vegetables,
(2) Dark-green vegetables,
(3) Deep-yellow vegetables,
(4) Tomatoes and tomato mixtures,
(5) Other vegetables,
(6) Vegetables and mixtures mostly vegetables baby food,
(7) Vegetables with meat, poultry, fish, and
(8) Mixtures mostly vegetables without meat, poultry, fish.

Measures

Outcome

Emphysema was assessed based on self-reported Yes/No response to the questions: Has a doctor or other health professional ever told you that you have emphysema?

Exposure

Dark-Green Vegetables and Vitamins

A 24-h dietary/food recall was used to collect dietary intake data. Food intake categories are defined by food code following the USDA Food and Nutrient Database for Dietary Studies (46). Based on previously reported links between vitamin K, vitamin A as well as dark green vegetable on lung health makes them suitable exposures for assessing development of emphysema. Dark-green vegetable is one of eight subtypes of vegetable as shown in **Table 1**. The estimated weight of the dark-green vegetable intake (in grams) was obtained from the 24 h dietary recall. Dark green vegetables is the main source of vitamin K and vitamin A can also be found in the dark green vegetables. Dichotomous (45) measures of vitamins and dark-green vegetable intake, were obtained by categorizing the dietary intake of vitamins into Recommended Dietary Allowances (RDAs) were not consumed (No) and RDAs were consumed (Yes) and "weight of the dark-green vegetables intake" into 0 gram (Intake: No) and >0 gm (Intake: Yes). RDAs for vitamins were stratified by age, gender, pregnancy, and lactation according to National Institutes of Health's website (https://ods.od.nih.gov).

Covariates

Age, gender, race/ethnicity, BMI, education level, marital status, smoking status, alcohol (heavy drinking status) intake, cadmium exposure, energy intake, and physical activity were identified as potential confounders.

The demographic data (age, race/ethnicity, education, marital status) was collected by employing a questionnaire. Age was reported in years. Gender was reported as either "Male" or "Female." Race was grouped into five categories: Non-Hispanic White, Non-Hispanic Black, Mexican American, other Hispanic, and other races.

Body Mass Index (kg/m^2) was calculated based on height and weight. Education was grouped into 4 categories: less than high school, high school graduate/GED or equivalent, some college or AA degree, and college graduate or above. Marital Status was grouped into two categories: single (widowed/divorced/separated/never married) and married (married or living with partner). Smoking status consisted of four categories: non-smoker, former smoker, someday smoker, and every day smoker, based on two questions "Did you smoke at least 100 cigarettes in life? (SMQ020)" and "Do you now smoke cigarettes? (SMQ040)." Non-smokers were defined as individuals who smoked less 100 cigarettes in life; Former-Smokers were those who smoked at least 100 cigarettes in their life and did not smoke currently; Someday smokers were adults who had smoked at least 100 cigarettes in their lifetime, who smoked now, but did not smoke every day; Every day smokers were adults who had smoked at least 100 cigarettes in their lifetime, and who now smoked every day. Heavy drinking was defined as "Yes" response to "Ever have 5 or more drinks every day?" for both male and female from 2007 to 2010 and to "Ever have 4/5 or more drinks every day?" for female and male separately from 2011 to 2016. The number of heavy drinking day and Average number alcoholic drinks/day in the past 12 months were calculated by questionnaire to provide detailed information on alcohol use behavior. Cadmium exposure (μg/L) was obtained from analyzing blood samples. Energy intake (kilocalorie) was defined as total energy of foods consumed in the 24-h dietary recall.

Statistical Analysis

After excluding participants with missing observations there were 17681 observations (2007–2008: 4,628, 2009–2010: 4,780, 2011–2012: 4,014, 2013–2014: 2,186, and 2015–2016: 2,077) based on NHANES data.

Descriptive measures were calculated and reported as mean (standard error) for continuous variables, and as frequency (or percentage), weighted frequency for categorical variables and lung emphysema status. Bivariate association between categorical variables were assessed using Rao-Scott's modified Chi-square test. Continuous variables were compared using linear regression adjusted by interview weights. The association between vitamins and odds of emphysema were estimated separately using logistic regression. To account for the sampling design, the models were adjusted for the sampling weight, sampling cluster, and sampling strata. Multivariate modeling was done by regressing response (emphysema) on vitamins intake, dark green vegetable together with non-modifiable confounders—age, gender, ethnicity; and modifiable confounders—BMI, education level, marital status, smoking status, alcohol (heavy drinking status) intake, cadmium exposure, and total energy intake. Ninety-five percentage confidence interval was reported together with the odds ratio estimates. The analysis was done in SAS 9.4 (SAS Institute).

RESULTS

Table 2 summarizes the characteristics of the study population. The complete case analysis involved 17,681 respondents. There were 396 (1.82%) participants with self-reported emphysema.

Overall, 32.06% participants recommended vitamin k consumption; 26.78% participants recommended vitamin A consumption; 12.49 % of respondents reported dark green vegetable consumption. The recommended vitamin K consumption; recommended vitamin A consumption; and dark green vegetable consumption among those with self-reported emphysema was 18.79, 7.19, and 7.19%, respectively.

Overall, 48.43% were females; Non-Hispanic Whites (69.38%), and Non-Hispanic Blacks (10.55%) were two most commonly reported race/ethnicity categories; 63.09% were married or living with partner; some college or advanced associate equivalent (32.10%) and college degree or above (30.39%) and were two most commonly reported education level; 14.47% were heavy drinkers; 55.21% never smoked, and 25.22% were former smokers (two most frequent smoking status). The mean age, BMI, blood cadmium level, and total energy intake were 47.40 years, 29.08 (Kg/m^2), 0.47 (μg/L), and 2,161.82 (kilocalorie), respectively.

Among those with self-reported emphysema, 58.11% were females; Non-Hispanic Whites (84.98%), and Non-Hispanic Blacks (5.52%) were two most commonly reported race/ethnicity categories; 53.22% were married or living with partner; some college or advanced associate equivalent (26.11%) and college degree or above (13.62%) were two most commonly reported education level; 35.77% were heavy drinkers; 50.06% were former smokers, and 37.86% were everyday smokers (two most frequent smoking status). The mean age, BMI, blood cadmium level, and total energy intake were 47.12 years, 29.07 (Kg/m^2), 0.46 (μg/L), and 2,164.89 (kilocalorie), respectively.

Among those with self-reported emphysema, 58.11% were females; Non-Hispanic Whites (84.98%), and Non-Hispanic Blacks (5.52%) were two most commonly reported race/ethnicity categories; 53.22% were married or living with partner; less than high school (34.19%), high school or GED equivalent (26.08%), and some college or AA equivalent (26.11%) were three most commonly reported education level; 35.77% were heavy drinkers; 50.06% were former smokers and 41.09% were never smokers (two most frequent smoking status). The mean age, BMI, and blood cadmium level was 62.41 years, 29.72 (Kg/m^2), and 0.95 (μg/L), respectively.

Relationship Among Dark-green Vegetables Intake, Vitamins, and Emphysema

The summary of findings examining the association between dark-green vegetables intake, vitamins, and risk of emphysema are summarized in **Tables 3**, **4**. After adjusting for modifiable and non-modifiable confounders, consumption of recommended vitamin K was associated with 39% decrease in odds (Odds Ratio: 0.61; 95% CI: 0.40–0.92, *P*-val: 0.02) of emphysema compared to those who consumed less than the recommended vitamin K dose. The association between consumption of recommended vitamin k and emphysema changed marginally when consumption of dark green vegetable was incorporated in the model (Odds Ratio: 0.62; 95% CI: 0.44–0.87, *P*-val: 0.01). Dark-green vegetable

TABLE 2 | Characteristics of Study Population, National Health and Nutrition Examination.

Variable	Levels	Overall ($n = 17,681$)	Emphysema	
			Yes ($n = 391$)	No ($n = 17,290$)
Vitamin K	Yes	4,976 (32.06) 61,371,378	75 (18.79) 652,992	4,901 (32.30) 60,718,385
Vitamin A	Yes	4,232 (26.78) 51,264,497	75 (7.19) 624,915	4,157 (12.59) 50,639,582
Dark-green Veg Intake	Yes	1,942 (12.49) 23,916,374	27 (7.19) 250,078	1,915 (12.59) 23,666,296
Gender	Female (1)	8,768 (48.43) 92,724,512	244 (58.11) 2,019,916	8,524 (48.26) 90,704,595
	Male (2)	8,913 (51.56) 98,707,458	147 (41.89) 1,456,217	8,766 (51.74) 97,251,242
Race/Ethnicity	Non-hispanic white (3)	8,097 (69.38) 132,824,555	286 (84.98) 2,954,148	7,811 (69.10) 129,870,407
	Non-hispanic black (4)	3,579 (10.55) 20,197,763	47 191,819 (5.52)	3,532 20,005,943 (10.64)
	Mexican American (1)	2,679 (8.13) 15,569,372	14 (1.72) 59,681	2665 (8.25) 15509691
	Other hispanic (2)	1,787 (5.30) 10,150,921	24 86,160 17,435 (2.48)	1,763 (5.35) 1,006,4761
	Other race - including multi-racial (5)	1,539 (6.63) 12,689,360	20 (5.30) 184,325	1,519 (6.65) 12,505,035
Heavy drinking status	No (0)	1,5019 (85.53) 163,724,962	246 (64.23) 2,232,619	14,773 (85.92) 161,492,343
	Yes (1)	2,662 (14.47) 27,707,008	145 (35.77) 1,243,514	2,517 (14.08) 26,463,494
Smoking status	Never smoked (0)	9,668 (55.21) 105,683,001	27 (8.64) 300,201	9,641 (56.07) 105,382,800
	Former smoker (1)	4,369 (25.22) 48,274,092	189 (50.06) 1,740,234	4,180 (24.76) 46,533,859
	Someday smoker (2)	654 (3.69) 7,065,257	10 (3.44) 119,527	644 (3.70) 6,945,729
	Every day smoker (3)	2,990 (15.89) 30,409,620	165 (37.86) 1,316,171	2,825 (15.48) 29,093,449
Education level	Less than high school	4,347 (15.29) 29,262,368	168 (34.19) 1,188,496	4,179 (14.94) 28,073,871
	High school/GED equivalent	4,047 (22.23) 42,559,180	98 (26.08) 906,455	3,949 (22.16) 41,652,725
	Some college/AA equivalent	5,161 (32.10) 61,442,603	86 (26.11) 907,731	5,075 (32.21) 60,534,872
	College graduate or above	4,126 (30.39) 58,167,819	39 (13.62) 473,450	4,087 (30.70) 57,694,369
Marital status	Married/living with partner	10,578 (63.09) 120,766,233	190 (53.22) 1,849,998	10,388 (63.27) 118,916,235
	Single	7,103 (36.91) 70,665,737	201 (46.78) 1,626,135	6,902 (36.73) 69,039,602
Age	Mean (std. error)	47.40 (0.29)	47.12 (0.29)	62.89 (0.75)
BMI		29.08 (0.10)	29.07 (0.10)	29.88 (0.55)
Cadmium		0.47 (0.01)	0.46 (0.01)	0.92 (0.03)
Total energy intake		2,161.82 (9.80)	2,164.89 (10.01)	1,995.73 (59.43)

The unit of BMI, Cadmium, and Total energy intake are (kg/m2), (ug/L), and kilocalorie, respectively. For marital status single includes: Widowed/Divorced/ Separated/Never Married.The values for categorical variables are raw frequency, (percentage), and weighted frequency, respectively. Apart from Dark Green Vegetable Intake and BMI, all the other variables had P-value < 0.05 based on bivariate association for categorical variables and linear regression for continuous variables.

consumption by itself, after adjusting for modifiable and non-modifiable confounders, was associated with 30% decrease in odds of emphysema, the findings did not attain statistical significance (Odds Ratio: 0.70; 95% CI: 0.32–1.52, *P*-val: 0.36).

Vitamin A was another vitamin strongly associated with dark-green vegetables. After adjusting for the effect of modifiable as well as non-modifiable confounders consumption of recommended vitamin A was associated with 33% decrease

TABLE 3 | Relationship among dark-green vegetables intake, vitamin K, and emphysema.

	Vitamin K	Dark green veg	Note
Model 1	0.62 (0.44,0.87) *P*-val: 0.01	0.96 (0.45,2.06) *P*-val: 0.92	Vitamin K and dark green veg are significantly associated (*P*-val: < 0.0001)
Model 2	–	0.70 (0.32,1.52) *P*-val: 0.36	
Model 3	0.61 (0.40,0.92) *P*-val: 0.02	–	

The estimates are the odds of lung disease associated with consumption of recommended vitamins dose compared to those that did not consume recommended vitamin dose.

The model is adjusted for: Adjusted for Age, gender (reference = "Male"), and ethnicity (reference = "Non-Hispanic White"), BMI, smoking status (reference = "Never Smoked"), heavy drinking status (reference = "No"), education level (reference = "College Graduate or Above"), marital status (reference = "Married or Living with Partner"), blood cadmium level, and total energy intake.

TABLE 4 | Relationship among dark-green vegetables intake, vitamin A, and emphysema.

Vitamin	Vitamin A	Dark green veg	Note
Model 1	0.69 (0.47,1.00) *P*-val: 0.05	0.75 (0.35,1.61) *P*-val: 0.46	Vitamin A and dark green veg are significantly associated (*P*-val: < 0.0001)
Model 2	–	0.70 (0.32,1.52) *P*-val: 0.36	
Model 3	0.67 (0.44,1.00) *P*-val: 0.05	–	

The estimates are the odds of lung disease associated with consumption of recommended vitamins dose compared to those that did not consume recommended vitamin dose.

The model is adjusted for: Adjusted for Age, gender (reference = "Male"), and ethnicity (reference = "Non-Hispanic White"), BMI, smoking status (reference = "Never Smoked"), heavy drinking status (reference = "No"), education level (reference = "College Graduate or Above"), marital status (reference = "Married or Living with Partner"), Cadmium exposure, and total energy intake.

in odds (Odds Ratio: 0.67; 95% CI: 0.44–1.00, P-val: 0.05) of emphysema compared to those who consumed less than recommended vitamin A dose. The estimates were similar when consumption of dark green vegetable was incorporated in the previous model (Odds Ratio: 0.69; 95% CI: 0.47–1.00, *P*-val: 0.05).

DISCUSSION

While we observed an inverse association between vegetables intake and lung disease as previously reported, for the first time we show an inverse association between vitamin K intake and vitamin A intake with emphysema. A cross-sectional study design was used to assess the association of vitamin K, dark green vegetables and Vitamin A with reported emphysema status derived from NHANES. After adjusting for relevant confounders, consumption of recommended amounts of vitamin K was associated with reduced risk of developing emphysema. Similarly consumption of recommended amounts of vitamin A was associated with reduced risk of developing emphysema.

A previous study has shown that reduced vitamin K status in COPD patients was associated with high mortality rates (39). The study also showed that elastin degradation is accelerated in chronic COPD and is partially regulated by Matrix Gla Protein (MGP), via a vitamin K-dependent pathway. Therefore, vitamin K has a potential role in COPD pathogenesis. Interestingly, we were able to show that consumption of recommended amounts of vitamin K is inversely associated with emphysema status. Therefore, vitamin K may impart a protective role by reducing or slowing down the emphysematous damage.

Specific vitamins and certain trace elements like iron, zinc, copper and selenium work in synergy to support the protective activities of the immune cells. Depleted amounts of these micronutrients can impact antibody production and affect the inflammation process or lung health (32). Along these lines analysis of the NHANES data showed an inverse association between vitamin A and emphysema. Therefore, supplementation with appropriate amounts of vitamin A can exhibit an anti-inflammatory related responses important to support regulated lung airway function (47, 48).

A population-based prospective cohort of Swedish men showed that high consumption of fruits and vegetables was inversely associated with reduced COPD incidence in both current and ex-smokers but not in never-smokers (16). Interestingly, women from the same population-based prospective cohort who consumed fruits and vegetables long-term showed that fruits but not vegetables was inversely associated with COPD incidence independent of the smoking status. It was clear from our analysis of the NHANES dataset that vitamin K as well as vitamin A likely from the dark green vegetables were inversely association with emphysema.

The strengths of our study are relatively large sample size, high generalizability, and comprehensive questionnaire data. However, there are several limitations. The most important one is that 24-h dietary recall potentially results in misclassification of exposure because 24-h dietary recall may be unrepresentative to the long-term dietary behaviors. However, the analysis suggested this misclassification is non-differential. Of all emphysema patients, 75.40% reported the 24-h diet is similar to usual, 7.60% consumed food more than usual, and 16.99% consumed less than usual. The distribution of comparing 24-h diet to "usual" among controls was similar as emphysema cases. Among controls, 76.41% reported the 24-h diet is similar to "usual," 7.55% more than "usual," and 16.06% less than "usual." Thus, this non-differential misclassification due to 24-h dietary recall could bias the result toward the null. The outcome was defined as Yes response to "Has a doctor or other health professional ever told you that you have emphysema?" Although under-diagnosis of emphysema could happen, to some degree respondents either with or without emphysema are unlikely to misreport their history of diagnosis. Thus, the misclassification of outcome is likely non-differential which biases the result toward the null. The association between dark-green vegetable intake and emphysema would be stronger if the above misclassification of exposure and outcome did not occur.

It is important to mention that with regards to monitoring lung function, there is no gold standard for measuring symptoms related to proper lung function, since none of the available methods is optimal in all regards (49). Some of the tests used in questionnaires hardly reflect the heterogeneity, variability, and severity of COPD or its phenotypes e.g., emphysema, as well as the numerous confounding factors contributing to the clinical presentation of the disease. This can lead to misclassification of outcome (49). Generally, COPD which encompasses chronic bronchitis and emphysema is commonly underdiagnosed. Along these lines, a previous study using NHANES dataset showed that 5.2% of US adults aged 40–79 reported being diagnosed with COPD during 2007–2012 (50). This study determined that multiple factors are associated with self-reported COPD diagnosis where the number of reported respiratory symptoms, probably non-related to COPD, had the strongest association. But after controlling for other factors, having mild lung obstruction was not associated with being diagnosed with COPD. Further, the overall COPD prevalence among US adults aged 40–79 years varied between 10.2 and 20.9% based on whether pre- or post-bronchodilator values were used and which diagnostic criterion was applied (51). The overall prevalence decreased by approximately 33% when airflow limitation was based on post-bronchodilator as compared to pre-bronchodilator spirometry, regardless of which diagnostic criterion was used (51).

A recent study showed that among those with spirometry-defined obstruction, 72.0% (SE, 1.9) in NHANES 2007–2012 were undiagnosed (52). Further, using multivariate models, undiagnosed obstructive disease was consistently associated in both surveys (NHANES 2007–2012 and NHANES III) with self-reported good/excellent health status, lower comorbidity burden, higher lung function, and being of racial/ethnic minority. On the other hand there was no association between undiagnosed disease or healthier profile and education level in either survey NHANES 2007–2012 or NHANES III (OR = 0.94, 95% = 0.61–1.44, where "high school and beyond" was compared to "below high school") (52). Although educational level of self-reporting diagnosed emphysema patients were different from control group, we suggest that the bias due to under diagnosis is non-differential, weakening the association between dark-green vegetable intake and emphysema.

Also, information bias is likely because of retrospective data collection and the intrinsic limitations of the 24-h dietary/food recall that the participants were subjected to. Potentially, participants may over-report their intake of fruits and vegetables, hence a recall bias (53). Unfortunately, data is not available to assess whether differential misclassification of dark green vegetable intake occurred due to misreporting and to determine the direction and magnitude of misclassification bias.

Although we controlled for well-documented risk factors namely age, gender, and race, BMI, education level, marital status, smoking status, alcohol intake, and blood cadmium level; residual confounding may still persist in this study. Food except for vegetables and fruits may contain unknown biologically active compounds, which may be correlated with vegetables and fruits but were not controlled for in the study. In addition, there is usually a complicated relationship between foods and food subtypes that may potentially modify the direction of association with lung diseases. Important to note that the inferences stayed same after including physical activity in the model.

In conclusion, the results suggest that consumption of dark green vegetable and recommended amounts of micronutrient such as vitamin K and vitamin A can help slow or halt the emphysematous process. Clearly, dietary or protective interventions with specific micronutrients early in life may promote a healthy lung and also curb emphysematous injury. More prospective cohorts and well-designed clinical trials are needed to promote the transition of individualized nutrient interventions into health policy. A replication using an expanded sample size followed by functional analysis would be beneficial.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Toy EL, Gallagher KF, Stanley EL, Swensen AR, Duh MS. The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: a review. *COPD*. (2010) 7:214–228. doi: 10.3109/15412555.2010.481697
2. Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008–2013. *Ann Am Thorac Soc*. (2018) 15:348–56. doi: 10.1513/AnnalsATS.201703-259OC
3. Heron MP. Deaths: leading causes for 2013. *Natl Vital Stat Rep*. (2016) 65:1–95.
4. Statistics NCfH. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities* (2016).
5. Marsh SE, Travers J, Weatherall M, Williams MV, Aldington S, Shirtcliffe PM, et al. Proportional classifications of COPD phenotypes. *Thorax*. (2008) 63:761–7. doi: 10.1136/thx.2007.089193
6. Thurlbeck WM, Henderson JA, Fraser RG, Bates DV. Chronic obstructive lung disease. A comparison between clinical, roentgenologic, functional and morphologic criteria in chronic bronchitis, emphysema, asthma and bronchiectasis. *J Occup Environ Med*. (1970) 12:533. doi: 10.1097/00005792-197003000-00001
7. Gibson P, Simpson J. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax*. (2009) 64:728–35. doi: 10.1136/thx.2008.108027
8. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? *Lancet*. (2015) 386:1075–85. doi: 10.1016/S0140-6736(15)00156-7

9. Amararathna M, Johnston M, Rupasinghe H. Plant polyphenols as chemopreventive agents for lung cancer. *Int J Mol Sci*. (2016) 17:1352. doi: 10.3390/ijms17081352
10. Dreher M. Whole fruits and fruit fiber emerging health effects. *Nutrients*. (2018) 10:1833. doi: 10.3390/nu10121833
11. Garcia-Larsen V, Arthur R, Potts JF, Howarth PH, Ahlström M, Haahtela T, et al. Is fruit and vegetable intake associated with asthma or chronic rhino-sinusitis in European adults? Results from the global allergy and asthma network of excellence (GA2LEN) survey. *Clin Transl Allergy*. (2017) 7:3. doi: 10.1186/s13601-016-0140-9
12. Grundy A, Poirier AE, Khandwala F, McFadden A, Friedenreich CM, Brenner DR. Cancer incidence attributable to insufficient fruit and vegetable consumption in Alberta in 2012. *CMAJ Open*. (2016) 4:E760. doi: 10.9778/cmajo.20160037
13. Guilleminault L, Williams JE, Scott AH, Berthon SB, Jensen M, Wood GL. Diet and asthma: is it time to adapt our message? *Nutrients*. (2017) 9:1227. doi: 10.3390/nu9111227
14. Hosseini B, Berthon BS, Wark P, Wood LG. Effects of fruit and vegetable consumption on risk of asthma, wheezing and immune responses: a systematic review and meta-analysis. *Nutrients*. (2017) 9:341. doi: 10.3390/nu9040341
15. Kaluza J, Larsson SC, Orsini N, Linden A, Wolk A. Fruit and vegetable consumption and risk of COPD: a prospective cohort study of men. *Thorax*. (2017) 72:500. doi: 10.1136/thoraxjnl-2015-207851
16. Kaluza J, Wolk A, Harris HR, Linden A. Long-term consumption of fruits and vegetables and risk of chronic obstructive pulmonary disease: a prospective cohort study of women. *Int J Epidemiol*. (2018) 47:1897–909. doi: 10.1093/ije/dyy178
17. Kromhout D, Spaaij CJK, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary guidelines. *Eur J Clin Nutr*. (2016) 70:869. doi: 10.1038/ejcn.2016.52
18. Meteran H, Thomsen SF, Miller MR, Hjelmborg J, Sigsgaard T, Backer V. Self-reported intake of fruit and vegetables and risk of chronic obstructive pulmonary disease: a nation-wide twin study. *Respir Med*. (2018) 144:16–21. doi: 10.1016/j.rmed.2018.09.013
19. Du H, Li L, Bennett D, Yang L, Guo Y, Key TJ, et al. Fresh fruit consumption and all-cause and cause-specific mortality: findings from the China kadoorie biobank. *Int J Epidemiol*. (2017) 46:1444–55. doi: 10.1093/ije/dyx042
20. Rauf A, Imran M, Butt MS, Nadeem M, Peters DG, Mubarak MS. Resveratrol as an anti-cancer agent: a review. *Crit Rev Food Sci Nutr*. (2018) 58:1428–47. doi: 10.1080/10408398.2016.1263597
21. Seyedrezazadeh E, Ansarin K, Pour Moghaddam M, Reza Vafa M, Sharma S, Kolahdooz F. Fruit and vegetable intake and risk of wheezing and asthma: a systematic review and meta-analysis. *Nutr Rev*. (2014) 72:411–28. doi: 10.1111/nure.12121
22. Stevens C, Navarro-Rosenblatt D, Chan DSM, Abar L, Vingeliene S, Norat T, et al. Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis. *Ann Oncol*. (2015) 27:81–96. doi: 10.1093/annonc/mdv381
23. Tarrazo-Antelo AM, Ruano-Ravina A, Abal Arca J, Barros-Dios JM. Fruit and vegetable consumption and lung cancer risk: a case-control study in Galicia, Spain. *Nutr Cancer*. (2014) 66:1030–7. doi: 10.1080/01635581.2014.936951
24. Voortman T, Kiefte-de Jong JC, Ikram MA, Stricker BH, van Rooij FJA, Lahousse L, et al. Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the rotterdam study. *Eur J Epidemiol*. (2017) 32:993–1005. doi: 10.1007/s10654-017-0295-2
25. Wang M, Qin S, Zhang T, Song X, Zhang S. The effect of fruit and vegetable intake on the development of lung cancer: a meta-analysis of 32 publications and 20 414 cases. *Eur J Clin Nutr*. (2015) 69:1184–92. doi: 10.1038/ejcn.2015.64
26. Berthon B, Wood L. Nutrition and respiratory health—feature review. *Nutrients*. (2015) 7:1618–43. doi: 10.3390/nu7031618
27. Ganguly K, Levanen B, Palmberg L, Akesson A, Linden A. Cadmium in tobacco smokers: a neglected link to lung disease? *Eur Respir Rev*. (2018) 27:170122. doi: 10.1183/16000617.0122-2017
28. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. *Ther Adv Chronic Dis*. (2016) 7:34–51. doi: 10.1177/2040622315609251
29. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest*. (2009) 135:173–80. doi: 10.1378/chest.08-1419
30. Ojo O, Lagan AL, Rajendran V, Spanjer A, Chen L, Sohal SS, et al. Pathological changes in the COPD lung mesenchyme–novel lessons learned from *in vitro* and *in vivo* studies. *Pulm Pharmacol Ther*. (2014) 29:121–8. doi: 10.1016/j.pupt.2014.04.004
31. Pirozzi CS, Gu T, Quibrera PM, Carretta EE, Han MK, Murray S, et al. Heterogeneous burden of lung disease in smokers with borderline airflow obstruction. *Respir Res*. (2018) 19:223. doi: 10.1186/s12931-018-0911-z
32. Maggini S, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. *Br J Nutr*. (2007) 98(Suppl. 1):S29–35. doi: 10.1017/S0007114507832971
33. Sezikli M, Cetinkaya ZA, Guzelbulut F, Yesil A, Cosgun S, Kurdas OO. Supplementing vitamins C and E to standard triple therapy for the eradication of Helicobacter pylori. *J Clin Pharm Ther*. (2012) 37:282–5. doi: 10.1111/j.1365-2710.2011.01286.x
34. Le Marchand L, Yoshizawa CN, Kolonel LN, Hankin JH, Goodman MT. Vegetable consumption and lung cancer risk: a population-based case-control study in Hawaii. *J Natl Cancer Inst*. (1989) 81:1158–64. doi: 10.1093/jnci/81.15.1158
35. Wallgren M. Clinical, endocrinological and spermatological studies after endotoxin injection in the boar. *Zentralbl Veterinarmed A*. (1989) 36:664–75. doi: 10.1111/j.1439-0442.1989.tb00778.x
36. Agudo A, Esteve MG, Pallares C, Martinez-Ballarin I, Fabregat X, Malats N, et al. Vegetable and fruit intake and the risk of lung cancer in women in Barcelona, Spain. *Eur J Cancer*. (1997) 33:1256–61. doi: 10.1016/S0959-8049(97)00050-6
37. Ziegler RG, Mason TJ, Stemhagen A, Hoover R, Schoenberg JB, Gridley G, et al. Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. *Am J Epidemiol*. (1986) 123:1080–93. doi: 10.1093/oxfordjournals.aje.a114336
38. Janssen R, Vermeer C. Vitamin K deficit and elastolysis theory in pulmonary elasto-degenerative diseases. *Med Hypotheses*. (2017) 108:38–41. doi: 10.1016/j.mehy.2017.07.029
39. Piscaer I, van den Ouweland JMW, Vermeersch K, Reynaert NL, Franssen FME, Keene S, et al. Low vitamin K status is associated with increased elastin degradation in chronic obstructive pulmonary disease. *J Clin Med*. (2019) 8:1116. doi: 10.3390/jcm8081116
40. De Moura FF, Moursi M, Lubowa A, Ha B, Boy E, Oguntona B, et al. Cassava intake and vitamin A status among women and preschool children in Akwa-Ibom, Nigeria. *PLoS ONE*. (2015) 10:e0129436. doi: 10.1371/journal.pone.0129436
41. Paiva SA, Godoy I, Vannucchi H, Favaro RM, Geraldo RR, Campana AO. Assessment of vitamin A status in chronic obstructive pulmonary disease patients and healthy smokers. *Am J Clin Nutr*. (1996) 64:928–34. doi: 10.1093/ajcn/64.6.928
42. Park HJ, Byun MK, Kim HJ, Kim JY, Kim YI, Yoo KH, et al. Dietary vitamin C intake protects against COPD: the Korea national health and nutrition examination survey in 2012. *Int J Chron Obstruct Pulmon Dis*. (2016) 11:2721–8. doi: 10.2147/COPD.S119448
43. Morichika D, Miyahara N, Fujii U, Taniguchi A, Oda N, Senoo S, et al. A retinoid X receptor partial agonist attenuates pulmonary emphysema and airway inflammation. *Respir Res*. (2019) 20:2. doi: 10.1186/s12931-018-0963-0
44. Caram LM, Amaral RA, Ferrari R, Tanni SE, Correa CR, Paiva SA, et al. Serum vitamin A and inflammatory markers in individuals with and without chronic obstructive pulmonary disease. *Mediat Inflamm*. (2015) 2015:862086. doi: 10.1155/2015/862086
45. Centers for Disease Control and Prevention, National Center for Health Statistics. *About the National Health and Nutrition Examination Survey*. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevent, 2007-2016. Available online at: http://www.cdc.gov/nchs/nhanes/about_nhanes.htm
46. U.S. Department of Agriculture, Agricultural Research Service. 2018. *USDA Food and Nutrient Database for Dietary Studies 2015-2016*. Food Surveys Research Group Home Page. Available online at: www.ars.usda.gov/nea/bhnrc/fsrg 2018, https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fndds/2015_2016_FNDDS_Doc.pdf

47. McGowan SE, Holmes AJ, Smith J. Retinoic acid reverses the airway hyperresponsiveness but not the parenchymal defect that is associated with vitamin A deficiency. *Am J Physiol Lung Cell Mol Physiol*. (2004) 286:L437–44. doi: 10.1152/ajplung.00158.2003
48. Timoneda J, Rodriguez-Fernandez L, Zaragoza R, Marin MP, Cabezuelo MT, Torres L, et al. Vitamin A deficiency and the lung. *Nutrients*. (2018) 10:1132. doi: 10.3390/nu10091132
49. Glaab T, Vogelmeier C, Buhl R. Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations. *Respir Res.* (2010) 11:79. doi: 10.1186/1465-9921-11-79
50. Tilert T, Paulose-Ram R, Howard D, Butler J, Lee S, Wang MQ. Prevalence and factors associated with self-reported chronic obstructive pulmonary disease among adults aged 40-79: the national health and nutrition examination survey (NHANES) 2007-2012. *EC Pulmonol Respir Med*. (2018) 7:650–62.
51. Tilert T, Dillon C, Paulose-Ram R, Hnizdo E, Doney B. Estimating the U.S. prevalence of chronic obstructive pulmonary disease using pre- and post-bronchodilator spirometry: the national health and nutrition examination survey (NHANES) 2007-2010. *Respir Res*. (2013) 14:103. doi: 10.1186/1465-9921-14-103
52. Martinez CH, Mannino DM, Jaimes FA, Curtis JL, Han MK, Hansel NN, et al. Undiagnosed obstructive lung disease in the united states. associated factors and long-term mortality. *Ann Am Thorac Soc*. (2015) 12:1788–95. doi: 10.1513/AnnalsATS.201506-388OC
53. Block Dietary Data S, Information Management S, National Cancer I. *DIETSYS Version 3.0 User's Guide: Health Habits and History Questionnaire, Diet History and Other Risk Factors: Dietary Analysis System*. Bethesda, MD. The Institute(1994).

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REVIEW
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Obesity or BMI Paradox? Beneath the Tip of the Iceberg

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The obesity paradox refers to extant evidence showing that obesity in older subjects or in patients with several chronic diseases may be protective and associated with decreased mortality. A number of mechanisms have been postulated to support the existence of obesity paradox; however, marked heterogeneity was found across studies and this has cast doubt on the actual presence of this phenomenon. The aim of the present narrative review is to summarize evidence underlying the concept of obesity paradox, focusing on limitations and bias related to this phenomenon, with emphasis on the use of body mass index (BMI). A major cause of the discrepancy between studies may be related to the use of BMI in the definition of obesity, that should consider, instead, excess body fat as the main characteristic of this disease and as the unique determinant of its complications. In addition, the adjustment for potential confounders (e.g., stage and grade of diseases, smoking habit, inability to capture the presence of signs of undernutrition in the normal-weight comparative group, consideration of body composition) may significantly scale down the protective role of obesity in terms of mortality. However, it is still necessary to acknowledge few biases (e.g., reverse causation, attrition bias, selection bias of healthy obese subjects or resilient survivors) that would still apply to obesity even when defined according with body composition. Further research should be prompted in order to promote correct phenotyping of patients in order to capture properly the trajectories of mortality in a number of diseases.

Keywords: obesity, obesity paradox, nutritional status, body composition, body mass index

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INTRODUCTION

The obesity paradox refers to extant evidence showing that obesity in older subjects or in patients with several chronic diseases may be protective and associated with decreased mortality. Gruberg et al. (1) first observed that overall mortality (1 year follow-up) was significantly higher in patients with coronary artery disease after percutaneous coronary intervention and normal body mass index (BMI) compared to overweight/obese subjects. Since then, a number of studies, encompassed by the umbrella term "reverse epidemiology," found that obesity, hypercholesterolemia, and hypertension were associated with improved survival among dialysis patients (2), in chronic heart failure (CHF) (3), after acute myocardial infarction (4), in chronic obstructive pulmonary disease (5), in older nursing home residents (6), in peripheral arterial disease, in stroke and thromboembolism, in post-operative complications during catheter ablation for atrial fibrillation and after cardiac surgery, in surgical intensive care unit, in patients undergoing non-bariatric surgery, in type 2 diabetes (reducing amputation risk among non-elderly diabetic men), and in critically ill and osteoporosis patients (7).

The aim of the present narrative review is to summarize evidence underlying the concept of obesity paradox, focusing on limitations and bias related to this phenomenon, with emphasis on the use of BMI.

BIOLOGICAL HYPOTHESES AND MECHANISMS UNDERLYING THE OBESITY PARADOX

Different mechanisms have been postulated to support the existence of obesity paradox.

Body structure and body composition: increased body weight may hinder the metabolic consequences of diseases and of treatments by providing adequate muscle and adipose reserves (8).

Lipid metabolism: high levels of total cholesterol and lipoproteins may improve the endotoxin-scavenging effect, while patients with CHF and low total serum cholesterol level are more prone to endotoxemia and its inflammatory consequences due to bacterial/endotoxin translocation from bowel wall edema (3).

The release of N-terminal pro-B-type natriuretic peptide (NT-proBNP) by cardiomyocytes, due to increased wall tension, may be considered as a major prognostic factor for mortality in acute coronary disease. NT-proBNP levels are significantly reduced in patients who are overweight or obese compared to subjects with a lower BMI after myocardial infarction (4).

Prothrombotic factors (e.g., thromboxane B2) are negatively correlated with BMI and leptin since their production is influenced by endothelial function that is paradoxically better in subjects with obesity than in non-obese individuals (4).

Increase in ghrelin production/sensitivity has been showed to be a compensatory mechanism to hinder the evolution of heart failure, since it may improve cardiac contractility by increasing left ventricular function and exercise capacity, while it reduces muscle wasting in patients with CHF; ghrelin also affects appetite and can be responsible for a parallel rise in food intake and weight gain (9).

Cytokines production: cardiometabolic risk is associated with augmented production of cytokines (e.g., tumor necrosis factor TNF-α). The production, by subcutaneous adipose tissue, of soluble TNF-α receptors I and II, which is correlated with BMI and percent body fat, in patients with heart failure, is lower in subjects with obesity. These receptors are supposed to bind TNF-α and to counteract its negative effects on the myocardium (7). Several adipokines (e.g., adiponectin, apelin, omentin, and others) produced by adipose tissue have shown to be cardioprotective and to exert a variety of favorable effects on cardiovascular function (10).

Endothelial/vascular aspects: increased mobilization of endothelial progenitor cells may protect patients with severe obesity from atherogenesis through promotion of regeneration processes in the damaged myocardium and the development of new blood vessels. This process leads to the reduction of the afterload due to higher flow-mediated dilation and lower intima-media thickness, to the enhancement of myocardial contractile function and metabolic processes in cardiomyocytes, to the reduction of apoptosis and fibrosis of the myocardium (11).

Cancer biology: obesity seems to be associated with lower stage disease, smaller tumor size, and less aggressive biological subtypes. Moreover, overweight and obesity may positively influence treatment outcome since excess adipose tissue affects pharmacokinetics of cancer treatment regimens, while providing a nutritional supply to deal with surgical and anticancer treatments (12, 13).

LIMITATIONS TO THE STUDIES ASSESSING THE PRESENCE OF THE OBESITY PARADOX

Significant heterogeneity was found across studies supporting the presence of the obesity paradox (e.g., study population, degree of control for confounding factors, length of follow-up), and this has cast doubt on the actual existence of this phenomenon (14, 15).

A wide range of normal BMIs (18.5–25.0 kg/m^2) may include heterogeneous groups, and mortality rates tend to be significantly higher at the lower end of the BMI range (15). In a systematic review conducted by Flegal et al. (16) (97 studies, around 3 million individuals, more than 270,000 deaths), the “obesity paradox” was significantly downsized. All-cause mortality was significantly greater in patients with BMI $\geq$ 35 kg/m^2 compared to normal weight subjects. Class I obesity (BMI 30- 34.9 kg/m^2) was not associated with greater all-cause mortality, and overweight was associated with a significantly lower mortality rate. Moreover, none of the different classes of BMI was associated with mortality in subjects aged 65 years and older. Another systematic review concerning obesity in the elderly (17) confirmed that obesity represents a mortality risk in older adults, but with different BMI thresholds compared to adult population (18). A U-shaped-curve correlation between BMI and mortality has been shown with an increased risk of death for low ($<$18.5 kg/m^2) as well as very high BMI values ($>$ 35 kg/m^2). But the nadir of the curves differs from what is known in younger obese subjects, and we can hypothesize a shift of the nadir toward a higher BMI (between 23.5 and 27.5 kg/m^2) in the elderly, which is at least 1–5 points higher than that in young and middle-aged adults (17).

Also, a selection bias has been accounted for by different authors (3, 4, 19, 20). Patients with obesity often present with comorbidities, and they undergo medical check-ups more frequently and consequently, all diseases associated with obesity paradox may have been diagnosed at earlier stages (12). Subjects with obesity, especially those affected by high levels of comorbidity, are more prone to early death and cannot be included in later cohorts. Thus, the obese population represented in these studies is characterized by obese but likely healthier individuals (15).

The increased survival of patients with high BMI may also be related to the lack of consideration, in the cohorts with lower BMI, though within the normal BMI range, of subjects with extremely low BMI and of causes explaining low BMI: significant unintentional weight loss due to the presence of high levels of comorbidity (e.g., greater predisposition to develop bleeding and anemia; higher prevalence and severity of hypertension and valvular regurgitation, chronic obstructive pulmonary disease, arrhythmias, infectious diseases) and of the "malnutrition-inflammation complex syndrome" (MICS): in coronary heart disease and dialysis patients, both protein-energy malnutrition and inflammation, or the combination of the two, are more frequent compared to the general population, while different aspects of MICS (e.g., low weight-for-height, hypocholesterolemia, hypocreatininemia) may be considered as risk factors of poor outcome in CHF and dialysis patients (20, 21). Comparing subjects with overweight or obesity to subjects belonging to this heterogeneous stratum may lead to a misinterpretation of the correlation between BMI and mortality (22).

In addition, in some studies, the protective effect of obesity was found in subjects who were significantly younger than their normal-weight counterparts (younger subjects usually have less severe coronary heart disease, a preserved cardiac function and thus better survival rates) (23) or in elders with overweight or obesity who could be considered "resistant" to negative consequences of higher BMI at younger age (6). On the other hand, subjects who were normal weight at the time of death could represent a high-risk group for mortality because of unintentional weight loss due to hormonal changes, decreased appetite, and/or chronic undetected medical or mental illness (22). Finally, some normal-weight subjects may have previously been obese but have lost weight due to illness (reverse causality), hence representing a high-risk of mortality with normal or low BMI being the consequence of a significant illness (13).

Several studies accounting for the presence of an obesity paradox have an important performance bias, since more appropriate medical treatments were administered to patients with a high BMI than in those with a normal BMI (4, 6, 7), together with an attrition bias (3, 6). The median follow-up period of these studies (around 2 years) could have been too short to show negative effects of obesity, while undernutrition may have a greater impact on mortality in a reduced period of time (time discrepancy). In a study conducted by Nigam et al. (24), comparing three different classes of BMI (< 25; 25–29.9; ≥ 30 kg/m^2), different mortality risks were described for subjects with overweight or obesity in the short term (<6 months) compared to a longer period of observation. In addition, among the three classes of BMI, they observed that incidence of cardiac-related mortality in the long term was higher in subjects with overweight or obesity than that observed in the normal BMI population. After myocardial infarction, the reduced obesity survival paradox was explained by younger age at the time of initial infarction and by a reduced prevalence of non-cardiovascular comorbidities (24).

Timing of BMI ascertainment may also significantly influence obesity paradox: different studies considered BMI assessed several years before, whereas other studies, which used BMI calculated at diagnosis or several months to 1–2 years after cancer diagnosis, did not find any association or lower mortality with higher BMI.

Similarly, timing of diagnosis of diseases, such as cardiovascular disease, in patients with obesity may occur earlier than in normal-weight subjects because presence of the obesity, and this can be at the origin of a lead time bias (25).

Other studies did not control for race/ethnicity or sex, while obesity-mortality association seems to be affected by these variables and obesity paradox is more evident in men than in women (26).

Finally, confounding factors have not been always considered in those studies. In fact, the adjustment for potential confounders may scale down the protective association of obesity with mortality (27–30). In a study conducted by Hakimi et al. (31) the association of higher BMI with reduced cancer-specific mortality was lost after adjusting for cancer stage and grade. Confounding by smoking is another major threat to BMI-mortality analysis. Indeed, differences in intensity, inhalation, frequency, and duration of smoking habit, and its association with lower body weight, may represent an important limitation to studies concerning obesity paradox (13, 22).

THE CASE OF BMI AS A PROXY OF OBESITY

Although observed associations between obesity and mortality do not prove causality, a major cause of the discrepancy across studies may be related to the use of BMI in the definition of obesity that should consider, instead, excess body fat as the main characteristic of this disease and as the unique determinant of its complications (32). BMI represents the sum of fat-mass index (FMI) and fat-free mass index (FFMI) (33). The latter accounts for skeletal muscle mass, bone, and organs, while FMI is composed of peripheral and visceral adipose tissues. All these components of BMI have different roles in contributing to health status, and changes in BMI are not related to a proportional and linear modification of body compartments (34). For these reasons, different authors have pointed out the limitations of BMI in defining nutritional status (35–37): BMI fails to reflect adiposity and body composition (and their distribution), and to detect "normal weight obese" subjects (38), patients with sarcopenic obesity (39), and the presence of undernutrition in overweight subjects (40, 41); BMI varies depending on sex (men and women do not have the same body composition at similar levels of BMI) and ethnicity (Asians, Chinese, and Aboriginal people have similar metabolic risk factors at significantly lower—$\sim$6 kg/m^2–BMI values compared to Caucasians) (42); BMI fails to account for fitness related to the proportion of lean mass to adiposity (43). Fat-free mass (FFM) is strictly correlated to cardiorespiratory fitness and to physical functional abilities (43). The correlation between BMI and mortality tends to be modified by the cardiorespiratory fitness status, as it happens in chronic-obstructive pulmonary disease (COPD): the risk of death in unfit men is two-fold higher compared to fit men regardless of obesity status (44). Caan et al. (45) have shown that body composition may partially explain the U-shaped association between BMI and cancer (e.g., colorectal cancer) survival. The correlation between BMI and fat mass (FM)—especially in subjects with obesity—is not linear, while the relationship between BMI and FFM tends to be linear. Therefore, higher BMI values are frequently associated with higher FFM (and not necessarily to obesity or to an increase of FM) and cancer patients who are overweight or obese have higher levels of lean mass than their normal-weight counterparts. On the contrary, lower BMI (and lower lean mass) is associated with higher risk of recurrence, surgical complications, treatment-related toxicities, and overall and cancer-specific mortality (45–48).

Similar results were found by Lin et al. (49) in patients with chronic kidney disease. Using BMI cut-points, 27.9% of patients were obese; while agreeing with the definition based on body fat percentage, the prevalence of obesity raised to 48.8% with a marked percentage of patients (29.4%) who had excess body fat with a normal BMI. When adjusting the regression models for either BMI or body fat percentage, obesity defined by BMI was associated with a significantly lower mortality hazard ratio (HR: 0.23; 95% CI: 0.07–0.71; $p = 0.011$), whereas the result was inverted when obesity was defined by body fat percentage (HR: 2.75; 95% CI: 1.28–5.89; $p = 0.009$). Subjects with excess fat mass, irrespective of BMI, were characterized by a reduced lean mass (e.g., sarcopenic obesity) and had higher death risk compared with patients with obesity defined by both BMI and body fat (HR: 5.11; 95% CI: 1.43–18.26; $p = 0.012$) (49).

Nonetheless, regardless of body composition, conflicting results emerged when using markers of central obesity in place of BMI. In a systematic review by Coutinho et al. (50), BMI, waist circumference, and waist-to-hip ratio were compared against mortality outcome in coronary artery disease (CAD) patients. Interestingly, central obesity was positively associated with higher mortality in individuals with CAD, whereas BMI was inversely associated with mortality. The effect of central obesity on mortality was observed even in patients with normal BMI (50).

Use of body composition analysis is indeed an attempt to overcome the misleading properties of BMI: in an elegant study by Gonzalez et al. (48), obesity paradox was explored in cancer patients using either BMI or body composition obtained by bioimpedance analysis, indicating that obesity paradox emerged when using BMI, but it was not confirmed by analyses based on body composition. Though just a minority of studies investigating the obesity paradox relied on body composition assessment, evidence supports the role of low lean mass as the actual predictor of mortality when used in place of BMI (51).

CONCLUSION

The actual paradox seems to be keeping defining obesity using BMI, which is not able to quantify body fat percentage and adiposity distribution, nor the degree of metabolic disturbances that it can underlie. In fact, obesity is characterized by a significant complexity related to alterations of nutritional status (energy and nutrient intake, body composition), to the interaction of psychological and social factors, to functional impairment, to hormonal and metabolic alterations, to the impairment of different organs (e.g., cardiovascular and respiratory systems) and quality of life that cannot be adequately described by BMI.

However, replacing BMI by body composition is not an easy fix for the issue of the obesity paradox: some of the above mentioned biases reported in previous studies would still apply to obesity even when defined by body composition methods, such as reverse causation and selection bias of healthy obese subjects or resilient survivors. In addition, no universal cut-points have been yet defined to classify obesity based on body fat that are accurate by sex, ethnicity, age, or physiological groups (e.g., post-menopausal women).

Body composition phenotypes, taking into account both body fat and lean mass, and metabolic and functional variables, and duration of obesity (as well as of normal weight), can capture properly the trajectories of mortality in a wealth of diseases. Further research should be prompted in order to promote correct phenotyping of patients. The obesity paradox is just a lesson to be learned.

AUTHOR CONTRIBUTIONS

LD led the study design, was actively involved in the study conception, design, strategic decisions, and drafted the manuscript. AL, AP, AG, and EP contributed to the analysis of the literature, interpreted the findings, and helped in drafting the manuscript. AL and EP participated in the study design and coordination and gave intellectual inputs on the manuscript. All authors have read and approved the manuscript.

REFERENCES

1. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. (2002) 39:578–84. doi: 10.1016/S0735-1097(01)01802-2
2. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int*. (2003) 63:793–808. doi: 10.1046/j.1523-1755.2003.00803.x
3. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol*. (2004) 43:1439–44. doi: 10.1016/j.jacc.2003.11.039
4. Wang L, Liu W, He X, Chen Y, Lu J, Liu K, et al. Association of overweight and obesity with patient mortality after acute myocardial infarction: a meta-analysis of prospective studies. *Int J Obes*. (2016) 40:220–8. doi: 10.1038/ijo.2015.176
5. Cao C, Wang R, Wang J, Bunjhoo H, Xu Y, Xiong W. Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. *PLoS ONE*. (2012) 7:e43892. doi: 10.1371/journal.pone.0043892
6. Veronese N, Cereda E, Solmi M, Fowler SA, Manzato E, Maggi S, et al. Inverse relationship between body mass index and mortality in older nursing home residents: a meta-analysis of 19,538

elderly subjects. *Obes Rev*. (2015) 16:1001–15. doi: 10.1111/obr.12309
7. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. *Diabetes Care*. (2013) 36(Suppl. 2):S276–81. doi: 10.2337/dcS13-2023
8. Casas-Vara A, Santolaria F, Fernandez-Bereciartua A, González-Reimers E, García-Ochoa A, Martínez-Riera A, et al. The obesity paradox in elderly patients with heart failure: analysis of nutritional status. *Nutrition*. (2012) 28:616–22. doi: 10.1016/j.nut.2011.10.006
9. Khatib MN, Simkhada P, Gode D. Cardioprotective effects of ghrelin in heart failure: from gut to heart. *Heart Views*. (2014) 15:74–76. doi: 10.4103/1995-705X.144792
10. Mattu HS, Randeva HS. Role of adipokines in cardiovascular disease. *J Endocrinol.* (2013) 216:T17–36. doi: 10.1530/JOE-12-0232
11. Biasucci LM, Graziani F, Rizzello V, Liuzzo G, Guidone C, De Caterina AR, et al. Paradoxical preservation of vascular function in severe obesity. *Am J Med*. (2010) 123:727–34. doi: 10.1016/j.amjmed.2010.02.016
12. Trestini I, Carbognin L, Bonaiuto C, Tortora G, Bria E. The obesity paradox in cancer: clinical insights and perspectives. *Eating Weight Disord*. (2018) 23:185–93. doi: 10.1007/s40519-018-0489-y
13. Lennon H, Sperrin M, Badrick E, Renehan AG. The obesity paradox in cancer: a review. *Curr Oncol Rep*. (2016) 18:56. doi: 10.1007/s11912-016-0539-4
14. Goyal A, Nimmakayala KR, Zonszein J. Is there a paradox in obesity? *Cardiol Rev*. (2014) 22:163–70. doi: 10.1097/CRD.0000000000000004
15. Antanopoulos AS, Oikonomou EK, Antoniades C, Tousoulis D. From the BMI paradox to the obesity paradox: the obesity–mortality association in coronary heart disease. *Obes Rev*. (2016) 17:989–1000. doi: 10.1111/obr.12440
16. Flegal KM, Ioannidis JPA. The obesity paradox: a misleading term that should be abandoned. *Obesity*. (2018) 26:629–30. doi: 10.1002/oby.22140
17. Donini LM, Savina C, Gennaro E, De Felice MR, Rosano A, Pandolfo MM, et al. A systematic review of the literature concerning the relationship between obesity and mortality in the elderly. *J Nutr Health Aging*. (2012) 16:89–98. doi: 10.1007/s12603-011-0073-x
18. Batsis JA, Mackenzie TA, Bartels SJ, Sahakyan KR, Somers VK, Lopez-Jimenez F. Diagnostic accuracy of body mass index to identify obesity in older adults: NHANES 1999-2004. *Int J Obes*. (2016) 40:761–7. doi: 10.1038/ijo.2015.243
19. Von Haehling S. The metabolic basis for the obesity paradox in heart failure. *Heart Metab*. (2013) 61:4–7.
20. Charnigo R, Guglin M. Obesity paradox in heart failure: statistical artifact, or impetus to rethink clinical practice? *Heart Fail Rev*. (2017) 22:13–23. doi: 10.1007/s10741-016-9577-0
21. Anand N, Chandrasekaran SC, Alam MN. The malnutrition inflammation complex syndrome-the micsing factor in the perio-chronic kidney disease interlink. *J Clin Diagn Res*. (2013) 7:763–7. doi: 10.7860/JCDR/2013/5329.2907
22. Tobias DK, Hu FB. Does being overweight really reduce mortality? *Obesity*. (2013) 21:1746–9. doi: 10.1002/oby.20602
23. Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. *J Am Coll Cardiol*. (2017) 70:2022–35. doi: 10.1016/j.jacc.2017.09.002
24. Nigam A, Wright RS, Allison TG, Williams BA, Kopecky SL, Reeder GS, et al. Excess weight at time of presentation of myocardial infarction is associated with lower initial mortality risks but higher long-term risks including recurrent re-infarction and cardiac death. *Int J Cardiol*. (2006) 110:153–9. doi: 10.1016/j.ijcard.2005.06.040
25. De Schutter A, Lavie CJ, Milani RV. The impact of obesity on risk factors and prevalence and prognosis of coronary heart disease-the obesity paradox. *Prog Cardiovasc Dis*. (2014) 56:401–8. doi: 10.1016/j.pcad.2013.08.003
26. Park Y, Peterson LL, Colditz GA. The plausibility of obesity paradox in cancer. *Cancer Res*. (2018) 78:1898–903. doi: 10.1158/0008-5472.CAN-17-3043
27. Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, et al. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation*. (2005) 112:1756–62. doi: 10.1161/CIRCULATIONAHA.104.530972
28. Cicoira M, Maggioni AP, Latini R, Barlera S, Carretta E, Janosi A, et al. Body mass index, prognosis and mode of death in chronic heart failure: results from the Valsartan Heart Failure Trial. *Eur J Heart Fail*. (2007) 9:397–402. doi: 10.1016/j.ejheart.2006.10.016
29. Frankenstein L, Zugck C, Nelles M, Schellberg D, Katus HA, Remppis BA. The obesity paradox in stable chronic heart failure does not persist after matching for indicators of disease severity and confounders. *Eur J Heart Fail*. (2009) 11:1189–94. doi: 10.1093/eurjhf/hfp150
30. Güder G, Gelbrich G, Edelmann F, Wachter R, Pieske B, Pankuweit S, et al. Competence network heart failure germany. Reverse epidemiology in different stages of heart failure. *Int J Cardiol*. (2015) 184:216–24. doi: 10.1016/j.ijcard.2015.02.009
31. Hakimi AA, Furberg H, Zabor EC, Jacobsen A, Schultz N, Ciriello G, et al. An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. *J Natl Cancer Inst*. (2013) 105:1862–70. doi: 10.1093/jnci/djt310
32. Villareal DT, Apovian CM, Kushner RF, Klein S, American Society for Nutrition; NAASO, The Obesity Society. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *Obes Res*. (2005) 13:1849–63. doi: 10.1038/oby.2005.228
33. Dulloo AG, Jacquet J, Solinas G, Montani JP, Schutz Y. Body composition phenotypes in pathways to obesity and the metabolic syndrome. *Int J Obes*. (2010) 34(Suppl. 2):S4–17. doi: 10.1038/ijo.2010.234
34. Rothman KJ. BMI-related errors in the measurement of obesity. *Int J Obes*. (2008) 32(Suppl. 3):S56–9. doi: 10.1038/ijo.2008.87
35. Pories WJ, Dohm LG, Mansfield CJ. Beyond the BMI: the search for better guidelines for bariatric surgery. *Obesity*. (2010) 18:865–71. doi: 10.1038/oby.2010.8
36. Mascie-Taylor CG, Goto R. Human variation and body mass index: a review of the universality of BMI cut-offs, gender and urban-rural differences, and secular changes. *J Physiol Anthropol*. (2007) 26:109–12. doi: 10.2114/jpa2.26.109
37. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *N Engl J Med*. (1998) 338:1–7. doi: 10.1056/NEJM199801013380101
38. Di Renzo L, Del Gobbo V, Bigioni M, Premrov MG, Cianci R, De Lorenzo A. Body composition analyses in normal weight obese women. *Eur Rev Med Pharmacol Sci*. (2006) 10:191–6.
39. Poggiogalle E, Migliaccio S, Lenzi A, Donini LM. Treatment of body composition changes in obese and overweight older adults: insight into the phenotype of sarcopenic obesity. *Endocrine*. (2014) 47:699–716. doi: 10.1007/s12020-014-0315-x
40. Kaidar-Person O, Person B, Szomstein S, Rosenthal RJ. Nutritional deficiencies in morbidly obese patients: a new form of malnutrition? Part B: minerals. *Obes Surg*. (2008) 18:1028–34. doi: 10.1007/s11695-007-9350-5
41. Kaidar-Person O, Person B, Szomstein S, Rosenthal RJ. Nutritional deficiencies in morbidly obese patients: a new form of malnutrition? Part A: vitamins. *Obes Surg*. (2008) 18:870–6. doi: 10.1007/s11695-007-9349-y
42. Razak F, Anand SS, Shannon H, Vuksan V, Davis B, Jacobs R, et al. Defining obesity cut points in a multiethnic population. *Circulation*. (2007) 115:2111–8. doi: 10.1161/CIRCULATIONAHA.106.635011
43. Yanek LR, Vaidya D, Kral BG, Dobrosielski DA, Moy TF, Stewart KJ, et al. Lean mass and fat mass as contributors to physical fitness in an overweight and obese African American Population. *Ethn Dis*. (2015) 25:214–9.
44. Spelta F, Fratta Pasini AM, Cazzoletti L, Ferrari M. Body weight and mortality in COPD: focus on the obesity paradox. *Eat Weight Disord.* (2018) 23:15–22. doi: 10.1007/s40519-017-0456-z
45. Caan BJ, Meyerhardt JA, Kroenke CM, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the obesity paradox: The association between body composition and colorectal cancer survival (C-SCANS study). *Cancer Epidemiol Biomarkers Prev*. (2017) 26:1008–15. doi: 10.1158/1055-9965.EPI-17-0200
46. Caan BJ, Feliciano EMC, Kroenker CH, Prado CM. The Importance of body composition in explaining the overweight paradox in cancer. *Cancer Res*. (2018) 78:1906–12. doi: 10.1158/0008-5472.CAN-17-3287
47. Schachar SS, Williams GR. The obesity paradox in cancer – moving beyond BMI. *Cancer Epidemiol Biomarkers Prev*. (2017) 26:13–6. doi: 10.1158/1055-9965.EPI-16-0439
48. Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. *Am J Clin Nutr*. (2014) 99:999–1005. doi: 10.3945/ajcn.113.071399

49. Lin TY, Lim PS, Hung SC. Impact of misclassification of obesity by body mass index on mortality in patients with CKD. *Kidney Int Rep*. (2017) 3:447–55. doi: 10.1016/j.ekir.2017.12.009

50. Coutinho T, Goel K, Corrêa de Sá D, Kragelund C, Kanaya AM, Zeller M, et al. Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. *J Am Coll Cardiol*. (2011) 57:1877–86. doi: 10.1016/j.jacc.2010.11.058

51. Prado CM, Gonzalez MC, Heymsfield SB. Body composition phenotypes and obesity paradox. *Curr Opin Clin Nutr Metab Care*. (2015) 18:535–51. doi: 10.1097/MCO.0000000000000216

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Identifying Usual Food Choice Combinations With Walnuts: Analysis of a 2005–2015 Clinical Trial Cohort of Overweight and Obese Adults

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Consumption of nuts has been associated with a range of favorable health outcomes. Evidence is now emerging to suggest that walnuts may also play an important role in supporting the consumption of a healthy dietary pattern. However, limited studies have explored how walnuts are eaten at different meal occasions. The aim of this study was to explore the food choices in relation to walnuts at meal occasions as reported by a sample of overweight and obese adult participants of weight loss clinical trials. Baseline usual food intake data were retrospectively pooled from four food-based clinical trials (n = 758). A nut-specific food composition database was applied to determine walnut consumption within the food intake data. The *a priori* algorithm of association rules was used to identify food choices associated with walnuts at different meal occasions using a nested hierarchical food group classification system. The proportion of participants who were consuming walnuts was 14.5% (n = 110). The median walnut intake was 5.14 (interquartile range, 1.10–11.45) g/d. A total of 128 food items containing walnuts were identified for walnut consumers. The proportion of participants who reported consuming unsalted raw walnut was 80.5% (n = 103). There were no identified patterns to food choices in relation to walnut at the breakfast, lunch, or dinner meal occasions. A total of 24 clusters of food choices related to walnuts were identified at others (meals). By applying a novel food composition database, the present study was able to map the precise combinations of foods associated with walnuts intakes at mealtimes using data mining. This study offers insights into the role of walnuts for the food choices of overweight adults and may support guidance and dietary behavior change strategies.

Keywords: food choices, walnuts, obesity, clinical trial, data mining

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INTRODUCTION

Nut consumption is recommended in food-based dietary guidelines across the globe (1). Habitual nut consumption has been associated with a reduced risk of metabolic syndrome and type 2 diabetes mellitus (2–8), with emerging evidence suggesting that nuts may play an important role in supporting the consumption of a healthy dietary pattern (9, 10). However, there is a large shortfall in optimal intake of nuts. A study examining dietary trends from 1990 to 2017 in 195 countries revealed that, on average, people ate only 12% of the recommended amount of nuts and seeds, which equated to ∼3 g/d, compared with the 21 g recommended per day (11). In Australia, nut intake was estimated at an average of 4.61 g/d, with only 5.6% of people consuming the recommended daily amount of nuts (12). As a result intervention studies have been developed to determine strategies for encouraging increased nut consumption.

The effectiveness of a range of population-level dietary intervention has been systematically evaluated over the past decade. Several promising interventions, such as mass media campaigns, food labeling, and food pricing strategies, have been identified (13). However, there is no consistent evidence on the effectiveness of these interventions on nuts consumption (11). Thus, understanding the role of nuts, which make up the recommended dietary patterns, is required to identify the challenges and opportunities to improving dietary intake of nuts. Given meal patterns are more likely to reflect eating (14), actual foods that comprised the meal-based intakes offer practical opportunities for dietary advice (15). Therefore, exploring how food choices are constructed in relation to nuts at meal occasions may play an important role in translating dietary recommendations for practical food choices of nuts. However, limited research has been conducted in this area.

A challenge to exploring food choices in relation to nuts at meals appears to be the interindividual and intraindividual variation in choosing different types of foods and the frequency of food intakes. An inaccessible number of food choice combinations may be created because of variation in food choices, which will be addressed by this research. Literature has suggested that exploring single foods that form a food combination offer a more precise food consumption distributions to represent dietary intake (16–19). Taking into account the time intervals of eating (for example, daily vs. weekly) while identifying closely related food groups at meals tends to improve the accuracy of intake estimation by comparisons to disaggregation alone.

Advances in data analysis techniques may provide alternative methods to overcome the challenges for exploring food choice within meals. The *a priori* algorithm has been used to explore food combination patterns at meal occasions in many studies (18, 20–23). The outcomes of the analyses are formed to suggest closely related food items at meal occasions. For example, at the lunch meal occasion, if cheese and ham were reported as consumed, then bread was also consumed. Knowing such relationships may help to personalize nutrition counseling for clients. Suggesting strategies for what clients can do practically is one strategy to increase the intake frequency of less frequently consumed foods, such as walnuts. The identified closely related food items within food combinations may also be used to suggest foods to be eaten together to improve dietary adherence to national recommendations, such as total nut intake.

Exploring a specific type of nuts in diets may provide insights into dietary habits in relation to nuts for dietary recommendations. The most produced and most consumed tree nuts globally are almonds, cashews, hazelnuts, pistachios, and walnuts (24). Although walnuts are rich in unsaturated fats, minerals, vitamins, fiber, and polyphenols, they stand out for their high polyunsaturated fatty acids content (25). Literature has suggested that the intake of walnuts was associated with decreasing the risk of cardiometabolic diseases (26–30). Thus, the aim of this study was to explore the food choices in relation to walnuts at meal occasions as reported by a sample of overweight and obese volunteers in weight loss trials.

MATERIALS AND METHODS

Study Participants

This study used data from four previously published food-based clinical trial studies (9, 31–33). All studies were registered with the Australian Clinical Trials Registry (ACTRN12608000453381, ACTRN12608000425392, ACTRN12610000784011, and ACTRN 12614000581662). The data from the four studies were linked and retrospectively pooled for analysis as a baseline cohort as reported here. Ethics approval was obtained for the initial studies and for this investigation. The original studies were food-based randomized controlled trials for weight loss, conducted between 2005 and 2015: study 1 (2005–2006) (31), study 2 (2009–2010) (32), study 3 (2010–2012) (33), and study 4 (2014–2015) (9) in the University of Wollongong, Australia. All study participants were recruited from the Illawarra, a major coastal region 70 km south of Sydney, Australia. The World Health Organization Body Mass Index (BMI) classifications were used to determine overweight (BMI of $\geq$25 kg/m^2) and obese (BMI of $\geq$30 kg/m^2) participants (34).

Detailed study protocol information and inclusion and exclusion criteria are presented in **Supplementary Table 1**. In brief, all trials had similar inclusion criteria, including overweight and obese female and male adults with a stable body weight prior to the trial. Exclusion criteria included inadequate conversational English for all studies, major illness (e.g., cancer) and chronic diseases (e.g., diabetes) for studies 1–3, and severe medical conditions for study 4.

Anthropometric Variables

Anthropometric variables were measured by trained research staff using standardized protocols. Height was measured using a stadiometer without shoes for all studies. Body weight (kg) was measured in an upright position (in minimal clothing with no shoes) using digital scales with a bioelectrical impedance component (Tanita TBF-662, Wedderburn Pty Ltd., Ingleburn, NSW, Australia).

Dietary Intake Data and Food Intake Data Preparation

Self-reported food intake data were assessed from a dietitian-administered diet history interview, which was validated previously (35). Participants were asked to recall their intakes during the interview, reflecting on usual weekly consumption recorded on the basis of participant-defined meal occasions. A food checklist was applied to capture commonly omitted food items during the interview. The food intake data were sorted to align with a 7-days equivalence to a weekly intake pattern based on the reported intake frequencies.

To evaluate potential underreporting of energy intake in this study, the Goldberg method was used (36). Self-reported energy intake (rEI) was divided with predicted basal metabolic rate (pBMR) values (36). pBMR was calculated by using age, weight, and sex as per the Mifflin equation (37). An rEI/pBMR value of 1.35 was therefore set as the cutoff value to determine potential underreporting of energy intake in this study (36, 38). Participants were categorized as plausible reporters and underreporters.

The dietary data in the four studies were analyzed using FoodWorks Professional nutrient analysis software (Xyris Software, Spring Hill, QLD, Australia). Different versions of FoodWorks were originally used (version 3 using the AUSNUT 1999 food composition database for study 1, version 6 using the AUSNUT 2007 food composition database for studies 2 and 3, and version 7 using the AUSNUT 2007 food composition database for study 4). Because the values of dietary intake measurements used are likely to influence the results, the more recent release of the AUSNUT 2011–13 food composition database was used for the analyses of this study to standardize dietary data (39). For this to occur, a previously developed matching file (40, 41) and "umbrella foods" list (41) were used to translate the food items from the AUSNUT 1999 and 2007 to the AUSNUT 2011–13 food composition database. All of the food matching was performed using the VLOOKUP function in Microsoft Excel (Microsoft Corporation, 2010, version 14.0.7). In order to determine walnut consumption, a nut-specific food composition database (42) was applied to the dietary intake data. Walnuts are commonly consumed alone or as part of mixed foods, such as carrot cake and brownies (42). The detailed food intake data preparation process has been reported elsewhere (23). In brief, major ($n = 24$), submajor ($n = 132$), and minor ($n = 515$) food groups in the AUSNUT 2011–13 food classification system (25, 39) were applied in the present study. For the purpose of food-level analyses, food intake was grouped into participant-defined meals, which were breakfast, lunch, and dinner. Other than "breakfast," "lunch," and "dinner," such as morning tea, afternoon tea, desserts, extras, and snacks, were grouped into an "other" meal occasion. Food items at the submajor and minor food group levels were examined (23). To prevent undue duplication, repeated food items at each food group level within meals were removed from the dataset. It aimed to make sure that each food group was included only once for each meal occasion at each food level. RStudio, version 1.0.44 (incorporating R, version 3.2.5; The R Foundation for Statistical Computing, Vienna, Austria), was used to explore the frequencies of individual food groups within the meals (43).

Statistical Analysis

Data extracted from the trials included the diet history data at baseline after randomization for studies 1, 2, and 3 and prior to randomization for study 4. The baseline body weight, baseline BMI, age, gender, education level, smoking status, and physical activity level data were also collated. Participants with missing data for education and physical activity were excluded from the analysis. Participants aged <19 years were also excluded. The final number of participants included in the analysis was 758. Normality of the pooled cohort data was tested using the Shapiro–Wilk test and visually inspected using a histogram and normal Q–Q plot. Baseline characteristics for the four study samples were summarized and compared using one-way analysis of variance for parametric continuous variables with *post-hoc* comparisons using Bonferroni adjustment and the Kruskal–Wallis H test for non-parametric distributed variables. The Pearson χ^2 statistic was used to compare the proportions with *post-hoc* comparisons conducted using Bonferroni-adjusted z tests to compare the columns.

Data mining techniques were used to identify food groups associated with walnut consumption, using RStudio, version 1.0.44 (incorporating R, version 3.2.5; The R Foundation for Statistical Computing, Vienna, Austria) (43). The detailed analysis method is described elsewhere (23). In brief, by letting I = I1, I2, ... In a set of binary attributes, called items were developed. In this case, items are considered to be the food items. By letting D be a database of transactions, each transaction d indicates the dietary intake record reported by one participant. Each transaction d is represented as a binary vector, with $d[k] = 1$ if a participant consumed the food item Ik, and $d[k] = 0$ if a participant did not consumer the food item (44, 45). In general, a set of food items (X or Y) is a set of some items in I. A transaction d satisfies X if for all items Ik in X, $t[k] = 1$ (44, 45). An association rule is a pair (X, Y) of sets of attributes, denoted by XY (44, 45), and is presented to indicate that if the antecedent X happens (also called the left-hand-side), the consequent Y also happens (also called the right-hand side), where $X, Y \subseteq I$ (44, 45).

A two-step descriptive method, the *a priori* algorithm of association rules was used in the present analysis (44, 45). First, a set of frequent item sets is generated. Second, the frequent item sets are used to generate association rules. Constraints, such as the support, confidence, and lift are applied to identify the interested association rules. Support is a frequency threshold that represents the percentage of the containing identified frequent item sets, X and Y (44, 45) (Equation 1). The confidence of a rule is the percentage of records D containing both antecedent X and consequent Y (Equation 2) (44, 45). Support and confidence are used to reflect the strength of an identified rule, where higher values imply a stronger relationship for the identified association rule (44, 45). Lift was applied to assess the dependency between antecedent and consequent (46) (Equation 3). A lift >1 indicates that antecedent and consequent food items are more likely to depend on each other.

$$support\ (X \Longrightarrow Y) = P(X \cup Y) \qquad (1)$$

$$\text{confidence (X} \Longrightarrow \text{Y)} = \frac{\text{support (X} \cup \text{Y)}}{\text{support (X)}} \qquad (2)$$

$$\text{lift (X} \Rightarrow \text{Y)} = \frac{\text{support (X} \cup \text{Y)}}{\text{support (X)} \times \text{support (Y)}} \qquad (3)$$

In the analyses reported here, the threshold of the possible food group combinations at events (meals) was set as one-quarter of study participants in the cohort (47). In other words, at least 25% of participants would need to have reported a specific combination of food groups in relation to walnuts for the food combination to be reported in the present analysis. The default value for the *a priori* algorithm within the R software (0.80) was

TABLE 1 | Characteristics of participants by clinical trial study.

Clinical trial (year)	Study 1 (2005)	Study 2 (2009)	Study 3 (2010)	Study 4 (2014–2015)	*P*-value
	***n* = 103**	***n* = 111**	***n* = 111**	***n* = 433**	
Age group, *n* (%)					0.696
20–34 years	16 (15.54)	12 (10.81)	7 (6.31)	78 (18.02)	
35–49 years	48 (46.60)	66 (59.46)	46 (41.44)	235 (54.27)	
50–64 years	38 (36.89)	33 (29.73)	55 (49.55)	120 (27.71)	
≥65 years	1 (0.97)	0 (0.00)	3 (2.70)	0 (0.00)	
Gender, *n* (%)					0.629
Male	32 (31.07)	26 (23.42)	28 (25.23)	115 (26.56)	
Female	71 (68.93)	85 (76.58)	83 (74.77)	318 (73.44)	
Education level, *n* (%)					0.041
High	51 (49.51)	43 (38.74)	68 (61.26)	213 (49.19)	
Medium	51 (49.51)	68 (61.26)	43 (38.74)	217 (50.12)	
Low	1 (0.98)	0 (0)	0 (0)	3 (0.69)	
Smoking, *n* (%)					0.035
Non-smoker	103 (100)	104 (93.69)	109 (98.20)	410 (94.69)	
Smoker	0 (0)	7 (6.31)	2 (1.80)	23 (5.31)	
Physical activity level, *n* (%)					<0.001
Adequate	21 (20.40)	17 (15.30)	25 (22.50)	176 (40.60)	
Low	82 (79.60)	94 (84.70)	86 (77.50)	257 (59.40)	
Body mass index (kg/m^2), median (IQR)	30.90 (27.70–33.30)	30.70 (28.47 –34.28)	29.87 (27.69–31.88)	32.28 (29.44–35.83)	<0.001
Percentage of body fat, mean ± SD	38.41 ± 6.51[a]	39.50 ± 7.10	38.44 ± 6.15	40.52 ± 7.04[b]	0.004
Weight status, *n* (%)					<0.001
Overweight	40 (38.83)	43 (38.74)	48 (43.24)	109 (25.17)	
Obese	63 (61.17)	68 (61.26)	63 (56.76)	324 (74.83)	
Basal metabolic rate (MJ/d), median (IQR)	6.48 (5.90–7.43)	6.59 (6.03–7.21)	6.23 (5.91–6.99)	6.70 (6.10–7.60)	<0.001
Total energy intake (MJ/d), median (IQR)	8.91 (7.09–11.64)	8..98 (7.58–10.78)	8.50 (7.36–9.98)	9.29 (7.67–11.44)	0.083
EI/BMR, median (IQR)	1.35 (1.13 –1.75)	1.39 (1.18–1.68)	1.00 (1.17–1.57)	1.39 (1.14–1.66)	0.909
Energy misreporting status, *n* (%)					0.570
Plausible reporters	51 (49.5)	58 (52.3)	51 (45.9)	230 (53.1)	
Underreporters	52 (50.5)	53 (47.7)	60 (54.1)	203 (46.9)	

BMR, basal metabolic rate; EI, energy intake; IQR, interquartile range; MJ, megajoule.
[a]*n = 102.*
[b]*n = 430.*

used for the values of confidences (43). At each event, many closely related food groups may be identified in the dataset, contributed by inherent variability related to food intakes. Thus, redundant closely related food groups were removed to minimize unnecessary complexity by comparing closely related food groups at events (46, 48).

RESULTS

Data for 758 participants were analyzed (**Table 1**). The proportion of participants who were consuming walnuts was 14.5% (n = 110). The median walnut intake was 5.14 (interquartile range, 1.10–11.45) g/d. A total of 128 food items containing walnuts were identified for walnut consumers. The proportion of participants who reported unsalted raw walnut was 80.5% (n = 103). Walnuts were also consumed as carrot cake (n = 14) and in a brownie with nuts (n = 11). Walnuts were consumed at breakfast (n = 18, 14.1%), lunch (n = 13, 10.1%), dinner (n = 7, 5.5%), and other meals (n = 90, 70.3%). The details of the food items containing walnuts at meals are shown in **Table 2**.

There was no identified food choice in relation to walnut at breakfast, lunch, or dinner. A total of 24 clusters of food choices related to walnuts at other meals were identified at the submajor food group level (**Figure 1A**) and eight combinations at the minor food group level (**Figure 1B**). The details of the food choice associations with walnuts are presented in **Table 3**.

At the submajor food group level, the highest proportion of reported food choices closely related to walnuts was "nuts and nut products" (60.1%). A total of 59.1% of the participants reported having the combination of "chocolate and chocolate-based confectionary" and "walnut." At the minor food group level, if either "other nuts and nut products and dishes," "apples,"

TABLE 2 | Food items containing walnuts at meal occasions.

Food items at meals	*n* (%)
Breakfast	18 (14.06)
Nut, walnut, raw, unsalted	18 (14.06)
Lunch	13 (10.16)
Cake or cupcake, carrot, commercial, iced	1 (0.78)
Cake or cupcake, carrot, homemade from basic ingredients, undefined fat, uniced	2 (1.56)
Nut, walnut, raw, unsalted	9 (7.03)
Slice, brownie, chocolate, with nuts, homemade from basic ingredients, fat not further defined	1 (0.78)
Dinner	7 (5.47)
Cake or cupcake, carrot, homemade from basic ingredients, undefined fat, uniced	1 (0.78)
Nut, walnut, raw, unsalted	6 (4.69)
Others	90 (70.31)
Cake or cupcake, carrot, commercial, iced	4 (3.13)
Cake or cupcake, carrot, homemade from basic ingredients, undefined fat, iced	1 (0.78)
Cake or cupcake, carrot, homemade from basic ingredients, undefined fat, uniced	5 (3.91)
Nut, walnut, raw, unsalted	70 (54.69)
Slice, brownie, chocolate, with nuts, homemade from basic ingredients, fat not further defined	10 (7.81)

"chocolate (plain, unfilled varieties)," "bananas," "wines, red," "coffee beverage," or "savory biscuits ≤1,800 kJ/100 g" were reported, "walnut" was also reported. If the participants reported consuming "other nuts and nuts products and dishes" and "black tea," "walnut" was also reported ($n = 30$).

DISCUSSION

To our knowledge, this study is the first to report food choices in relation to walnuts in overweight and obese adult participants. By applying a novel nut food composition database, the present study has mapped the precise combinations of consumed foods associated with walnuts at mealtimes using a data mining tool. This study offers insights into the role of walnuts, which make up food choices at meals and may support nutritional guidance and dietary behavior change strategies for the intake of nuts.

Nuts are one of the key components of healthy dietary patterns (e.g., Mediterranean diet) and dietary guidelines (49, 50). They are a good source of unsaturated fatty acids and are high in fiber, vitamins, minerals, plant sterols, and polyphenol composition (25). Habitual walnut consumption has been associated with a reduced risk of cardiometabolic disease (30, 51, 52). Walnuts are high in polyunsaturated fatty acids (PUFAs) and are especially rich in α-linolenic acid and linoleic acids (25). α-Linolenic acid is an essential precursor of long-chain omega-3 PUFAs (53). The previous studies have suggested that increased level of α-linolenic acid is associated with improvements in insulin sensitivity and anti-inflammatory and antiatherogenic effects (54, 55). The unique fatty acids composition of walnut appears to play a pivotal role in the beneficial effects of cardiometabolic diseases prevention.

Adding walnut into a diet tends to improve overall dietary quality. In Australia, on average, ∼35% of total daily energy consumed was from "discretionary foods" (56), which are recognized to be high in saturated fats, added sugars, salt, and/or alcohol. Low compliance with recommendations on the consumption of fruit and vegetables has remained fairly consistent over time (57). A clinical trial that provided participants with walnuts reported improvements in overall dietary quality (58). Previous research has also suggested that the provision of walnuts in the context of healthy eating advice resulted in significant increases in the quality of the overall diet patterns (59), with increased fruit consumption and decreased discretionary food consumption reported (10). Nut consumers may also have higher intakes of vegetables (60, 61). Such patterns of nut consumption, across a range of clinical trials, have demonstrated a positive association with surrogate endpoints, such as lower blood pressure and concentrations of low-density lipoprotein and triglyceride (62, 63).

However, there are many barriers to adding nuts into a diet. The current food supply is complex with a large number of foods available to the general public. Given the relative cost of consuming walnuts, food prices are the leading factor driving food decisions (64, 65), particularly for low socioeconomic status groups (66). Food literacy and skills are required to incorporate recommendations into everyday food choices practicalities (67–69). Therefore, the findings of the present study may provide examples for food selections associated with walnuts to use used in developing easier and more practical dietary strategies to improve nuts consumption.

The present exploratory cohort also suggests that walnuts were more likely to be consumed at small meals, such as midmeals or snacks. No food associations were reported at main meals, such as breakfast, lunch, and dinner. This creates an opportunity for consumer education related to the incorporation of walnuts into recipes at times when they may not be traditionally eating within the diet. Snack food choices play a vital role in the obesity epidemic along with the effects of energy imbalance (70). In Australia, there is a shift in meal patterns away from three-meals-per-day model and toward a "grazing pattern" of

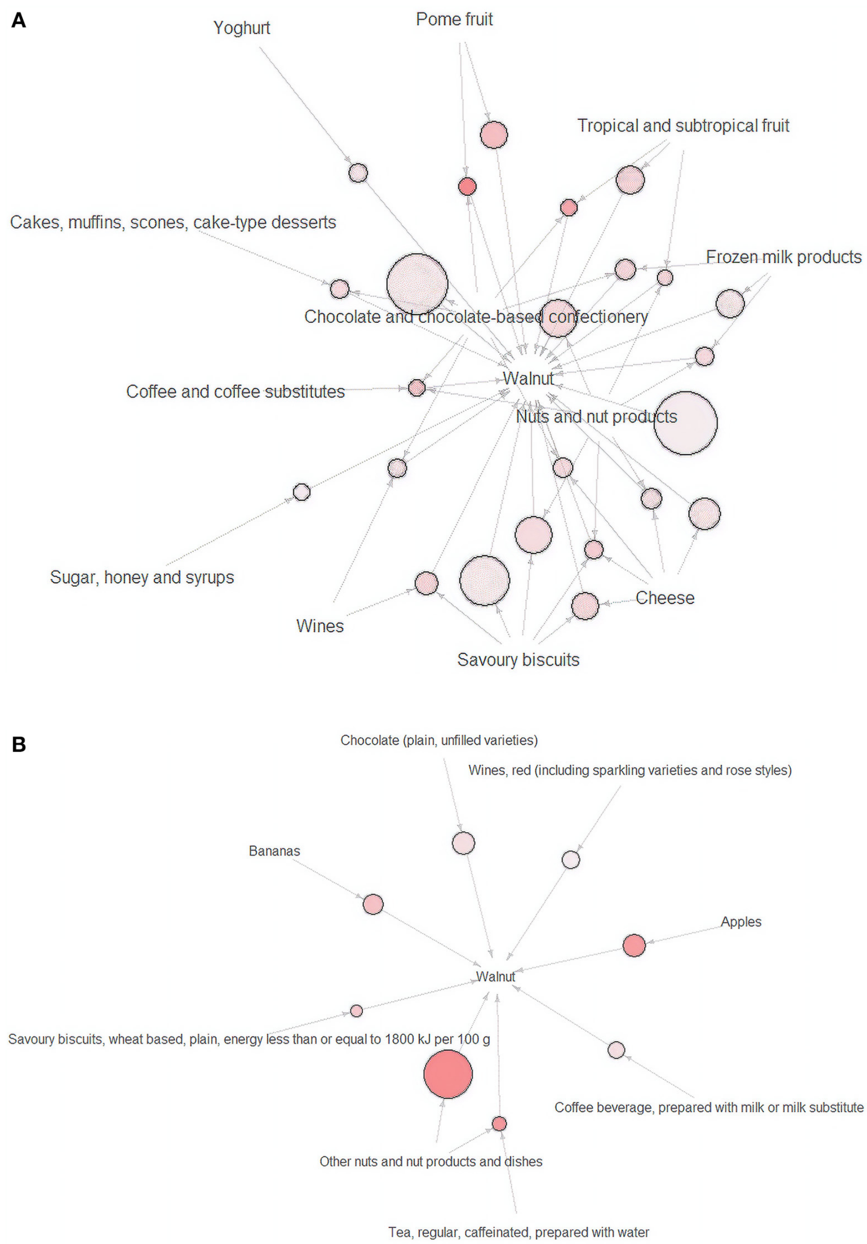

FIGURE 1 | (A) Visualization of closely related food groups for walnuts at the submajor food group level ($n = 24$) and **(B)** visualization of closely related food groups for walnuts at the minor food groups level ($n = 8$). Arrows shows closely related food groups relationships. The size of the sphere represents the value of support. The intensity of the color indicates the value of lift.

eating (71). This shift in meal patterns has been suggested to promote obesity (71). Particular circumstances that are also common in today's lifestyles (e.g., being rushed, having too little sleep, and experiencing psychosocial stress) can make consumers even more challenged to make healthy snack food choices (72–74). Thus, offering information on specific food choices at snacks times is required for the everyday practicalities associated with navigating the food system. The present results suggest that there were trends in food choices for walnuts at small meals in overweight and obese people. Thus, these findings may help to provide more practical dietary strategies to substitute "unhealthy" food choices with walnuts to improve overall dietary intake.

There are several strengths and limitations to the present study. The food choices associated with walnuts were generated by applying a data mining method and a nested hierarchical food grouping system that was not used in the previous study. In order to explore the food combinations associated with walnuts,

TABLE 3 | Identified association rules between food choices and walnuts at other meals.

Food choice 1	Food choice 2	Food choice 3	Walnut	Support	Confidence	Lift
SUBMAJOR FOOD GROUP LEVEL						
Nuts and nut products			Walnut	0.6091	0.8072	1.0325
Chocolate and chocolate-based confectionery			Walnut	0.5909	0.8125	1.0392
Savory biscuits			Walnut	0.5091	0.8116	1.0381
Chocolate and chocolate-based confectionery	Nuts and nut products		Walnut	0.4273	0.8393	1.0735
Nuts and nut products	Savory biscuits		Walnut	0.4182	0.8364	1.0698
Cheese			Walnut	0.3727	0.8200	1.0488
Frozen milk products			Walnut	0.3545	0.8125	1.0392
Tropical and subtropical fruit			Walnut	0.3545	0.8478	1.0844
Cheese	Savory biscuits		Walnut	0.3455	0.8444	1.0801
Pome fruit			Walnut	0.3455	0.8837	1.1303
Savory biscuits	Wines		Walnut	0.3091	0.8500	1.0872
Cheese	Nuts and nut products		Walnut	0.3000	0.8250	1.0552
Chocolate and chocolate-based confectionery	Frozen milk products		Walnut	0.3000	0.8462	1.0823
Cheese	Chocolate and chocolate-based confectionery		Walnut	0.2909	0.8421	1.0771
Cakes, muffins, scones, cake-type desserts	Chocolate and chocolate-based confectionery		Walnut	0.2818	0.8378	1.0717
Cheese	Nuts and nut products	Savory biscuits	Walnut	0.2818	0.8611	1.1014
Chocolate and chocolate-based confectionery	Wines		Walnut	0.2818	0.8158	1.0435
Frozen milk products	Nuts and nut products		Walnut	0.2818	0.8378	1.0717
Yogurt			Walnut	0.2818	0.8158	1.0435
Chocolate and chocolate-based confectionery	Pome fruit		Walnut	0.2727	0.9375	1.1991
Chocolate and chocolate-based confectionery	Tropical and subtropical fruit		Walnut	0.2636	0.9063	1.1592
Chocolate and chocolate-based confectionery	Coffee and coffee substitutes	Nuts and nut products	Walnut	0.2636	0.8788	1.1240
Sugar, honey and syrups			Walnut	0.2636	0.8056	1.0304
Nuts and nut products	Tropical and subtropical fruit		Walnut	0.2545	0.8485	1.0853
MINOR FOOD GROUP LEVEL						
Other nuts and nut products and dishes			Walnut	0.5273	0.8923	1.1413
Apples			Walnut	0.3364	0.8810	1.1268
Chocolate (plain, unfilled varieties)			Walnut	0.3364	0.8222	1.0517
Bananas			Walnut	0.3182	0.8537	1.0919
Wines, red (including sparkling varieties and rose styles)			Walnut	0.3000	0.8049	1.0295
Coffee beverage, prepared with milk or milk substitute			Walnut	0.2909	0.8205	1.0495
Other nuts and nut products and dishes	Tea, regular, caffeinated, prepared with water		Walnut	0.2727	0.8824	1.1286
Savory biscuits, wheat based, plain, energy ≤1,800 kJ per 100 g			Walnut	0.2545	0.8485	1.0853

detailed food choice data at meals reflecting the individual usual food consumption patterns were required. The dietary intake data used in this study was derived from a diet history interview. It uses an open-ended interview approach and probes to encourage participants to describe their usual food consumption from the first meal of the day to the end of the day (75). Although such information did focus on food choices at self-defined meals, the richness of food intake data allowed us to capture food choices association with walnuts at meal occasions (76), which may not be captured when using other dietary assessment, such as a food frequency questionnaire. While this study is considered to be one of the first food pattern applications of the *a priori* algorithm using a clinical trial dataset, there are some limitations to be acknowledged. For the purpose of the pooled data, it was assumed that all dietary data were collected in the same manner. While the dietitians involved in each of the clinical trials were all trained, it cannot be guaranteed that the procedures followed across an 11-years period did remain identical. Further, the matching of the food items in the pooled analysis was conducted by one researcher. While this was guided by a pre-constructed matching file, there may have been variations in the data over time that required subjective judgments to be made. Finally, the threshold of 25% of participants having each combination means that less common food associations may not have been captured. This specification was set for this specific analysis and should be determined based on the data characteristics and planned outcomes of the study. Nevertheless, although the health effect of walnut consumption has been frequently assessed, studies that assessed how walnuts are consumed in a diet are considerably less frequent. The pooled data analysis of clinical trials appears to offer new opportunities to complement the current evidence for the health effects of nuts by providing translational evidence toward improved the nut consumption.

In conclusion, this study offered the example of food choices associated with walnuts made by overweight and obese volunteers. It provided insights into practical strategies for improving nut intakes at the individual level. To date, less is known about the ways to incorporate walnuts into a diet during a clinical study. The present study applied a descriptive data mining tool (the *a priori* algorithm of association rules) and nested hierarchical food grouping system to examine the food choices that were associated with walnuts at meal occasions; providing data at a much deeper level. Food choices associated with walnuts at meal occasions may assist in the development of easier and more practical strategies for making food choices to improve nut consumption.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: data can be requested from the corresponding author. Requests to access these datasets should be directed to YP, yasmine@uow.edu.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Wollongong Human Research Ethics Committee. The participants provided their written informed consent to participant in each trial. Consent included further use of their data for research purposes.

AUTHOR CONTRIBUTIONS

YP, EN, and LT: study design. VG, EN, and YP: data collation. VG: data analysis. YP, VG, and EN: data interpretation. YP, EN, and LT: funding. VG and YP: manuscript preparation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2020.00149/full#supplementary-material

REFERENCES

1. Herforth A, Arimond M, Álvarez-Sánchez C, Coates J, Christianson K, Muehlhoff E. A global review of food-based dietary guidelines. *Adv Nutr.* (2019) 10:590–605. doi: 10.1093/advances/nmy130
2. Liu K, Hui S, Wang B, Kaliannan K, Guo X, Liang L. Comparative effects of different types of tree nut consumption on blood lipids: a network meta-analysis of clinical trials. *Am J Clin Nutr.* (2020) 111:219–27. doi: 10.1093/ajcn/nqz280
3. Ntzouvani A, Antonopoulou S, Nomikos T. Effects of nut and seed consumption on markers of glucose metabolism in adults with prediabetes: a systematic review of randomised controlled trials. *Br J Nutr.* (2019) 122:361–75. doi: 10.1017/S0007114519001338
4. Morgillo S, Hill AM, Coates AM. The effects of nut consumption on vascular function. *Nutrients.* (2019) 11:116. doi: 10.3390/nu11010116
5. Becerra-Tomás N, Paz-Graniel I, Kendall C, Kahleova H, Rahelić D, Sievenpiper JL, et al. Nut consumption and incidence of cardiovascular diseases and cardiovascular disease mortality: a meta-analysis of prospective cohort studies. *Nutr Rev.* (2019) 77:691–709. doi: 10.1093/nutrit/nuz042
6. Xiao Y, Xia J, Ke Y, Cheng J, Yuan J, Wu S, et al. Effects of nut consumption on selected inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Nutrition.* (2018) 54:129–43. doi: 10.1016/j.nut.2018.02.017
7. Xiao Y, Huang W, Peng C, Zhang J, Wong C, Kim JH, et al. Effect of nut consumption on vascular endothelial function: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr.* (2018) 37:831–9. doi: 10.1016/j.clnu.2017.04.011
8. De Souza RGM, Schincaglia RM, Pimente GD, Mota JF. Nuts and human health outcomes: a systematic review. *Nutrients.* (2017) 9:1311. doi: 10.3390/nu9121311
9. Tapsell LC, Lonergan M, Batterham MJ, Neale EP, Martin A, Thorne R, et al. Effect of interdisciplinary care on weight loss: a randomised controlled trial. *BMJ Open.* (2017) 7:e014533. doi: 10.1136/bmjopen-2016-014533
10. Neale EP, Tapsell LC, Martin A, Batterham MJ, Wibisono C, Probst YC. Impact of providing walnut samples in a lifestyle intervention for weight

loss: a secondary analysis of the HealthTrack trial. *Food Nutr Res.* (2017) 61:1344522. doi: 10.1080/16546628.2017.1344522
11. Afshin A, Sur PJ, Fay KA, Cornaby L, Ferrara G, Salama JS, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* (2019) 393:1958–72. doi: 10.1016/S0140-6736(19)30041-8
12. Nikodijevic CJ, Probst YC, Batterham MJ, Tapsell LC, Neale EP. Nut consumption in a representative survey of Australians: a secondary analysis of the 2011–2012 National Nutrition and Physical Activity Survey. *Public Health Nutr.* 1–11. doi: 10.1017/S1368980019004117. [Epub ahead of print].
13. Afshin A, Penalvo J, Del Gobbo L, Kashaf M, Micha R, Morrish K, et al. CVD prevention through policy: a review of mass media, food/menu labeling, taxation/subsidies, built environment, school procurement, worksite wellness, and marketing standards to improve diet. *Curr Cardiol Rep.* (2015) 17:98. doi: 10.1007/s11886-015-0658-9
14. Leech RM, Worsley A, Timperio A, McNaughton SA. Understanding meal patterns: definitions, methodology and impact on nutrient intake and diet quality. *Nutr Res Rev.* (2015) 28:1–21. doi: 10.1017/S0954422414000262
15. St-Onge M-P, Ard J, Baskin ML, Chiuve SE, Johnson HM, Kris-Etherton P, et al. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American Heart Association. *Circulation.* (2017) 135:e96–121. doi: 10.1161/cir.0000000000000476
16. Krebs-Smith SM, Cronin FJ, Haytowitz DB, Cook DA. Contributions of food groups to intakes of energy, nutrients, cholesterol, and fiber in women's diets: effect of method of classifying food mixtures. *J Am Dietet Assoc.* (1990) 90:1541–6.
17. Prynne CJ, Wagemakers JJMF, Stephen AM, Wadsworth MEJ. Meat consumption after disaggregation of meat dishes in a cohort of British adults in 1989 and 1999 in relation to diet quality. *Eur J Clin Nutr.* (2008) 63:660–6. doi: 10.1038/ejcn.2008.7
18. Burden S, Probst YC, Steel DG, Tapsell LC. Identification of food groups for use in a self-administered, computer-assisted diet history interview for use in Australia. *J Food Compos Anal.* (2009) 22:130–6. doi: 10.1016/j.jfca.2008.10.004
19. Probst YC, De Agnoli K, Batterham M, Tapsell L. Video-recorded participant behaviours: the association between food choices and observed behaviours from a web-based diet history interview. *J Hum Nutr Dietet.* (2009) 22:21–8. doi: 10.1111/j.1365-277X.2008.00929.x
20. Hearty ÁP, Gibney MJ. Analysis of meal patterns with the use of supervised data mining techniques—artificial neural networks and decision trees. *Am J Clin Nutr.* (2008) 88:1632–42. doi: 10.3945/ajcn.2008.26619
21. Woolhead C, Gibney MJ, Walsh MC, Brennan L, Gibney ER. A generic coding approach for the examination of meal patterns. *Am J Clin Nutr.* (2015) 102:316–23. doi: 10.3945/ajcn.114.106112
22. Murakami K, Livingstone MBE, Sasaki S. Establishment of a meal coding system for the characterization of meal-based dietary patterns in Japan. *J Nutr.* (2017) 147:2093–101. doi: 10.3945/jn.117.254896
23. Guan VX, Probst YC, Neale EP, Batterham MJ, Tapsell LC. Identifying usual food choices at meals in overweight and obese study volunteers: implications for dietary advice. *Br J Nutr.* (2018) 120:472–80. doi: 10.1017/S0007114518001587
24. International Nut and Dried Fruit Council Foundation. *INC 2017/2018 Statistical Yearbook.* (2018). Available online at: https://www.nutfruit.org/consumers/news/detail/inc-2017-2018-statistical-yearbook (accessed July 8, 2020).
25. Food Standards Australia New Zealand. *AUSNUT 2011-13–Australian Food, Supplement and Nutrient Database for Estimation of Population Nutrient Intakes*. Canberra, ACT: FSANZ (2014).
26. Li J, Jiang B, Santos HO, Santos D, Singh A, Wang L. Effects of walnut intake on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Phytother Res.* (2020). doi: 10.1002/ptr.6740. [Epub ahead of print].
27. Fang Z, Dang M, Zhang W, Wang Y, Kord-Varkaneh H, Nazary-Vannani A, et al. Effects of walnut intake on anthropometric characteristics: a systematic review and dose-response meta-analysis of randomized controlled trials. *Complement Ther Med.* (2020) 50:102395. doi: 10.1016/j.ctim.2020.102395
28. Açik M, Çakiroglu FP. Effects of walnut consumption on inflammatory markers: a review. *J Hyg Eng Des.* (2020) 30:17–25. Available online at: http://www.jhed.mk/categories/view/481/456
29. Mohammadi-Sartang M, Bellissimo N, Totosy de Zepetnek JO, Bazyar H, Mahmoodi M, Mazloom Z. Effects of walnuts consumption on vascular endothelial function in humans: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN.* (2018) 28:52–8. doi: 10.1016/j.clnesp.2018.07.009
30. Guasch-Ferré M, Li J, Hu FB, Salas-Salvadó J, Tobias DK. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: an updated meta-analysis and systematic review of controlled trials. *Am J Clin Nutr.* (2018) 108:174–87. doi: 10.1093/ajcn/nqy091
31. Tapsell L, Batterham M, Huang XF, Tan SY, Teuss G, Charlton K, et al. Short term effects of energy restriction and dietary fat sub-type on weight loss and disease risk factors. *Nutr Metab Cardiovasc Dis.* (2010) 20:317–25. doi: 10.1016/j.numecd.2009.04.007
32. Tapsell LC, Batterham MJ, Charlton KE, Neale EP, Probst YC, O'Shea JE, et al. Foods, nutrients or whole diets: effects of targeting fish and LCn3PUFA consumption in a 12mo weight loss trial. *BMC Public Health.* (2013) 13:1231. doi: 10.1186/1471-2458-13-1231
33. Tapsell LC, Batterham MJ, Thorne RL, O'Shea JE, Grafenauer SJ, Probst YC. Weight loss effects from vegetable intake: a 12-month randomised controlled trial. *Eur J Clin Nutr.* (2014) 68:778–85. doi: 10.1038/ejcn.2014.39
34. World Health Organisation. *Obesity and Overweight*. WHO (2018). Available online at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed January 21, 2020).
35. Martin GS, Tapsell LC, Denmeade S, Batterham MJ. Relative validity of a diet history interview in an intervention trial manipulating dietary fat in the management of type II diabetes mellitus. *Prev Med.* (2003) 36:420–8. doi: 10.1016/S0091-7435(02)00054-3
36. Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. *Eur J Clin Nutr.* (1991) 45:569–81.
37. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr.* (1990) 51:241–7. doi: 10.1093/ajcn/51.2.241
38. Black AE, Cole TJ. Biased over- or under-reporting is characteristic of individuals whether over time or by different assessment methods. *J Am Dietet Assoc.* (2001) 101:70–80. doi: 10.1016/S0002-8223(01)00018-9
39. Food Standards Australia New Zealand. *AUSNUT 2011–13 Food Measures Database File*. Canberra, ACT: FSANZ (2014). Available online at: http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/classificationofsupps/Pages/default.aspx (accessed February 29, 2016).
40. Food Standards Australia and New Zealand. *AUSNUT 2011–13–AUSNUT 1999 Matching File*. Canberra, ACT: FSANZ (2014). Available online at: https://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/ausnutdatafiles/Pages/matchingfile.aspx (accessed August 20, 2016).
41. Neale EP, Probst YC, Tapsell LC. Development of a matching file of Australian food composition databases (AUSNUT 2007 to 2011–13). *J Food Compos Anal.* (2016) 50:30–5. doi: 10.1016/j.jfca.2016.05.003
42. Nikodijevic CJ, Probst YC, Neale EP. Development of a database for estimation of the nut content of Australian single-ingredient and multi-ingredient foods. *J Food Compos Anal.* (2019) 82:103236. doi: 10.1016/j.jfca.2019.103236
43. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2016). Available online at: https://www.R-project.org/ (accessed August 20, 2016).
44. Agrawal R, Imieliski T, Swami A. Mining association rules between sets of items in large databases. *SIGMOD Rec.* (1993) 22:207–16. doi: 10.1145/170036.170072
45. Agrawal R, Srikant R, editors. Fast algorithms for mining association rules. In: *Proceedings of 20th International Conference on Very Large Databases*. San Francisco, CA: Morgan Kaufmann Publishers Inc (1994).
46. Han J, Pei J, Kamber M. (Editors). Data mining: Concepts and techniques. In *The Morgan Kaufmann Series in Data Management Systems, 3rd Edn*,

Elsevier (2012). Available online at: http://www.sciencedirect.com/science/article/pii/B9780123814791000204
47. Haytowitz DB, Pehrsson PR, Holden JM. The identification of key foods for food composition research. *J Food Compos Anal.* (2002) 15:183–94. doi: 10.1006/jfca.2001.1046
48. Pasquier N, Taouil R, Bastide Y, Stumme G, Lakhal L. Generating a condensed representation for association rules. *J Intell Inform Syst.* (2005) 24:29–60. doi: 10.1007/s10844-005-0266-z
49. National Health and Medical Research Council. *Australian Guide to Healthy Eating*. Canberra, ACT: NHMRC (2013).
50. Tapsell L, Neale E, Nolan-Clark D. Dietary patterns may sustain weight loss among adults. *Curr Nutr Rep.* (2014) 3:35–42. doi: 10.1007/s13668-013-0072-0
51. Tindall AM, Johnston EA, Kris-Etherton PM, Petersen KS. The effect of nuts on markers of glycemic control: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr.* (2019) 109:297–314. doi: 10.1093/ajcn/nqy236
52. Neale EP, Guan V, Tapsell LC, Probst YC. Effect of walnut consumption on markers of blood glucose control: a systematic review and meta-analysis. *Br J Nutr.* 1–33. doi: 10.1017/S0007114520001415. [Epub ahead of print].
53. Li, Tsao R, Yang R, Kramer JKG, Hernandez M. Fatty acid profiles, tocopherol contents, and antioxidant activities of heartnut (*Juglans ailanthifolia* Var. *cordiformis*) and Persian Walnut (*Juglans regia* L.). *J Agric Food Chem.* (2007) 55:1164–9. doi: 10.1021/jf062322d
54. Kim Y, Keogh JB, Clifton PM. Benefits of nut consumption on insulin resistance and cardiovascular risk factors: multiple potential mechanisms of actions. *Nutrients.* (2017) 9:1271. doi: 10.3390/nu9111271
55. Baum SJ, Kris-Etherton PM, Willett WC, Lichtenstein AH, Rudel LL, Maki KC, et al. Fatty acids in cardiovascular health and disease: a comprehensive update. *J Clin Lipidol.* (2012) 6:216–34. doi: 10.1016/j.jacl.2012.04.077
56. Australian Bureau of Statistics. *Australian Health Survey: First Results, 2011–12*. Canberra, ACT: ABS (2015).
57. Australian Bureau of Statistics. *National Health Survey: First Results, 2014–15*. Canberra, ACT: ABS (2015).
58. Njike VY, Ayettey R, Petraro P, Treu JA, Katz DL. Walnut ingestion in adults at risk for diabetes: effects on body composition, diet quality, and cardiac risk measures. *BMJ Open Diabetes Res Care.* (2015) 3:e000115. doi: 10.1136/bmjdrc-2015-000115
59. Wibisono C, Probst Y, Neale E, Tapsell L. Changes in diet quality during a 12 month weight loss randomised controlled trial. *BMC Nutr.* (2017) 3:38. doi: 10.1186/s40795-017-0157-z
60. O'Neil CE, Keast DR, Fulgoni VL, Nicklas TA. Tree nut consumption improves nutrient intake and diet quality in US adults: an analysis of national health and nutrition examination survey (NHANES) 1999–2004. *Asia Pac J Clin Nutr.* (2010) 19:142–50.
61. O'Neil CE, Fulgoni VL, Nicklas TA. Tree Nut consumption is associated with better adiposity measures and cardiovascular and metabolic syndrome health risk factors in U.S. adults: NHANES 2005–2010. *Nutr J.* (2015) 14:64. doi: 10.1186/s12937-015-0052-x
62. Anil S, Charlton KE, Tapsell LC, Probst Y, Ndanuko R, Batterham MJ. Identification of dietary patterns associated with blood pressure in a sample of overweight Australian adults. *J Hum Hypertension.* (2016) 30:672–8. doi: 10.1038/jhh.2016.10
63. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ. Associations between dietary patterns and blood pressure in a clinical sample of overweight adults. *J Acad Nutr Dietet.* (2017) 117:228–39. doi: 10.1016/j.jand.2016.07.019
64. Ni Mhurchu C, Eyles H, Schilling C, Yang Q, Kaye-Blake W, Genç M, et al. Food prices and consumer demand: differences across income levels and ethnic groups. *PLoS ONE.* (2013) 8:e75934. doi: 10.1371/journal.pone.0075934
65. Waterlander WE, Jiang Y, Nghiem N, Eyles H, Wilson N, Cleghorn C, et al. The effect of food price changes on consumer purchases: a randomised experiment. *Lancet Public Health.* (2019) 4:e394–405. doi: 10.1016/S2468-2667(19)30105-7
66. Zorbas C, Eyles H, Orellana L, Peeters A, Mhurchu CN, Riesenberg D, et al. Do purchases of price promoted and generic branded foods and beverages vary according to food category and income level? Evidence from a consumer research panel. *Appetite.* (2020) 144:104481. doi: 10.1016/j.appet.2019.104481
67. Vidgen HA, Gallegos D. Defining food literacy and its components. *Appetite.* (2014) 76:50–9. doi: 10.1016/j.appet.2014.01.010
68. Poelman MP, Dijkstra SC, Sponselee H, Kamphuis CBM, Battjes-Fries MCE, Gillebaart M, et al. Towards the measurement of food literacy with respect to healthy eating: the development and validation of the self perceived food literacy scale among an adult sample in the Netherlands. *Int J Behav Nutr Phys Act.* (2018) 15:54. doi: 10.1186/s12966-018-0687-z
69. Azevedo Perry E, Thomas H, Samra HR, Edmonstone S, Davidson L, Faulkner A, et al. Identifying attributes of food literacy: a scoping review. *Public Health Nutr.* (2017) 20:2406–15. doi: 10.1017/S1368980017001276
70. O'Connor L, Brage S, Griffin SJ, Wareham NJ, Forouhi NG. The cross-sectional association between snacking behaviour and measures of adiposity: the Fenland Study, UK. *Br J Nutr.* (2015) 114:1286–93. doi: 10.1017/S000711451500269X
71. Leech RM, Timperio A, Livingstone KM, Worsley A, McNaughton SA. Temporal eating patterns: associations with nutrient intakes, diet quality, and measures of adiposity. *Am J Clin Nutr.* (2017) 106:1121–30. doi: 10.3945/ajcn.117.156588
72. Chaput J-P. Sleep patterns, diet quality and energy balance. *Physiol Behav.* (2014) 134:86–91. doi: 10.1016/j.physbeh.2013.09.006
73. Jabs J, Devine CM. Time scarcity and food choices: an overview. *Appetite.* (2006) 47:196–204. doi: 10.1016/j.appet.2006.02.014
74. Zellner DA, Loaiza S, Gonzalez Z, Pita J, Morales J, Pecora D, et al. Food selection changes under stress. *Physiol Behav.* (2006) 87:789–93. doi: 10.1016/j.physbeh.2006.01.014
75. Burke BS. The dietary history as a tool in research. *J Am Dietet Assoc.* (1947) 23:1041–6.
76. Guan VX, Probst YC, Neale EP, Tapsell LC. Evaluation of the dietary intake data coding process in a clinical setting: implications for research practice. *PLoS ONE.* (2019) 14:e0221047. doi: 10.1371/journal.pone.0221047

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Ultra-Processed Food Is Positively Associated With Depressive Symptoms Among United States Adults

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Ultra-processed foods (UPFs) are popular in the United States. In recent years, there has been an increasing interest in the health impact of UPF. This study is conducted to assess the association between UPF consumption and depressive symptoms among United States adults. Data were collected from the National Health and Nutrition Examination Survey 2011–2016. Dietary data were obtained through 24-h dietary recall interviews. Depressive symptoms were detected by a nine-item Patient Health Questionnaire; participants with more than 10 points were diagnosed with depressive symptoms. Results of logistic regression revealed a positive association between UPF consumption and depressive symptoms. The study suggests that UPF may increase the risk of depressive symptoms, particularly in people with less exercise.

Keywords: depressive symptoms, ultra-processed food, dose-response, cross-sectional study, NHANES

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INTRODUCTION

Food processing aims to improve food availability, safety, digestibility, transportability, and storage life (1). Since the mid-nineteenth century, the mechanization of the food industry has made it possible to produce, transport, and sell processed foods on a large scale. To better understand the impact of the nature, purpose, and extent of food processing on human health and disease, a novel food classification method—NOVA (a name, not an acronym) was proposed. An updated version of NOVA classified all foods into four groups (2): (1) unprocessed or minimally processed foods; (2) processed culinary ingredients; (3) processed foods; (4) ultra-processed foods (UPFs) and drink products. Among them, UPFs are attracting increasing attention.

UPFs are essentially industrial formulations mostly or entirely made from industrial ingredients, with little or no whole foods. They often contain substances not used in home cooking, especially the additives for sensory properties of food (3). Typical UPFs include carbonated beverages, bagged snacks, mass-produced packaged bread and buns, and ice cream. Because of their super-palatability, convenience, and long storage life, UPFs dominate the food supply in high-income countries, particularly in the United States (US), where UPFs account for 57.5% of total energy intake (4). At the same time, UPF consumption is increasing rapidly in middle-income countries (5).

UPF producers prioritize taste, cost, storage, and stability during transport, whereas neglecting nutritional quality (6). UPFs are common in the western dietary pattern and generally rich in total fat, saturated fat, added sugar, and salt, whereas poor in fiber and vitamin density (7, 8), which is detrimental to mental health (9, 10). Beyond poor nutritional quality, UPFs also contain all kinds of additives, along with neo-formed contaminants produced during food processing and packaging (11–13), some of which may have an adverse effect on intestinal flora (14, 15), inducing the development of inflammation-associated diseases (16, 17), such as depression.

In recent years, the impact of high UPF consumption has aroused widespread public concerns, stimulating extensive researches to investigate adverse health outcomes related to UPF. Researches have demonstrated an association between UPF consumption and increased risk of all-cause mortality (18–20), cancer (21), type 2 diabetes (22), and cardiovascular diseases (23). Additionally, positive associations with frailty (24), overweight/obesity (25) were reported in other studies. Among these studies, two European studies explored the association between UPF and mental disorders (26, 27). However, both two studies were conducted in a population with relatively low UPF consumption. There is a lack of a large-scale study to assess the association between UPF consumption and depressive symptoms in the US population. Thus, we conducted this study to evaluate the relationship between UPF consumption and depressive symptoms in US adults aged more than 20 years.

MATERIALS AND METHODS

Data Source, Population, and Sampling

This study used data collected from the National Health and Nutrition Examination Survey (NHANES), which is administered by the National Centers for Health Statics at the Centers for Disease Control and Prevention. NHANES is conducted to assess the health and nutritional status of the US population of all ages. Data are collected using a complex, multistage probability sampling design to make the sample nationally representative. Participants received a detailed interview in their home and physical examination, dietary survey, and clinical laboratory tests at a mobile examination center on another day. All participants provided written informed consent, and the Research Ethics Review Board approved the study protocol.

Data from three survey cycles (2011–2012, 2013–2014, and 2015–2016) were analyzed in this study. A total of 29,902 respondents participated in three survey cycles. The response rates of data collected through interviews in the three survey cycles were 72.6, 71.0, and 61.3%, respectively. In this study, we excluded 12,854 participants younger than 20 years old, 298 pregnant or lactating females, 2,438 participants with an unfinished depression questionnaire, and 675 participants without 24-h recall data. Finally, 13,637 individuals were included in our study (**Figure 1**).

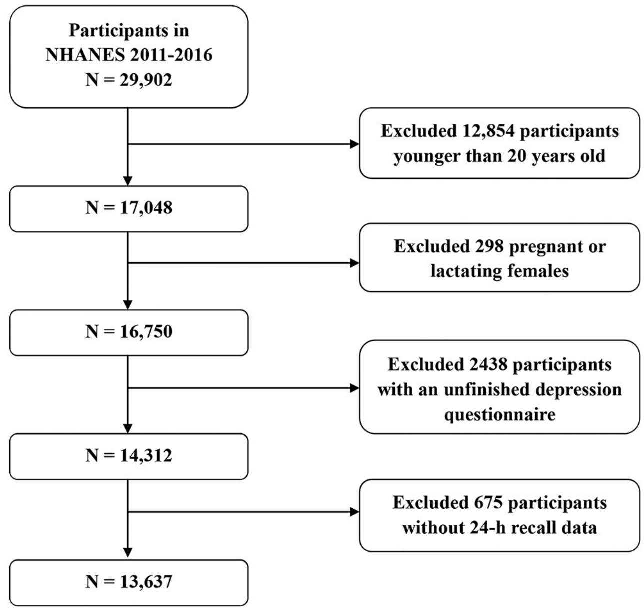

FIGURE 1 | Flow chart of screening process for the selection of the study participants.

Dietary Assessment

Interviewer-administered 24-h dietary recall interview was used to estimate the consumption of foods and beverages. The validity of 24-h dietary recall has been proved in biomarker-based studies (28, 29). All participants are eligible for an in-person dietary interview by trained interviewers in the mobile exam center. The effective Automated Multiple-Pass Method was used to collect dietary data (30). The Automated Multiple-Pass Method is computerized with a five-step multiple-pass approach: collect a quick recall list of foods consumed the previous day, probe for forgotten foods, collect time and occasion of eating, collect detailed information of consumed foods, and final probe. Daily intakes of nutrients and energy were calculated based on self-reported consumed foods, according to the guidance of the Food and Nutrient Database for Dietary Studies.

Twenty-four-hour dietary recall is not representative of usual dietary habits. For reflecting participants' diet more precisely, a sensitivity analysis was conducted (**Supplementary Table 2**). During the dietary survey, all participants were asked, "was the amount of food that you ate yesterday much more than usual, usual, or much less than usual;" only participants who answered "usual" were included in the sensitivity analysis.

Abbreviations: UPF, ultra-processed foods; NHANES, National Health and Nutrition Examination Surveys; FNDDS, Food and Nutrient Database for Dietary Studies; PHQ-9, Nine-item Patient Health Questionnaire; BMI, Body mass index; OR, odds ratio; CI, confidence intervals; PUFAs, polyunsaturated fatty acids.

Food Classification According to NOVA

NOVA classifies all foods into four categories according to the degree of processing (2). In this study, we mainly follow UPF with interest. UPFs are manufactured industrial foods, which usually contain abundant fat, saturated fat, sugar, and salt. Generally, UPFs do not contain or only contain a small percentage of unprocessed or minimally processed foods. According to the NOVA food classification system, we classified all food items as UPF or non-UPF. To ensure the accuracy of food classification and the consistency with other studies, we referred to the published literature (31, 32). The details of food classification are shown in the **Supplementary Material**.

The proportion of UPF in total energy intake (%UPF) was calculated to reflect participants' UPF consumption. UPF consumption was divided into quartiles as the exposure variable.

Assessment of Depressive Symptoms

The nine-item Patient Health Questionnaire (PHQ-9) was used to detect depressive symptoms in NHANES. PHQ-9 consists of nine items, all based on the description of depression in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Each item has four options: "No" (0 points), "several days" (1 point), "more than half of the time" (2 points), and "almost every day" (3 points). The total scores are the sum of the scores of all the items, ranging from 0 to 27. In the present study, participants whose PHQ-9 score $\geq$ 10 were classified as depressive symptoms. This criterion has been confirmed to have good specificity and sensitivity (33). Additionally, in sensitive analysis, individuals who self-reported using antidepressants have also seemed depressive symptoms for testing the stability of the results (**Supplementary Table 3**).

Covariates

For controlling the potential confounding factors, we adjusted some covariates in multivariate models. Sociodemographic characteristics included sex, age (20–44 years, 45–59 years, 60 years, or older), race (Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian, or other races), educational level (below high school, high school, or over high school), annual family income (<\$20,000, \$20,000–<\$45,000, \$45,000–<\$75,000, $\geq$\$75,000), and marital status (married/living with a partner, divorced/separated/widowed/single). Body mass index (BMI) was calculated as weight (kilogram) divided by height squared (square meter) and categorized as underweight or normal weight (<25 kg/m^2), pre-obesity (25–<30 kg/m^2), or obesity ($\geq$30 kg/m^2).

Lifestyle characteristics were also considered. Physical activities were evaluated by the Global Physical Activity Questionnaire. Activity levels were divided into active (more than 300 min of moderate-intensity physical activity a week), moderately active (150–300 min of moderate-intensity, or 75–150 min of vigorous-intensity aerobic physical activity per week), and active (<150 min of moderate-intensity physical activity a week). With regard to smoking status, participants were categorized as current smoker, former smoker, and never smoker. Drinking alcohol was defined if they had at least 12 alcohol drinks a year.

In addition, we adjusted some chronic diseases. Blood pressure was measured in the mobile exam center and calculated by the mean of three blood pressure measurements; hypertension was defined as systolic pressure $\geq$ 130 mmHg and diastolic pressure $\geq$ 80 mmHg. About two-thirds of NHANES participants did not finish fasting blood glucose measures, so the definition of diabetes was based on self-reported clinical diagnosis. Heart disease and chronic bronchitis were also self-reported.

Statistical Analysis

According to the official guidance of NHANES, we constructed new simple weights by taking one-third of the 2-year weights. New weights were used in an analysis to make an estimate representative of the US civilian non-institutionalized resident population.

We used weighted percentages or means for describing categorical and continuous variables, respectively. For comparing the distribution of sociodemographic characteristics, lifestyle, and dietary intake between the depressive symptoms group and non-depressive symptoms group, we used Cochran–Mantel–Haenszel chi-square test for categorical variables and Student's *t*-test for continuous variables. The multiple adjusted logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for depressive symptoms according to UPF consumption, with the lowest quartile as reference. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, race, educational level, annual family income, marital status, BMI, physical activity, smoking, drinking, hypertension, diabetes, heart disease, and chronic bronchitis. The significance of the linear trend was calculated using the median value of each quartile as a continuous variable in each model. In addition, we conducted stratified analyses to test differed associations among people with different physical activity levels. We also assessed the dose–response relationship by restricted cubic spline with knots at the 5th, 25th, 50th, 75th, and 95th percentiles of the exposure distribution, adjusted for all covariates. Stata 15.0 was used for organizing the data and statistical analyses. All reported probabilities (*p*-values) were two-sides with a statistical significance level of 0.05.

RESULTS

Table 1 described the demographic and behavioral characteristics of the 13,637 participants included in this analysis. In the analytic sample, participants consumed an average of 1,201 kcal/day of UPF consumption, equivalent to 55% of total energy intake. Depressed individuals tended to consume more UPF. Among all included participants, 1,208 (8.9%) of them met the definition of depressive symptoms. Women had a significantly higher prevalence (11.3%) of depressive symptoms than men (6.4%). Compared with individuals without depressive symptoms, those with depressive symptoms (PHQ-9 score $\geq$ 10) were middle-aged, less education, lower-income, more obese, and living alone. Depressed individuals were also physically inactive, and they were more likely to smoke. In addition, elevated UPF consumption was associated with low dietary quality (**Table 2**). People with high UPF consumption tended to intake fewer vitamins and trace elements (n-3 fatty acid, dietary fiber, vitamin C, vitamin E, folate, calcium, and zinc) but more saturated fats, sugars, and energy.

Table 3 presents the association between UPF consumption and depressive symptoms. Without adjusting any covariates, a significantly positive association ($p = 0.002$) was observed between UPF consumption and depressive symptoms; the crude OR with 95% CI was 1.43 (1.10–1.85) for the highest vs. lowest quartile. Model 1 adjusted age and sex, showing the same results as the unadjusted model. Further adjusting for BMI, race, marital status, educational level, family income, smoking,

TABLE 1 | Descriptive characteristics of the study participants, NHANES 2011–2016 ($N = 13,637$).

	All participants ($n = 13,637$)	Without depressive symptoms: PHQ < 10 ($n = 12,429$)	With depressive symptoms: PHQ ≥ 10 ($n = 1,208$)	*p*-value
Age (%)[a]				0.002
20–44 years	43.0 (40.8, 45.2)	43.1 (40.8, 45.4)	41.7 (37.1, 46.5)	
45–59 years	29.2 (27.7, 30.6)	28.6 (27.2, 30.0)	35.7 (31.1, 40.6)	
60 years and older	27.8 (26.3, 29.5)	28.3 (26.6, 30.1)	22.6 (19.4, 26.2)	
Sex (%)[a]				<0.001
Men	49.9 (48.9, 51.0)	51.0 (50.0, 52.0)	38.1 (33.5, 42.4)	
Women	50.1 (49.0, 51.1)	49.0 (48.0, 50.0)	61.9 (57.6, 66.5)	
Race (%)[a]				<0.001
Hispanic	14.3 (11.7, 17.5)	14.1 (11.4, 17.2)	16.9 (13.2, 21.2)	
Non-Hispanic White	66.6 (62.3, 70.6)	66.8 (62.5, 70.9)	63.8 (57.7, 69.4)	
Non-Hispanic Black	11.0 (8.9, 13.5)	10.9 (8.8, 13.4)	11.9 (9.0, 15.6)	
Non-Hispanic Asian	5.1 (4.0, 6.4)	5.4 (4.3, 6.7)	1.8 (1.2, 2.8)	
Other races	3.0 (2.6, 3.6)	2.8 (2.3, 3.4)	5.6 (3.8, 8.1)	
BMI (%)[a]				<0.001
<25 kg/m^2	29.1 (27.1, 30.8)	29.4 (27.6,31.3)	25.3 (20.9, 30.6)	
25–<30 kg/m^2	33.1 (31.7, 34.5)	33.8 (32.3, 35.3)	24.9 (20.7, 29.6)	
≥30 kg/m^2	37.8 (36.1, 39.5)	36.7 (35.0, 38.5)	49.8 (44.9, 54.7)	
Marital status (%)[a]				<0.001
Married/living with partner	61.3 (58.9, 63.6)	62.9 (60.5, 65.1)	44.0 (40.0, 48.2)	
Widowed/divorced/ Separated/never married	38.7 (38.7, 41.1)	37.1 (34.9, 39.5)	56.0 (51.8, 60.0)	
Educational level (%)[a]				<0.001
<high school	14.3 (12.6, 16.3)	13.5 (11.8, 15.5)	23.3 (19.5, 27.5)	
High school	21.3 (19.7, 23.0)	20.9 (19.2, 22.6)	25.5 (22.2, 29.2)	
>high school	64.4 (61.4, 67.3)	65.6 (65.6, 68.5)	51.2 (46.6, 55.8)	
Annual family income (%)[a]				<0.001
<$20,000	16.4 (16.5, 20.6)	16.7 (14.9, 18.6)	37.6 (32.3, 43.2)	
$20,000–<$45,000	27.8 (26.2, 29.5)	27.3 (25.8, 29.1)	32.4 (28.1, 37.1)	
$45,000–<$75,000	20.5 (18.9, 22.2)	20.8 (19.1, 22.6)	17.6 (13.7, 22.1)	
≥$75,000	33.3 (30.3, 36.3)	35.2 (32.2, 38.2)	12.4 (9.1, 16.7)	
Physical activity (%)[a]				<0.001
Active	18.0 (18.8, 19.1)	18.4 (17.2, 19.6)	13.0 (10.5, 15.8)	
Moderate active	15.2 (14.1, 16.3)	15.7 (14.6, 16.9)	8.8 (6.9, 11.2)	
Inactive	66.8 (65.3, 68.4)	65.9 (64.2, 67.4)	78.2 (74.8, 81.2)	
Smoking status (%)[a]				<0.001
Current smoker	25.3 (23.8, 26.9)	25.6 (24.1, 27.2)	21.8 (18.2, 26.0)	
Former smoker	19.6 (18.4, 20.9)	17.7 (16.6, 18.8)	40.5 (35.7, 45.6)	
Never smoker	55.1 (53.5, 56.7)	56.7 (55.1, 58.3)	37.7 (33.0, 42.4)	
Had at least 12 alcohol drinks a year (%)[a]	78.3 (76.1, 80.0)	78.0 (76.0, 80.0)	79.2 (76.0, 82.1)	0.56
Current hypertension (%)[a]	36.1 (34.8, 37.4)	36.1 (34.7, 37.5)	35.8 (31.7, 40.1)	0.22
Ever had diabetes (%)[a]	10.5 (9.8, 11.4)	10.0 (9.2, 10.9)	16.5 (13.8, 19.5)	<0.001
Ever had heart disease (%)[b]	7.0 (6.4, 7.6)	6.5 (5.9, 7.1)	13.0 (10.6, 15.9)	<0.001
Ever had chronic bronchitis (%)[b]	6.1 (5.3, 6.9)	5.3 (4.7, 6.0)	14.4 (11.5, 17.9)	<0.001
UPF% (% of total energy intake)[b]	54.9 (54.0, 55.7)	54.5 (53.8, 55.3)	58.3 (56.0, 60.6)	<0.001

All percentages and means are weighted; percentages include missing data.
[a]*Categorical variables are represented as % (95%CI).*
[b]*Continuous variables are represented as means (standard errors).*

TABLE 2 | Nutrient intake according to quartiles of UPF consumption among US adults aged 20 years, NHANES 2011–2016 (*N* = 13,637).

	Ultra-processed food consumption (% of total energy intake)				
	Quartile 1 (*n* = 3,392)	**Quartile 2 (*n* = 3,532)**	**Quartile 3 (*n* = 3,317)**	**Quartile 4 (*n* = 3,396)**	***P*[c]**
Energy (kcal/day)	2,021 ± 944	2,157 ± 933	2,199 ± 903	2,210 ± 956	<0.001
Protein %[a]	18.0 ± 6.4	16.3 ± 5.3	15.3 ± 5.0	14.0 ± 4.4	<0.001
Total carbohydrates %[a]	44.4 ± 12.6	47.7 ± 10.7	48.8 ± 10.6	50.0 ± 10.4	<0.001
Total fats %[a]	33.6 ± 10.8	34.0 ± 8.9	34.3 ± 8.5	35.5 ± 8.4	<0.001
Sugars (g/day, 1,000 kcal)[b]	43.7 ± 24.8	51.7 ± 23.8	55.3 ± 24.4	57.2 ± 27.1	<0.001
Saturated fats (g/day, 1,000 kcal)[b]	11.6 ± 4.9	12.0 ± 4.3	12.5 ± 4.2	13.1 ± 4.2	<0.001
n-3 fatty acid (g/day, 1,000 kcal)[b]	1.00 ± 0.70	0.92 ± 0.55	0.87 ± 0.47	0.85 ± 0.43	<0.001
n-6 fatty acid (g/day, 1,000 kcal)[b]	7.9 ± 4.1	8.0 ± 3.3	8.0 ± 3.4	8.2 ± 3.4	0.01
Fiber (g/day, 1,000 kcal)[b]	9.8 ± 5.5	9.0 ± 4.4	8.1 ± 4.0	7.0 ± 3.4	<0.001
Vitamin A (μg/day, 1,000 kcal)[b]	364 ± 490	353 ± 354	319 ± 499	250 ± 241	<0.001
Vitamin C (mg/day, 1,000 kcal)[b]	51.1 ± 57.4	43.8 ± 43.7	39.0 ± 43.2	29.8 ± 37.8	<0.001
Vitamin D (μg/day, 1,000 kcal)[b]	2.7 ± 3.6	2.5 ± 2.7	2.3 ± 2.4	1.7 ± 2.0	<0.001
Vitamin E (mg/day, 1,000 kcal)[b]	4.8 ± 3.2	4.6 ± 2.9	4.2 ± 2.6	3.9 ± 2.8	<0.001
Folate (μg/day, 1,000 kcal)[b]	263 ± 150	266 ± 150	256 ± 165	246 ± 173	<0.001
Calcium (mg/day, 1,000 kcal)[b]	473 ± 239	479 ± 236	465 ± 220	444 ± 211	<0.001
Phosphorus (mg/day, 1,000 kcal)[b]	715 ± 195	686 ± 198	655 ± 180	610 ± 175	<0.001
Magnesium (mg/day, 1,000 kcal)[b]	174 ± 60	160 ± 61	144 ± 50	124 ± 51	<0.001
Zinc (mg/day, 1,000 kcal)[b]	5.9 ± 2.9	5.5 ± 2.3	5.4 ± 2.3	4.8 ± 2.3	<0.001
Selenium (μg/day, 1,000 kcal)[b]	62.3 ± 28.3	56.0 ± 21.6	53.5 ± 20.2	49.3 ± 17.3	<0.001

Values are means ± standard deviations.
[a]*Dietary protein, carbohydrates and fats are expressed as percentages of total daily energy intake.*
[b]*For adjusting energy intake, nutrients intake expressed as grams, milligrams, or micrograms per 1,000 kcal.*
[c]*Analysis of variance was used to test the differences in nutrient intake according to quartile of UPF consumption.*

TABLE 3 | Weighted odds ratios (95% confidence intervals) for depressive symptoms across quartiles of UPF% (*N* = 13,637).

	Cases/participants	**UPF% range**	**Crude**	**Model 1**	**Model 2**
UPF (%)					
Quartile 1	272/3,392	<37%	Ref	Ref	Ref
Quartile 2	299/3,532	37–<55%	1.00 (0.76–1.30)	1.00 (0.76–1.31)	1.07 (0.79–1.44)
Quartile 3	275/3,317	55–<73%	1.16 (0.89–1.52)	1.17 (0.90–1.53)	1.16 (0.87–1.54)
Quartile 4	362/3,396	≥73%	1.43 (1.10–1.85)**	1.43 (1.10–1.85)**	1.34 (1.00–1.78)*
P[c]			0.002	0.003	0.03

Model 1 adjusted for age and sex.
Model 2 adjusted for age, sex, race, BMI, educational level, annual family income, marital status, physical activity, drinking, smoking, current hypertension, diabetes history, heart disease history, and chronic bronchitis.
[c]*P for linearity was calculated by using the median value of each quartiles as a continuous variable in each model.*
**p* < 0.05; ***p* < 0.01.

drinking, hypertension, diabetes, heart disease, and chronic bronchitis, the results were still stable; the OR (95% CI) of UPF consumption and depressive symptoms was 1.34 (1.00–1.78) for the highest vs. lowest quartile in the fully adjusted model. Dose–response relationship between UPF consumption and depressive symptoms is shown in **Figure 2**. In the restricted cubic spline model, a positively linear association was found between the two (p for non-linearity = 0.34). Stratified analyses were performed to assess whether this association was modified by physical activities in **Table 4**. In models 2 and 3, this positive association between UPF consumption and depressive symptoms was only significant in people with poor physical activity. Among physically active people, the effect on depressive symptoms of UPF was small and not significant.

Sensitivity analysis only including participants with self-reported "usual intake" showed similar results (**Supplementary Table 2**). In addition, when both participants with PHQ-9 score ≥ 10 and antidepressant users considered as depressive symptoms (**Supplementary Table 3**), the positive association between UPF consumption and depressive symptoms was more significant.

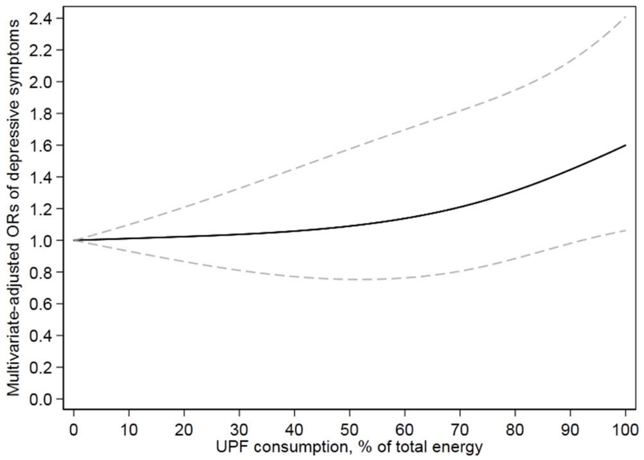

FIGURE 2 | Dose–response relationship of ultra-processed food and risk of depressive symptoms. Model adjusted for age, sex, race, BMI, educational level, annual family income, marital status, physical activity, drinking, smoking, current hypertension, diabetes history, heart disease history, and chronic bronchitis. Solid line and dash line represent the estimated relative risks and their 95% CIs, respectively.

DISCUSSION

In this study, we found UPF consumption was positively associated with depressive symptoms in US adults. After adjusting for sociodemographic characteristics, health behaviors, and chronic disease, participants whose UPF contributed more than 73% of total energy intake had a 35% higher risk of depressive symptoms compared with whose UPF contributed <34% of total energy intake.

Several studies evaluated the effect of UPF or partial components on depressive symptoms. One study from the French NutriNet-Santé cohort reported that high UPF consumption was positively associated with depressive symptoms (27). Another prospective study from the Spain SUN cohort, although conducted in specific university graduates, also found a consistent positive association (26). Nevertheless, both studies were conducted in a population with relatively low UPF consumption; 32% contribute to the total energy in the NutriNet-Santé study, and 276 g/day in the SUN study (vs. 55% and 943 g/day in this study). Our results showed that

TABLE 4 | Weighted odds ratios (95% confidence intervals) for depressive symptoms according to quartiles of UPF%, stratified by physical activity levels.

	Cases/participants	Crude	Model 1	Model 2
Active				
Quartile 1	36/602	Ref	Ref	Ref
Quartile 2	26/562	0.38 (0.18–0.83)	0.38 (0.17–0.83)*	0.36 (0.16–0.83)*
Quartile 3	38/586	0.96 (0.47–1.93)	0.98 (0.48–2.01)	0.85 (0.41–1.76)
Quartile 4	48/585	0.89 (0.51–1.67)	0.87 (0.49–1.57)	0.76 (0.39–1.45)
P^c		0.77	0.63	0.91
Inactive				
Quartile 1	219/2,395	Ref	Ref	Ref
Quartile 2	218/2,369	0.97 (0.71–1.34)	0.97 (0.70–1.33)	1.07 (0.76–1.51)
Quartile 3	224/2,327	1.22 (0.92–1.62)	1.19 (0.90–1.59)	1.21 (0.92–1.60)
Quartile 4	280/2,375	1.45 (1.10–1.90)**	1.41 (1.07–1.86)*	1.36 (1.02–1.82)*
P^c		0.002	0.003	0.01
Moderate active				
Quartile 1	25/460	Ref	Ref	Ref
Quartile 2	32/466	1.42 (0.62–3.25)	1.51 (0.69–3.32)	1.83 (0.89–3.76)
Quartile 3	28/455	1.10 (0.43–2.80)	1.17 (0.47–2.87)	1.18 (0.48–2.88)
Quartile 4	34/455	1.69 (0.73–3.88)	1.81 (0.84–3.93)	1.83 (0.87–3.87)
P^c		0.34	0.19	0.22

Model 1 adjusted for age and sex.
Model 2 adjusted for age, sex, race, BMI, educational level, annual family income, marital status, physical activity, drinking, smoking, current hypertension, diabetes history, heart disease history, and chronic bronchitis.
^{c}P for linearity was calculated by using the median value of each quartile as a continuous variable in each model.
$*p < 0.05$; $**p < 0.01$.

this positive association still existed in the US population with relatively high UPF consumption. In addition, in Whitehall's study (34), a dietary pattern, mainly containing some typical UPF, for instance, sweetened desserts, fried food, processed meat, refined grains, and high-fat dairy products, was associated with the increased risk for depressive symptoms. In contrast, an association between "processed" pattern and depressive symptoms was non-significant in another UK longitudinal study (35).

This positive association between UPF consumption and depressive symptoms could be explained by the following reasons. First, as a typical part of western dietary pattern, although the nutritional value of different types varies greatly, UPF is often accompanied by low diet quality. A NHANES study reported an inverse dose–response association between UPF and overall diet quality (4). Another study also suggested that reducing the intake of UPF was a potentially effective measure to improve the nutritional quality (8). Low diet quality is widely recognized as a risk factor for depression (36). In this study, as the increase of UPF consumption, the content of nearly all "healthy nutrients," such as zinc, iron, copper, selenium, dietary fiber and vitamins, also presented the obvious declined trend, many of which are considered to be protective factors of depression (37, 38).

Beyond limited nutritional intakes, high consumption of UPF interfered with the intake of "healthy foods" or minimally processed foods (39), declining the diet quality indirectly. Besides, food additives and neo-formed contaminants derived from processing may also contribute to depressive symptoms. Phthalates and bisphenols are widely used as plasticizers in food packaging; a recent study reported that UPF consumption was associated with higher urinary phthalate metabolites concentrations; some researchers believe that exposure to phthalates would increase the risk of depressive symptoms. Moreover, in a study of Korean teenagers and children, artificial sweetener consumption was related to the increased θ-β ratio (ratios of the θ and β waves in the frontocentral brain areas), which is considered to be linked to some negative emotions, including depressive symptoms (40).

The adverse effect of UPF on the gut microbiome might also contribute to depressive symptoms. As the "virtual endocrine organ" (41), the gut microbiome ferments dietary fiber into short-chain fatty acids that are beneficial to normal intestinal function (42). Poor nutritional quality of UPF may lead to a reduction of probiotics (43). Additionally, some additives could also impact the composition and function of the gut microbiome. An animal experiment found that food-grade titanium dioxide, as a whitening agent, could affect bacterial metabolism and promote biofilm formation to impact bacterial function, although it had little effect on gut microbial composition (44). Impaired gut microbiome may cause intestinal metabolism disorder and inflammatory bowel disease and then affect the central nervous system through the microbiome–gut–brain axis (45, 46), leading to the increased risk of depressive symptoms.

In this study, the association between UPF and depressive symptoms is more significant among inactive people, which may be mediated by obesity. Previous literature has described a positive association between UPF and obesity (25, 47, 48).

This study has several advantages. First, the sample from NHANES is large-size and nationally representative, in favor of reliable results. Additionally, we adjusted for many potential related factors of depressive symptoms in logistic regression models for reducing the interference of covariates as far as possible. However, we have to admit that there are some limitations to this study. Reverse causality is a major limitation of this study; a cross-sectional study was restricted to make causal inferences. Second, food processing methods are many and varied; the degree of processing is difficult to quantify. For some foods, such as canned fruits, it is hard to classify them precisely. Third, the dietary survey in this study was not specially designed to distinguish the degree of food processing; a certain degree of misclassification bias existed inevitably. Fourth, one single 24-h dietary recall may not reflect participants' daily diet precisely (49), and the accuracy of a 24-h dietary recall interview is largely dependent on participants' memory. Poor memory of depressive participants may lead to low dietary intake reporting, making the positive association null. Additionally, the PHQ-9 depression scale is a self-assessment scale reflecting the recent mental state of subjects, not a clinical diagnostic standard for depression. Compared with healthy subjects, people with depressive symptoms may be more reluctant to reply to the scale and cooperate with the research survey, resulting in non-response bias. Indeed, in NHANES, some adults did not respond to the PHQ-9.

In conclusion, a positive association was found between UPF consumption and the risk of depressive symptoms in this study. It is warranted to confirm this cross-sectional association prospectively in the US population. Besides, not only the nutritional quality but also non-nutritional factors may play a role in this positive association. Further studies will be needed to explore specific food additives or neo-formed contaminants' impact on depressive symptoms.

DATA AVAILABILITY STATEMENT

Publicly available datasets were generated in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NCHS Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LZ and DZ: conceptualization. LZ and XY: data curation. JS: methodology. LZ: writing—original draft. DZ: writing—review and editing. All authors: contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2020.600449/full#supplementary-material

REFERENCES

1. Ludwig DS. Technology, diet, and the burden of chronic disease. *JAMA*. (2011) 305:1352–3. doi: 10.1001/jama.2011.380
2. Monteiro C, Cannon G, Levy R, Moubarac J-C, Jaime P, Martins A. NOVA. The star shines bright. Position paper 2. *World Nutr*. (2016) 7:28–38. Available online at: https://www.worldnutritionjournal.org/index.php/wn/article/view/5/4
3. Monteiro CA, Levy RB, Claro RM, Castro IRRd, Cannon G. A new classification of foods based on the extent and purpose of their processing. *Cad Saude Publica*. (2010) 26:2039–49. doi: 10.1590/s0102-311x2010001100005
4. Martinez Steele E, Popkin BM, Swinburn B, Monteiro CA. The share of ultra-processed foods and the overall nutritional quality of diets in the US: evidence from a nationally representative cross-sectional study. *Popul Health Metrics*. (2017) 15:6. doi: 10.1186/s12963-017-0119-3
5. Monteiro CA, Moubarac JC, Cannon G, Ng SW, Popkin B. Ultra-processed products are becoming dominant in the global food system. *Obesity Rev*. (2013) 14(Suppl. 2):21–8. doi: 10.1111/obr.12107
6. Moodie R, Stuckler D, Monteiro C, Sheron N, Neal B, Thamarangsi T, et al. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet*. (2013) 381:670–9. doi: 10.1016/S0140-6736(12)62089-3
7. Luiten CM, Steenhuis IH, Eyles H, Ni Mhurchu C, Waterlander WE. Ultra-processed foods have the worst nutrient profile, yet they are the most available packaged products in a sample of New Zealand supermarkets. *Public Health Nutr*. (2016) 19:530–8. doi: 10.1017/s1368980015002177
8. Rauber F, da Costa Louzada ML, Steele EM, Millett C, Monteiro CA, Levy RB. Ultra-processed food consumption and chronic non-communicable diseases-related dietary nutrient profile in the UK (2008–2014). *Nutrients*. (2018) 10:587. doi: 10.3390/nu10050587
9. Owen L, Corfe B. The role of diet and nutrition on mental health and wellbeing. *Proc Nutr Soc*. (2017) 76:425–6. doi: 10.1017/s0029665117001057
10. Li Y, Lv MR, Wei YJ, Sun L, Zhang JX, Zhang HG, et al. Dietary patterns and depression risk: a meta-analysis. *Psychiatry Res*. (2017) 253:373–82. doi: 10.1016/j.psychres.2017.04.020
11. Scrinis G, Monteiro CA. Ultra-processed foods and the limits of product reformulation. *Public Health Nutr*. (2018) 21:247–52. doi: 10.1017/s1368980017001392
12. Martinez Steele E, Monteiro CA. Association between dietary share of ultra-processed foods and urinary concentrations of phytoestrogens in the US. *Nutrients*. (2017) 9:209. doi: 10.3390/nu9030209
13. Buckley JP, Kim H, Wong E, Rebholz CM. Ultra-processed food consumption and exposure to phthalates and bisphenols in the US national health and nutrition examination survey, 2013–2014. *Environ Int*. (2019) 131:105057. doi: 10.1016/j.envint.2019.105057
14. Laudisi F, Stolfi C, Monteleone G. Impact of food additives on gut homeostasis. *Nutrients*. (2019) 11:2334. doi: 10.3390/nu11102334
15. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*. (2015) 519:92–6. doi: 10.1038/nature14232
16. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci Biobehav Rev*. (2012) 36:764–85. doi: 10.1016/j.neubiorev.2011.12.005
17. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. (2010) 67:446–57. doi: 10.1016/j.biopsych.2009.09.033
18. Rico-Campà A, Martínez-González MA, Alvarez-Alvarez I, Mendonça RD, de la Fuente-Arrillaga C, Gómez-Donoso C, et al. Association between consumption of ultra-processed foods and all cause mortality: SUN prospective cohort study. *BMJ (Clin Res ed)*. (2019) 365:l1949. doi: 10.1136/bmj.l1949
19. Blanco-Rojo R, Sandoval-Insausti H, López-Garcia E, Graciani A, Ordovás JM, Banegas JR, et al. Consumption of ultra-processed foods and mortality: a national prospective cohort in Spain. *Mayo Clin Proc*. (2019) 94:2178–88. doi: 10.1016/j.mayocp.2019.03.035
20. Kim H, Hu EA, Rebholz CM. Ultra-processed food intake and mortality in the USA: results from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994). *Public Health Nutr*. (2019) 22:1777–85. doi: 10.1017/s1368980018003890
21. Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, Méjean C, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *BMJ (Clin Res ed)*. (2018) 360:k322. doi: 10.1136/bmj.k322
22. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Debras C, Druesne-Pecollo N, et al. Ultraprocessed food consumption and risk of type 2 diabetes among participants of the Nutrinet-Santé prospective cohort. *JAMA Intern Med*. (2019) 180:283–91. doi: 10.1001/jamainternmed.2019.5942
23. Srour B, Fezeu LK, Kesse-Guyot E, Alles B, Mejean C, Andrianasolo RM, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Sante). *BMJ (Clin Res ed)*. (2019) 365:l1451. doi: 10.1136/bmj.l1451
24. Sandoval-Insausti H, Blanco-Rojo R, Graciani A, López-García E, Moreno-Franco B, Laclaustra M, et al. Ultra-processed food consumption and incident frailty: a prospective cohort study of older adults. *J Gerontol A Biol Sci Med Sci*. (2020) 75:1126–33. doi: 10.1093/gerona/glz140
25. Juul F, Martinez-Steele E, Parekh N, Monteiro CA, Chang VW. Ultra-processed food consumption and excess weight among US adults. *Br J Nutr*. (2018) 120:90–100. doi: 10.1017/s0007114518001046
26. Gomez-Donoso C, Sanchez-Villegas A, Martinez-Gonzalez MA, Gea A, Mendonca RD, Lahortiga-Ramos F, et al. Ultra-processed food consumption and the incidence of depression in a Mediterranean cohort: the SUN Project. *Eur J Nutr*. (2020) 59:1093–103. doi: 10.1007/s00394-019-01970-1
27. Adjibade M, Julia C, Alles B, Touvier M, Lemogne C, Srour B, et al. Prospective association between ultra-processed food consumption and incident depressive symptoms in the French NutriNet-Sante cohort. *BMC Med*. (2019) 17:78. doi: 10.1186/s12916-019-1312-y
28. Prentice RL, Mossavar-Rahmani Y, Huang Y, Van Horn L, Beresford SA, Caan B, et al. Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers. *Am J Epidemiol*. (2011) 174:591–603. doi: 10.1093/aje/kwr140
29. Subar AF, Kipnis V, Troiano RP, Midthune D, Schoeller DA, Bingham S, et al. Using intake biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: the OPEN study. *Am J Epidemiol*. (2003) 158:1–13. doi: 10.1093/aje/kwg092

30. Blanton CA, Moshfegh AJ, Baer DJ, Kretsch MJ. The USDA automated multiple-pass method accurately estimates group total energy and nutrient intake. *J Nutr*. (2006) 136:2594–9. doi: 10.1093/jn/136.10.2594
31. Martínez Steele E, Baraldi L, Louzada M, Moubarac J, Mozaffarian D, Monteiro C. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. *BMJ Open*. (2016) 6:e009892. doi: 10.1136/bmjopen-2015-009892
32. Martínez Steele E, Juul F, Neri D, Rauber F, Monteiro C. Dietary share of ultra-processed foods and metabolic syndrome in the US adult population. *Prev Med*. (2019) 125:40–8. doi: 10.1016/j.ypmed.2019.05.004
33. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x
34. Akbaraly TN, Brunner EJ, Ferrie JE, Marmot MG, Kivimaki M, Singh-Manoux A. Dietary pattern and depressive symptoms in middle age. *Br J Psychiatry*. (2009) 195:408–13. doi: 10.1192/bjp.bp.108.058925
35. Northstone K, Joinson C, Emmett P. Dietary patterns and depressive symptoms in a UK cohort of men and women: a longitudinal study. *Public Health Nutr*. (2018) 21:831–7. doi: 10.1017/s1368980017002324
36. Molendijk M, Molero P, Ortuño Sánchez-Pedreño F, Van der Does W, Angel Martínez-González M. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. *J Affect Disord*. (2018) 226:346–54. doi: 10.1016/j.jad.2017.09.022
37. Xu H, Li S, Song X, Li Z, Zhang D. Exploration of the association between dietary fiber intake and depressive symptoms in adults. *Nutrition (Burbank, Los Angeles County, Calif)*. (2018) 54:48–53. doi: 10.1016/j.nut.2018.03.009
38. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes with depression in the US adults. *J Affect Disord*. (2018) 228:68–74. doi: 10.1016/j.jad.2017.12.004
39. Canella DS, Louzada MLdC, Claro RM, Costa JC, Bandoni DH, Levy RB, et al. Consumption of vegetables and their relation with ultra-processed foods in Brazil. *Rev Saude Publica*. (2018) 52:50. doi: 10.11606/s1518-8787.2018052000111
40. Saad JF, Kohn MR, Clarke S, Lagopoulos J, Hermens DF. Is the theta/beta EEG marker for ADHD inherently flawed? *J Atten Disord*. (2018) 22:815–26. doi: 10.1177/1087054715578270
41. Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF, Dinan TG. Minireview: gut microbiota: the neglected endocrine organ. *Mol Endocrinol*. (2014) 28:1221–38. doi: 10.1210/me.2014-1108
42. Shepherd SJ, Lomer MCE, Gibson PR. Short-chain carbohydrates and functional gastrointestinal disorders. *Am J Gastroenterol*. (2013) 108:707–17. doi: 10.1038/ajg.2013.96
43. Clemente JC, Pehrsson EC, Blaser MJ, Sandhu K, Gao Z, Wang B, et al. The microbiome of uncontacted Amerindians. *Sci Adv*. (2015) 1:e1500183. doi: 10.1126/sciadv.1500183
44. Pinget G, Tan J, Janac B, Kaakoush NO, Angelatos AS, O'Sullivan J, et al. Impact of the food additive titanium dioxide (E171) on gut microbiota-host interaction. *Front Nutr*. (2019) 6:57. doi: 10.3389/fnut.2019.00057
45. Ghaisas S, Maher J, Kanthasamy A. Gut microbiome in health and disease: linking the microbiome-gut-brain axis and environmental factors in the pathogenesis of systemic and neurodegenerative diseases. *Pharmacol Ther*. (2016) 158:52–62. doi: 10.1016/j.pharmthera.2015.11.012
46. Koopman M, El Aidy S, consortium MI. Depressed gut? The microbiota-diet-inflammation trialogue in depression. *Curr Opin Psychiatry*. (2017) 30:369–77. doi: 10.1097/YCO.0000000000000350
47. Beslay M, Srour B, Méjean C, Allès B, Fiolet T, Debras C, et al. Ultra-processed food intake in association with BMI change and risk of overweight and obesity: a prospective analysis of the French NutriNet-Santé cohort. *PLoS Med*. (2020) 17:e1003256. doi: 10.1371/journal.pmed.1003256
48. Sandoval-Insausti H, Jiménez-Onsurbe M, Donat-Vargas C, Rey-García J, Banegas JR, Rodríguez-Artalejo F, et al. Ultra-processed food consumption is associated with abdominal obesity: a prospective cohort study in older adults. *Nutrients*. (2020) 12:2368. doi: 10.3390/nu12082368
49. Subar AF, Freedman LS, Tooze JA, Kirkpatrick SI, Boushey C, Neuhouser ML, et al. Addressing current criticism regarding the value of self-report dietary data. *J Nutr*. (2015) 145:2639–45. doi: 10.3945/jn.115.219634

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SYSTEMATIC REVIEW
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Associations of Fish and Omega-3 Fatty Acids Consumption With the Risk of Venous Thromboembolism. A Meta-Analysis of Prospective Cohort Studies

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Objective: This study aims to investigate the effect of fish and omega-3 fatty acids consumption on the risk of VTE.

Methods: A comprehensive literature search in the databases of PubMed, Web of Science, and Embase (up to September 2020), was conducted to identify the prospective cohort studies concerning the associations of fish and omega-3 fatty acids consumption with the risk of VTE. The pooled relative risk (RR) of VTE for the highest vs. lowest category of fish and omega-3 fatty acids consumption, as well as their corresponding 95% confidence interval (CI) were calculated.

Results: A total of seven articles with eight prospective cohort studies were included. Specifically, six studies were related to fish consumption, and the overall multi-variable adjusted RR showed no significant relationship between fish consumption and the risk of VTE (RR = 1.02, 95% CI: 0.93–1.11; $P = 0.709$). In the four studies related to omega-3 fatty acids consumption, the overall multi-variable adjusted RR suggested that omega-3 fatty acids consumption was associated with a lower risk of VTE (RR = 0.89, 95% CI: 0.80–0.98; $P = 0.024$). Moreover, two studies were related to recurrent VTE, and the overall multi-variable adjusted RR demonstrated a significant inverse association between omega-3 fatty acids consumption and the risk of recurrent VTE (RR = 0.45, 95% CI: 0.25–0.81; $P = 0.008$).

Conclusion: Although current evidence is still insufficient to demonstrate any relationship between fish consumption and the risk of VTE, omega-3 fatty acids consumption seems to be associated with a lower risk of both VTE and recurrent VTE. Further large well-designed prospective cohort studies are warranted to elaborate the issues examined in this study.

Keywords: fish consumption, omega-3 fatty acids consumption, venous thromboembolism, meta-analysis, prospective cohort studies

INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common cardiovascular disease (CVD) in adult populations (1–3). As a major cause of cardiovascular mortality, VTE constitutes a significant public health burden due to debilitating long-term complications (4, 5). In contrast with the declining rate of arterial CVD over the past decades (6, 7), the incidence of VTE remains stable or even slightly increased (8, 9). Moreover, VTE is also considered as a chronic and recurrent disease. Although anticoagulant therapy efficiently prevents VTE recurrence, approximately one-third of patients suffer recurrent VTE within 10 years (10, 11). Furthermore, the risk of mortality in patients with VTE is higher than that in general population (12). Thus, there is an urgent need to reduce the VTE risk. The identification of lifestyle factors influencing VTE appears to be an important step in both primary and secondary prevention.

Fish serves as an important determinant of healthy diet, and omega-3 fatty acids (eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) are identified as key bioactive compounds (13). Omega-3 fatty acids are reported to be associated with downregulation of inflammation (14), platelet function (15), platelet-endothelium interactions (16, 17), and tissue factor expression (18), which are key pathways in VTE pathogenesis. To our best knowledge, the effect of fish and omega-3 fatty acids consumption on the risk of VTE has been investigated by a number of prospective cohort studies with conflicting results (13, 19–24). In 2016, a systematic review also indicated that the epidemiological evidence is insufficient to demonstrate any relationship between fish consumption and risk of VTE (25). However, the estimate effects were not pooled and omega-3 fatty acids and recurrent VTE were also ignored. To address these issues above, a meta-analysis of prospective cohort studies was therefore systematically performed. It was hypothesized that fish and omega-3 fatty acids consumption was associated with a lower risk of VTE.

METHODS

Search Strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic review and Meta-analyses (PRISMA) guidelines (26). The electronic databases of PubMed, Web of Science, and Embase were searched up to September 2020, using a series of logic combinations of keywords and in-text words that are related to venous thromboembolism ("venous thromboembolism," "deep vein thrombosis," "pulmonary embolism"), fish ("fish," "seafood"), and omega-3 fatty acids ("fish oil," "omega-3," "n-3 fatty acids," "n-3 fatty acid") (27). No language restrictions were set in the search strategy. We first screened the titles and abstracts of all publications. Then, the full articles were read to identify eligible studies. To avoid missing literature, a manual search was also conducted from the reference lists of all articles selected for inclusion.

Study Selection

The title and abstract screening of relevant articles was done separately by two researchers (YZ and JD) to identify eligible studies for inclusion. The potentially eligible articles were selected through full text review in line with the inclusion and exclusion criteria according to PICOS strategy. The included studies were required to meet the following criteria: (1) the participants were general population; (2) the exposure of interest was the consumption of fish or omega-3 fatty acids; (3) the comparison was the highest vs. lowest category of exposure; (4) the outcomes included the risk of VTE; (5) prospective cohort studies. The exclusion criteria were listed as follows: (1) duplicated or irrelevant articles; (2) reviews, letters or case reports; (3) randomized controlled trials; (4) non-human studies.

Data Extraction

Data extraction was conducted by two independent reviewers (YZ and JD); disagreements were resolved by consensus. The following information was collected: first author, year of publication, location, age, gender, sample size, number of cases, follow-up, outcome, category of exposure, effect estimates, and adjustments. The corresponding effect estimates adjusted for the maximum number of confounding variables with corresponding 95% CIs for the highest vs. lowest level were extracted. For the studies reported effect estimates by gender separately, they were processed independently (22). Moreover, Varraso' study was consisted of two different cohorts: the NHS (Nurses' Health Study) and HPFS (Health Professionals Follow-up Study) (21). They were considered as two independent studies.

Quality Assessment

Quality assessment was conducted according to the Newcastle-Ottawa (NOS) criteria for non-randomized studies (28), which is based on three broad perspectives: the selection process of study cohorts, the comparability among different cohorts, and the identification of either the exposure or outcome of study cohorts. Disagreements with respect to the methodological quality were resolved by discussion and mutual-consultation.

Statistical Analyses

RR was considered as the common measure of the associations of fish and omega-3 fatty acids consumption with the risk of VTE, and HR was directly converted into RR. The I^2 statistic, which measures the percentage of the total variation across studies due to heterogeneity, was examined ($I^2 > 50\%$ was considered heterogeneity). If significant heterogeneity was observed among studies, the random-effects model was used; otherwise, the fixed-effects model was acceptable. Begg's tests were performed to assess the publication bias (29), and statistical analyses were performed using STATA version 11.0 (StataCorp LP, College Station, Texas). A p-value ≤ 0.05 was accepted as statistically significant. Subgroup analysis for sample size, gender, location and adjustment of cigarette smoking, physical activity and hypertension, were conducted.

RESULTS

Study Identification and Selection

Figure 1 represents the detailed flow diagram of articles included in the present meta-analysis. Our initial literature searches yielded a total of 207 potentially relevant articles (PubMed 35, Embase 112, and Web of Science 60). After eliminating 70 duplicated articles, 137 articles were screened by titles and abstracts. 78 irrelevant studies, 22 reviews, case reports or letters, 11 non-human studies, 17 randomized control trials studies and two studies with duplicated or inappropriate data (outcome was PE death) were removed (30, 31). Eventually, a total of seven articles with eight prospective studies were identified for this meta-analysis (13, 19–24).

Study Characteristics

The main characteristics of the included studies were showed in **Table 1**. These studies were published between 2006 and 2019, which included eight prospective cohort studies. Four studies were performed in USA (19–21) and the other four ones were conducted in European country [Norway (13, 23), Denmark (22), Switzerland (24)]. The follow-up duration ranged from 0.5 to 19 years. Five studies included both male and female participants (13, 19, 22–24), and three studies included only female or male participants (20, 21). The sample size ranged from 595 to 80,263. The fish and omega-3 fatty acids consumption was assessed by food-frequency questionnaire (FFQ) in all studies. The diagnosis of VTE was obtained in registered medical record (imaging or autopsy) and food was considered as the source of omega-3 fatty acids in all included studies. Six and four studies were related to the associations of fish (19–23) and omega-3 fatty acids (19, 21, 23) consumption with the risk of VTE, respectively. Two studies were related to the relationship between omega-3 fatty acids consumption and the risk of recurrent VTE (13, 24).

Association Between Fish Consumption and the Risk of VTE

The overall multi-variable adjusted RR suggested no significant relationship between fish consumption and the risk of VTE (RR = 1.02, 95% CI: 0.93–1.11; $P = 0.709$) (**Figure 2**). No substantial level of heterogeneity was found among various studies ($P = 0.176$, $I^2 = 33\%$). Begg's rank-correlation test showed no evidence of publication bias ($P = 0.548$). The results of subgroup analysis were showed in **Table 2**. The sensitivity analysis showed only minimal changes in magnitude of the pooled RR when any study was excluded from the meta-analysis, suggesting that no individual study had excessive influence on these robust aggregate results (data not shown).

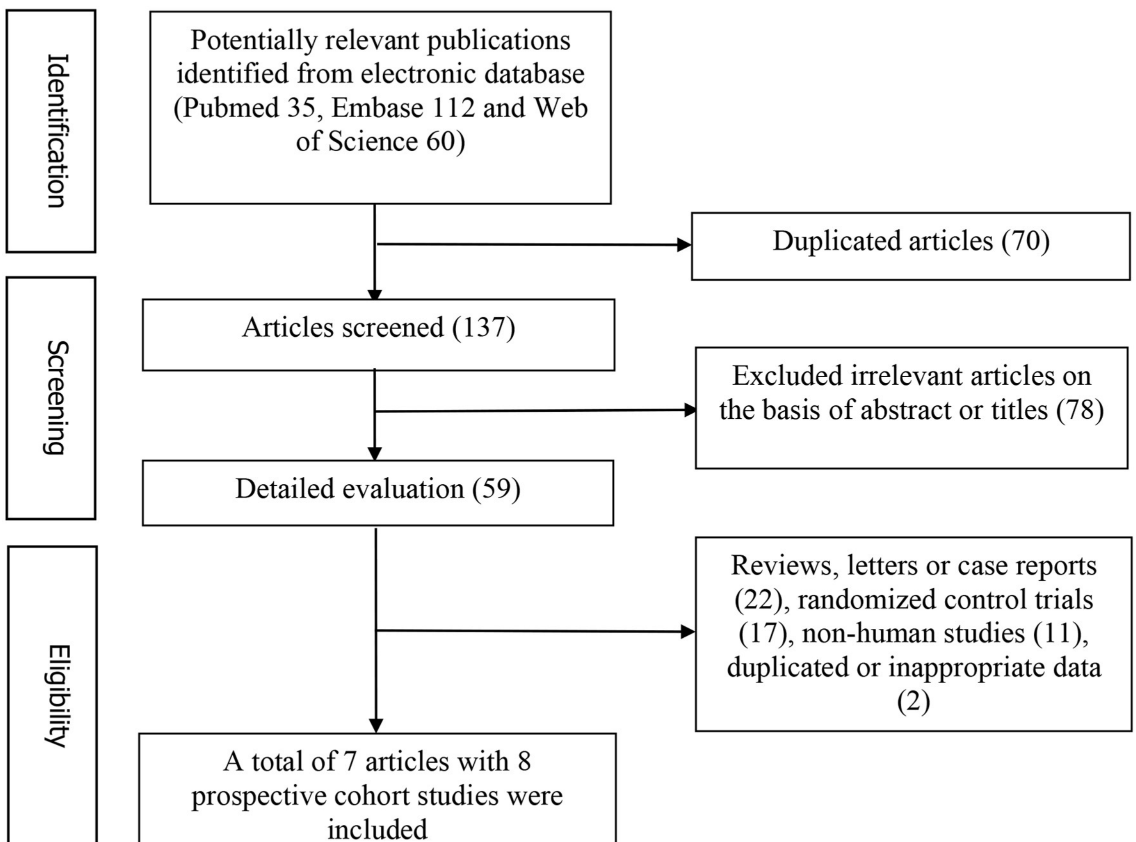

FIGURE 1 | Flow chart for the identification of studies that were included in this meta-analysis.

TABLE 1 | Characteristics of the individual studies included in this meta-analysis.

References	Location	Age and BMI	Gender	Sample Size	Number of cases	Follow-up years	Outcome	Category of exposure	Effect estimates	Adjustments	NOS
Steffen (19)	USA	54 27.5	Both	14,962	196	12.5	VTE	Fish		Age, race, gender, field center, energy intake, vitamin supplement use, BMI, diabetes, vegetable, fruit, whole grain, red and processed meat	8
								Quintile 1	1		
								Quintile 2	0.58 (0.37, 0.90)		
								Quintile 3	0.60 (0.39, 0.92)		
								Quintile 4	0.55 (0.35, 0.88)		
								Quintile 5	0.70 (0.44, 1.10)		
								Omega-3 Fatty Acids			
								Quintile 1	1		
								Quintile 2	0.56 (0.36, 0.87)		
								Quintile 3	0.64 (0.42, 0.99)		
								Quintile 4	0.54 (0.34, 0.85)		
								Quintile 5	0.70 (0.43, 1.13)		
Lutsey (20)	USA	55–69 27	Female	37,393	1,950	19	VTE	Fish		Age, energy intake, education, smoking status, and physical activity, BMI, diabetes	7
								< 0.5 Servings/week	1		
								0.5-1 Servings/week	1.13 (0.95, 1.34)		
								1-1.5 Servings/week	1.16 (0.98, 1.36)		
								1.5-2.5 Servings/week	1.07 (0.91, 1.26)		
								≥2.5 Servings/week	1.22 (1.03, 1.46)		
Varraso NHS (21)	USA	30–55 25	Female	80,263	1,540	14	VTE	Fish		Age, total physical activity level, physical inactivity level, BMI, total caloric intake, smoking, pack-years of smoking, race/ethnicity, spouse's educational attainment, parity, menopausal status, nonaspirin nonsteroidal anti-inflammatory drug use, warfarin use, multivitamin supplement use, hypertension, coronary heart disease, and rheumatologic disease	9
								Quintile 1	1		
								Quintile 2	0.94 (0.80, 1.11)		
								Quintile 3	0.92 (0.79, 1.09)		
								Quintile 4	0.96 (0.82, 1.13)		
								Quintile 5	0.95 (0.80, 1.11)		
								Omega-3 Fatty Acids			
								Quintile 1	1		
								Quintile 2	0.96 (0.82, 1.12)		
								Quintile 3	0.92 (0.78, 1.08)		
								Quintile 4	0.98 (0.84, 1.15)		
								Quintile 5	0.94 (0.80, 1.10)		
Varraso HPFS (21)	USA	40–75 25	Male	49,238	1,352	12	VTE	Fish		Age, total physical activity level, physical inactivity level, BMI, total caloric intake, smoking, pack-years of smoking, race/ethnicity, spouse's educational attainment, parity, menopausal status, nonaspirin nonsteroidal anti-inflammatory drug use, warfarin use, multivitamin supplement use, hypertension, coronary heart disease, and rheumatologic disease	9
								Quintile 1	1		
								Quintile 2	1.02 (0.85, 1.22)		
								Quintile 3	0.83 (0.69, 0.99)		
								Quintile 4	0.96 (0.81, 1.15)		
								Quintile 5	0.96 (0.80, 1.14)		
								Omega-3 Fatty Acids			
								Quintile 1	1		
								Quintile 2	1.01 (0.86, 1.19)		
								Quintile 3	0.88 (0.74, 1.04)		
								Quintile 4	0.91 (0.77, 1.08)		
								Quintile 5	0.91 (0.76, 1.08)		

(Continued)

TABLE 1 | Continued

References	Location	Age and BMI	Gender	Sample Size	Number of cases	Follow-up years	Outcome	Category of exposure	Effect estimates	Adjustments	NOS
Varraso	USA	40–75	Male	49,238	1,352	12	VTE	Fish		Age, total physical activity level, physical inactivity level, BMI, total caloric intake, smoking, pack-years of smoking, race/ethnicity, spouse's educational attainment, parity, menopausal status, nonaspirin nonsteroidal anti-inflammatory drug use, warfarin use, multivitamin supplement use, hypertension, coronary heart disease, and rheumatologic disease	9
HPFS (21)		25						Quintile 1	1		
								Quintile 2	1.02 (0.85, 1.22)		
								Quintile 3	0.83 (0.69, 0.99)		
								Quintile 4	0.96 (0.81, 1.15)		
								Quintile 5	0.96 (0.80, 1.14)		
								Omega-3 Fatty Acids	1		
								Quintile 1	1.01 (0.86, 1.19)		
								Quintile 2	0.88 (0.74, 1.04)		
								Quintile 3	0.91 (0.77, 1.08)		
								Quintile 14	0.91 (0.76, 1.08)		
								Quintile 5			
Severinsen	Denmark	50–64	Male	26,674	641	10.2	VTE	Fish		Total energy intake, smoking, BMI, dietary intake of fruits and vegetables	7
Male (22)		26.2						Quintile 1	1		
								Quintile 2	0.98 (0.71, 1.35)		
								Quintile 3	1.09 (0.78, 1.51)		
								Quintile 4	1.02 (0.74, 1.42)		
								Quintile 5	0.90 (0.64, 1.28)		
Severinsen	Denmark	50–64	Female	29,340	641	10.2	VTE	Fish	1	Total energy intake, smoking, BMI, use of hormone replacement therapy, dietary intake of fruits and vegetables	7
Female		24.8						Quintile 1	0.70 (0.47, 1.04)		
(22)								Quintile 2	0.74 (0.50, 1.10)		
								Quintile 3	0.85 (0.57, 1.27)		
								Quintile 4	1.19 (0.77, 1.83)		
								Quintile 5			
Reiner (24)	Switzerland	75	Both	826	97	0.5	Recurrent	Omega-3 Fatty Acids		Age, gender, BMI, cancer, provoked VTE, prior VTE and periods of anticoagulation as a time-varying covariate	7
		26.4					VTE	Low	1		
								Medium	0.39 (0.15, 0.99)		
								High	0.17 (0.03, 0.96)		
Isaksen	Norway	25–97	Both	21,970	541	12.5	VTE	Fish		Age, sex and BMI	8
(23)		25.5						Quartile 1	1		
								Quartile 2	0.93 (0.71, 1.23)		
								Quartile 3	0.98 (0.75, 1.27)		
								Quartile 4	0.99 (0.76, 1.29)		
								Omega-3 Fatty Acids	1		
								Quartile 1	0.74 (0.57, 0.96)		
								Quartile 2	0.77 (0.59, 0.99)		
								Quartile 3	0.78 (0.61, 1.00)		
								Quartile 4			
Isaksen	Norway	25–97	Both	595	98	12.5	Recurrent	Omega-3 Fatty Acids		Age, sex, and BMI	7
(13)		27.4					VTE	Quartile 1	1		
								Quartile 2	1.01 (0.61, 1.66)		
								Quartile 3	0.51 (0.27, 0.95)		

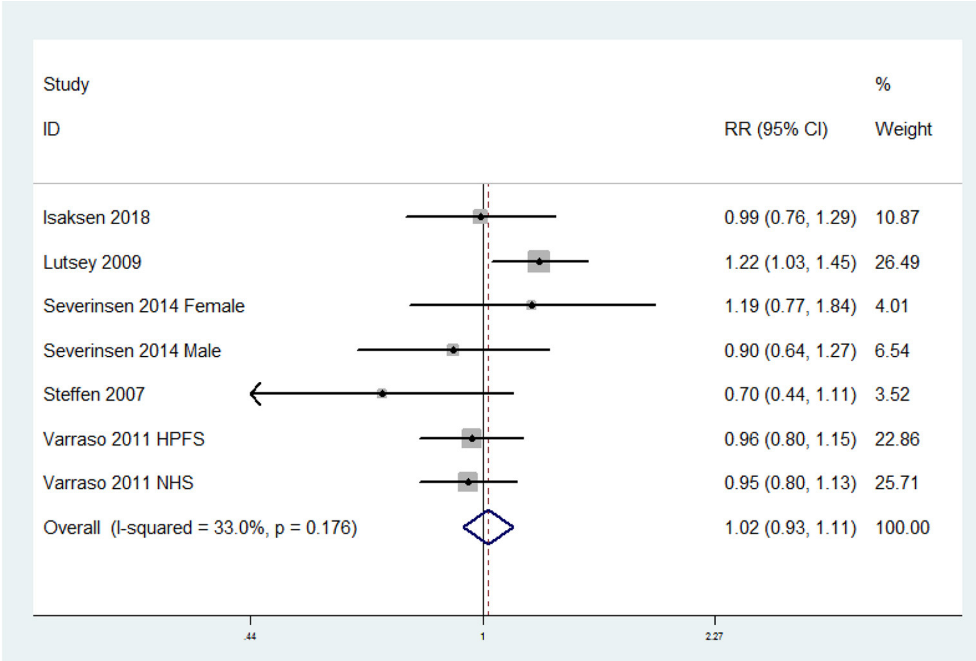

FIGURE 2 | Forest plot of meta-analysis: Overall multi-variable adjusted RR of VTE for the highest vs. lowest category of fish consumption.

Association Between Omega-3 Fatty Acids Consumption and the Risk of VTE

The overall multi-variable adjusted RR suggested that omega-3 fatty acids consumption was associated with a lower risk of VTE (RR = 0.89, 95% CI: 0.80–0.98; $P = 0.024$) (**Figure 3**). No substantial level of heterogeneity was found among various studies ($P = 0.469$, $I^2 = 0\%$). Begg's rank-correlation test showed no evidence of publication bias ($P = 0.308$). The results of subgroup analysis were showed in **Table 3**. The sensitivity analysis showed only minimal changes in magnitude of the pooled RR when any study was excluded from the meta-analysis, suggesting that no individual study had excessive influence on these robust aggregate results (data not shown).

Association Between Omega-3 Fatty Acids Consumption and the Risk of Recurrent VTE

The overall multi-variable adjusted RR showed that omega-3 fatty acids consumption was associated with a lower risk of recurrent VTE (RR = 0.45, 95% CI: 0.25–0.81; $P = 0.008$) (**Figure 4**). No substantial level of heterogeneity was found among various studies ($P = 0.244$, $I^2 = 26.4\%$). Begg's rank-correlation test showed no evidence of publication bias ($P = 1.00$).

TABLE 2 | Subgroup analyses of fish consumption and the risk of VTE.

Subgroup	Number of studies	Pooled RR	95% CI	Heterogeneity
All	6	1.02	0.93–1.11	$P = 0.18$; $I^2 = 33\%$
Sample size				
<30,000	2	0.91	0.72–1.14	$P = 0.20$; $I^2 = 38\%$
>30,000	4	1.04	0.94–1.14	$P = 0.18$; $I^2 = 36\%$
Gender				
Male	2	0.95	0.81–1.11	$P = 0.74$; $I^2 = 0\%$
Female	3	1.09	0.90–1.32	$P = 0.12$; $I^2 = 54\%$
Location				
USA	4	1.00	0.84–1.18	$P = 0.05$; $I^2 = 62\%$
Other	2	1.00	0.82–1.20	$P = 0.61$; $I^2 = 0\%$
Adjustment of cigarette smoking				
Adjusted	4	1.04	0.94–1.14	$P = 0.18$; $I^2 = 36\%$
Unadjusted	2	0.91	0.72–1.14	$P = 0.20$; $I^2 = 38\%$
Adjustment of physical activity				
Adjusted	3	1.04	0.88–1.22	$P = 0.07$; $I^2 = 62\%$
Unadjusted	3	0.95	0.80–1.13	$P = 0.41$; $I^2 = 0\%$
Adjustment of hypertension				
Adjusted	2	0.95	0.84–1.08	$P = 0.93$; $I^2 = 0\%$
Unadjusted	4	1.08	0.96–1.22	$P = 0.13$; $I^2 = 43\%$

DISCUSSIONS

In the present meta-analysis, a total of eight prospective cohort studies were identified for examination. No significant relationship between fish consumption and the risk of VTE was obtained, whereas omega-3 fatty acids consumption was associated with a lower risk of both VTE and recurrent VTE.

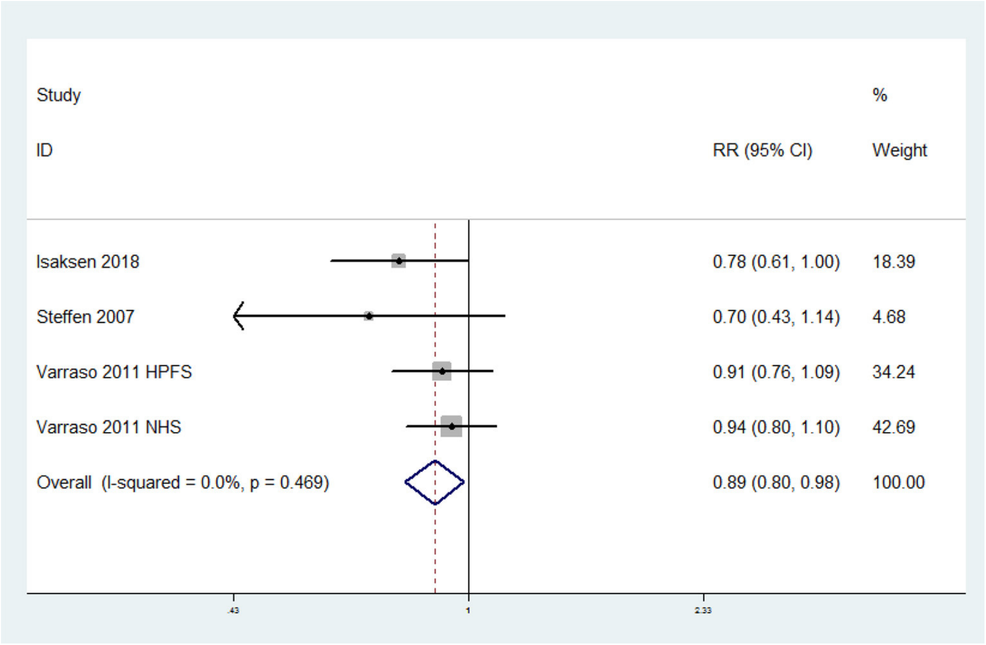

FIGURE 3 | Forest plot of meta-analysis: Overall multi-variable adjusted RR of VTE for the highest vs. lowest category of omega-3 fatty acids consumption.

TABLE 3 | Subgroup analyses of omega-3 fatty acids consumption and the risk of VTE.

Subgroup	Number of studies	Pooled RR	95% CI	Heterogeneity
All	4	0.89	0.80–0.98	$P = 0.47$; $I^2 = 0\%$
Sample size				
<30,000	2	0.76	0.61–0.95	$P = 0.70$; $I^2 = 0\%$
>30,000	2	0.93	0.82–1.04	$P = 0.79$; $I^2 = 0\%$
Gender				
Male	1	0.91	0.76–1.09	/
Female	1	0.94	0.80–1.10	/
Location				
USA	3	0.91	0.81–1.02	$P = 0.53$; $I^2 = 0\%$
Other	1	0.78	0.61–1.00	/
Adjustment of cigarette smoking				
Adjusted	2	0.93	0.82–1.04	$P = 0.79$; $I^2 = 0\%$
Unadjusted	2	0.76	0.61–0.95	$P = 0.70$; $I^2 = 0\%$
Adjustment of physical activity				
Adjusted	2	0.93	0.82–1.04	$P = 0.79$; $I^2 = 0\%$
Unadjusted	2	0.76	0.61–0.95	$P = 0.70$; $I^2 = 0\%$
Adjustment of hypertension				
Adjusted	2	0.93	0.82–1.04	$P = 0.79$; $I^2 = 0\%$
Unadjusted	2	0.76	0.61–0.95	$P = 0.70$; $I^2 = 0\%$

Several studies have demonstrated the impact from omega-3 fatty acids on downregulation of inflammation (14), tissue factor expression (18, 32), platelet function (15), platelet-endothelium interactions (16, 17), and hepatic excretion of coagulation factors (33), which are significant molecular pathways in VTE pathogenesis. Omega-3 fatty acids may also alternate cell membrane permeability and functionality, which leads to antiarrhythmic properties (14). Moreover, some randomized control trials demonstrated that omega-3 fatty acids (both supplementation and circulating level) was associated with a lower risk of VTE after orthopedics surgery (34, 35). On the other hand, a cross-sectional observational study also found a negative relationship between fish consumption and VTE (36). These findings strongly support the potential beneficial effect of omega-3 fatty acids. However, inconsistent results were obtained with regard to experimental animal study. One study demonstrated that omega-3 fatty acids could prevent VTE (37), while some other studies rejected it (38, 39). These inconsistent results in rodents may be difficult to translate to human, especially elderly patients with various risk factors. Moreover, the differences in VTE pathophysiology may account for this discrepancy. The low-dose and long-term protective mechanisms of omega-3 fatty acids may apply to elderly patients with chronic pro-inflammatory and pro-thrombotic backgrounds, whereas animal models consist of an acute and short-term injury with a relatively short exposure to omega-3 fatty acids (24). Therefore, further animal study will be helpful to deepen our understanding.

Notably, this topic has been discussed by a systematic review in 2016 by Mattiuzzi et al. (25). It claimed that the epidemiological evidence was insufficient to demonstrate any relationship between fish consumption and the risk of VTE. However, the estimate effects were not pooled and omega-3 fatty acids and recurrent VTE were also ignored. It also indicated that cigarette smoking and physical activity should be considered as

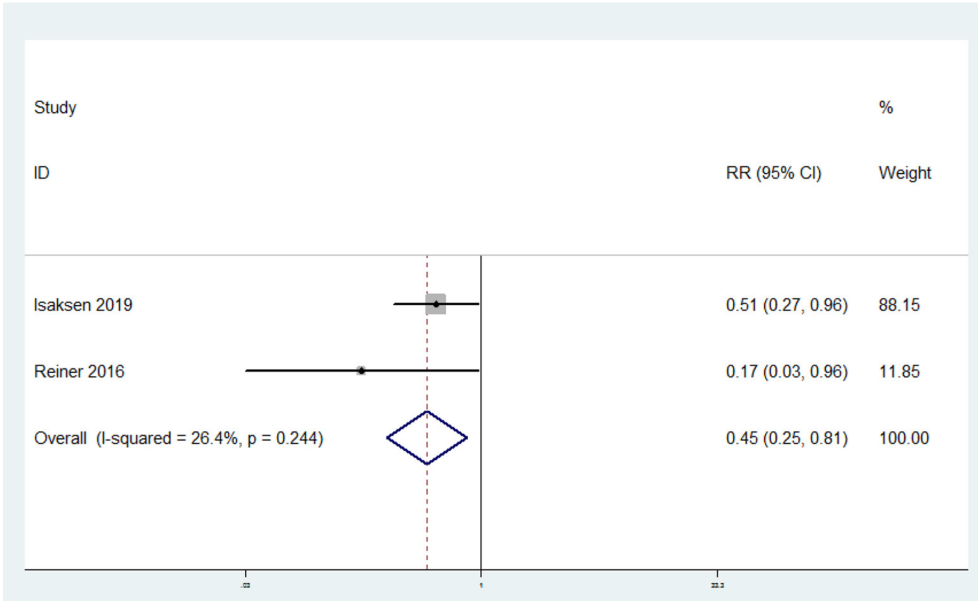

FIGURE 4 | Forest plot of meta-analysis: Overall multi-variable adjusted RR of recurrent VTE for the highest vs. lowest category of omega-3 fatty acids consumption.

confounders. To address these issues above, the present study was therefore systematically preformed. We found an inverse association between omega-3 fatty acids consumption and the risk of VTE, which disappeared when cigarette smoking, physical activity and hypertension was adjusted (**Table 3**). Nevertheless, the reliability of results may be reduced by the small number of studies. As a consequence, more studies with adjustment of these confounding factors are still needed.

So far, the bioavailability of the omega-3 fatty acids is rarely considered in defeating diseases. The formation of phospholipids and regulation of membrane properties are closely associated with the biological effect of omega-3 fatty acids. For example, the omega-3 fatty acids content in erythrocyte membranes (40) and fatty acid-based membrane lipidomics (41) are served as important reliable indicator for omega-3 fatty acids consumption. On the contrary, as the most general indicator, FFQ could not reflect its biological effective quantity in the body. Further studies with bioavailability of omega-3 fatty acids are still needed. On the other hand, as another important polyunsaturated fatty acid, omega-6 fatty acids should also be considered. The metabolites of omega-6 fatty acids are proinflammatory/proaggregatory agent (42), which contributes to the risk of all-cause mortality, coronary heart disease mortality and cardiovascular events (43). Indeed, omega-3 and omega-6 fatty acids are supposed to balance each other when they are consumed in the diet at a ratio of around 1 to 1 (44). The increase in omega-6/omega-3 fatty acids ratio could shift the balance into a proinflammatory/proaggregatory state, and contributed to platelet aggregation, coagulation and thrombosis (44). Therefore, more studies with detail information on omega-6 fatty acids consumption are needed.

Interestingly, the associations of fish and omega-3 fatty acids consumption with the risk of VTE are inconsistence. Several speculations may account for this discrepancy. First, the reliability of the results might be weakened since only limited studies were included. Second, some neglected substances might work against the effect of omega-3 fatty acids since the components in fish are rather complicated. Third, the processing method of fish may also matter. The effect from fresh fish consumption on VTE risk was stronger than that from dried or salted fish, steamed fish paste and deep-fried fish (omega-3 fatty acids were mainly derived from fresh fish) (31). Fourth, the content of omega-3 fatty acids in fatty fish can be up to 7–8 folds higher than that in lean fish. It is possible that a high intake of (lean) fish is associated with a relatively low intake of omega-3 fatty acids (23). On the other hand, different results were obtained with regard to the category of VTE (provoked and unprovoked, DVT and PE) (13, 23). However, the limitation of current evidence precluded a subgroup analysis. More well-designed prospective cohort studies with fish and VTE specification are needed.

Our study has several strengths. First, this is the first meta-analysis of prospective cohort studies aiming at the associations of fish and omega-3 fatty acids consumption with the risk of VTE based on the most comprehensive literature search to date. Second, most of the included studies were analyzed based on adjusted results and large samples. Third, our result may be helpful for health professionals and policy makers to better consider the effect of diet on VTE risk. However, this meta-analysis was also limited in some aspects. First, due to the limitation of relevant literature, only 8 prospective cohort studies were identified. Second, the classification of exposure may vary greatly among individuals. Third, the selection of adjusted factors was not uniform. Fourth, only a few studies have considered the processing method of fish and category of fish (lean and fatty) or VTE (provoked and unprovoked, DVT and PE), some issues could not be addressed. Last but not the least, the consumption of omega-6 fatty acids, which could influence the results of our study, was not considered. These limitations might weaken the significance of this study.

CONCLUSIONS

Although current evidence is still insufficient to demonstrate any relationship between fish consumption and the risk of VTE, omega-3 fatty acids consumption seems to be associated with a lower risk of both VTE and recurrent VTE. However, further well-designed prospective cohort studies are still needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YZ conceived the idea, performed the statistical analysis, and drafted this meta-analysis. YZ and JD selected retrieved relevant papers. HG assessed each study. JL and YL were the guarantors of the overall content. All authors revised and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2020.614784/full#supplementary-material

REFERENCES

1. Huang W, Goldberg R, Anderson F, Kiefe C, Spencer F. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). *Am J Med*. (2014) 127:829–39. doi: 10.1016/j.amjmed.2014.03.041
2. Naess I, Christiansen S, Romundstad P, Cannegieter S, Rosendaal F, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. (2007) 5:692–9. doi: 10.1111/j.1538-7836.2007.02450.x
3. Cushman M, Tsai A, White R, Heckbert S, Rosamond W, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med*. (2004) 1:19–25. doi: 10.1016/j.amjmed.2004.01.018
4. Heit J. Venous thromboembolism: disease burden, outcomes and risk factors. *J Thromb Haemost*. (2005) 3:1611–7. doi: 10.1111/j.1538-7836.2005.01415.x
5. Silverstein M, Heit J, Mohr D, Petterson T, O'Fallon W, Melton L. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. (1998) 158:585–93. doi: 10.1001/archinte.158.6.585
6. Mannsverk J, Wilsgaard T, Mathiesen E, Løchen M, Rasmussen K, Thelle D, et al. Trends in modifiable risk factors are associated with declining incidence of hospitalized and nonhospitalized acute coronary heart disease in a population. *Circulation*. (2016) 133:74–81. doi: 10.1161/CIRCULATIONAHA.115.016960
7. Vangen-Lønne A, Wilsgaard T, Johnsen S, Løchen M, Njølstad I, Mathiesen E. Declining incidence of ischemic stroke: what is the impact of changing risk factors? the Tromsø study 1995 to 2012. *Stroke*. (2017) 48:544–50. doi: 10.1161/STROKEAHA.116.014377
8. Arshad N, Isaksen T, Hansen J, Brækkan S. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. *Eur J Epidemiol*. (2017) 32:299–305. doi: 10.1007/s10654-017-0238-y
9. Heit J, Ashrani A, Crusan D, McBane R, Petterson T, Bailey K. Reasons for the persistent incidence of venous thromboembolism. *Thromb Haemost*. (2017) 117:390–400. doi: 10.1160/TH16-07-0509
10. Mozaffarian D, Benjamin E, Go A, Arnett D, Blaha M, Cushman M, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. (2015) 131:29–322. doi: 10.1161/CIR.0000000000000152
11. Konstantinides S, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Kardiol Pol*. (2014) 72:997–1053. doi: 10.5603/KP.2014.0211
12. Søgaard K, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen H. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation*. (2014) 130:829–36. doi: 10.1161/CIRCULATIONAHA.114.009107
13. Isaksen T, Evensen L, Brækkan S, Hansen J. Dietary intake of marine polyunsaturated n-3 fatty acids and risk of recurrent venous thromboembolism. *Thromb Haemost*. (2019) 119:2053–63. doi: 10.1055/s-0039-1697663
14. Surette M. The science behind dietary omega-3 fatty acids. *CMAJ*. (2008) 178:177–80. doi: 10.1503/cmaj.071356
15. Hansen J, Olsen J, Wilsgård L, Lyngmo V, Svensson B. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. *Eur J Clin Nutr*. (1993) 47:497–507.
16. Hansen J, Svensson B, Wilsgård L, Osterud B. Serum enriched with n-3 polyunsaturated fatty acids inhibits procoagulant activity in endothelial cells. *Blood Coagul Fibrinolysis*. (1991) 2:515–9. doi: 10.1097/00001721-199108000-00004
17. Caterina R, Cybulsky M, Clinton S, Gimbrone M, Libby P. Omega-3 fatty acids and endothelial leukocyte adhesion molecules. *Prostaglandins Leukot Essent Fatty Acids*. (1995) 52:191–5. doi: 10.1016/0952-3278(95)90021-7

18. Moertl D, Berger R, Hammer A, Hutuleac R, Koppensteiner R, Kopp C. Dose-dependent decrease of platelet activation and tissue factor by omega-3 polyunsaturated fatty acids in patients with advanced chronic heart failure. *Thromb Haemost*. (2011) 106:457–65. doi: 10.1160/TH11-03-0169
19. Steffen L, Folsom A, Cushman M, Jacobs D, Rosamond W. Greater fish, fruit, and vegetable intakes are related to lower incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology. *Circulation*. (2007) 115:188–95. doi: 10.1161/CIRCULATIONAHA.106.641688
20. Lutsey P, Steffen L, Virnig B, Folsom A. Diet and incident venous thromboembolism: the Iowa Women's Health Study. *Am Heart J*. (2009) 157:1081–7. doi: 10.1016/j.ahj.2009.04.003
21. Varraso R, Kabrhel C, Goldhaber S, Rimm E, Camargo C. Prospective study of diet and venous thromboembolism in US women and men. *Am J Epidemiol*. (2012) 175:114–26. doi: 10.1093/aje/kwr377
22. Severinsen M, Overvad K, Andersen V, Tjønneland A, Schmidt E, Kristensen S. Fish intake and venous thromboembolism: a Danish follow-up study. *Thromb Res*. (2014) 133:352–6. doi: 10.1016/j.thromres.2013.12.018
23. Isaksen T, Evensen L, Johnsen S, Jacobsen B, Hindberg K, Brækkan S, et al. Dietary intake of marine n-3 polyunsaturated fatty acids and future risk of venous thromboembolism. *Res Pract Thromb Haemost*. (2018) 3:59–69. doi: 10.1002/rth2.12168
24. Reiner M, Stivala S, Limacher A, Bonetti N, Méan M, Egloff M, et al. Omega-3 fatty acids predict recurrent venous thromboembolism or total mortality in elderly patients with acute venous thromboembolism. *J Thromb Haemost*. (2017) 15:47–56. doi: 10.1111/jth.13553
25. Mattiuzzi C, Cervellin G, Franchini M, Lippi G. Fish intake and venous thromboembolism: a systematic literature review. *Clin Appl Thromb Hemost*. (2016) 22:309–13. doi: 10.1177/1076029615585992
26. Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. (2009) 339:b2700. doi: 10.1136/bmj.b2700
27. Morvaridzadeh M, Sepidarkish M, Yavari M, Tahvilian N, Heydarian A, Khazdouz M, et al. The effects of omega-3 fatty acid supplementation on inflammatory factors in HIV-infected patients: a systematic review and meta-analysis of randomized clinical trials. *Cytokine*. (2020) 136:155298. doi: 10.1016/j.cyto.2020.155298
28. Zhang Y, Zhang D. Relationship between nut consumption and metabolic syndrome: a meta-analysis of observational studies. *J Am Coll Nutr*. (2019) 38:499–505. doi: 10.1080/07315724.2018.1561341
29. Begg B, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. (1994) 50:1088–101. doi: 10.2307/2533446
30. Hansen-Krone I, Enga K, Südduth-Klinger J, Mathiesen E, Njølstad I, Wilsgaard T, et al. High fish plus fish oil intake is associated with slightly reduced risk of venous thromboembolism: the Tromsø Study. *J Nutr*. (2014) 144:861–7. doi: 10.3945/jn.113.189548
31. Ohira T, Iso H, Yamagishi K, Tamakoshi A, JACC Study Group. Fish intake and death from pulmonary embolisms among Japanese men and women-The Japan Collaborative Cohort (JACC) study. *Circ J*. (2018) 82:2063–70. doi: 10.1253/circj.CJ-18-0040
32. Hansen J, Olsen J, Wilsgård L, Osterud B. Effects of dietary supplementation with cod liver oil on monocyte thromboplastin synthesis, coagulation and fibrinolysis. *J Intern Med Suppl*. (1989) 731:133–9. doi: 10.1111/j.1365-2796.1989.tb01447.x
33. Vanschoonbeek K, Wouters K, Meijden P, Gorp P, Feijge M, Herfs M, et al. Anticoagulant effect of dietary fish oil in hyperlipidemia: a study of hepatic gene expression in APOE2 knock-in mice. *Arterioscler Thromb Vasc Biol*. (2008) 28:2023–9. doi: 10.1161/ATVBAHA.107.156992
34. Zheng X, Jia R, Li Y, Liu T, Wang Z. Omega-3 fatty acids reduce post-operative risk of deep vein thrombosis and pulmonary embolism after surgery for elderly patients with proximal femoral fractures: a randomized placebo-controlled, double-blind clinical trial. *Int Orthop*. (2020) 44:2089–93. doi: 10.1007/s00264-020-04610-0
35. Shiozawa J, Miyazaki T, Nagayama M, Kaneko H, Hiki M, Hada S, et al. Serum polyunsaturated fatty acid (PUFAS) levels as a risk factor for the post-operative development of venous thromboembolism (VTE) in patients with end-stage knee osteoarthritis who receiving Total Knee Arthroplasty (TKA). *Osteoarth Cartil*. (2016) 24:S514. doi: 10.1016/j.joca.2016.01.941
36. Bhoopat L, Rojnuckarin P, Hiransuthikul N, Intragumtornchai T. Low vegetable intake is strongly associated with venous thromboembolism in Thai population. *Blood Coagul Fibrinolysis*. (2010) 21:758–63. doi: 10.1097/MBC.0b013e3283403537
37. Kuma H, Nagashima R, Hatae H, Tsuda T, Hamasaki N. Beneficial effect of EPA (20:5 n-3 PUFA) on preventing venous thromboembolism: a rat tail thrombosis model experiment. *Thromb Res*. (2013) 131:107–8. doi: 10.1016/j.thromres.2012.09.014
38. Reiner M, Martinod K, Stivala S, Savarese G, Camici G, Lüscher T, et al. Dietary omega-3 alpha-linolenic acid does not prevent venous thrombosis in mice. *Thromb Haemost*. (2015) 113:177–84. doi: 10.1160/TH14-03-0200
39. Andriamampandry M, Leray C, Freund M, Cazenave J, Gachet C. Antithrombotic effects of (n-3) polyunsaturated fatty acids in rat models of arterial and venous thrombosis. *Thromb Res*. (1999) 93:9–16. doi: 10.1016/S0049-3848(98)00149-2
40. Stark K, Van Elswyk M, Higgins M, Weatherford C, Salem N. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. *Prog Lipid Res*. (2016) 63:132–52. doi: 10.1016/j.plipres.2016.05.001
41. Ferreri C, Masi A, Sansone A, Giacometti G, Larocca A, Menounou G, et al. Fatty acids in membranes as homeostatic, metabolic and nutritional biomarkers: recent advancements in analytics and diagnostics. *Diagnostics*. (2016) 7:1. doi: 10.3390/diagnostics7010001
42. DiNicolantonio J, O'Keefe J. Importance of maintaining a low omega-6/omega-3 ratio for reducing inflammation. *Open Heart*. (2018) 5:e000946. doi: 10.1136/openhrt-2018-000946
43. Ramsden C, Zamora D, Leelarthaepin B, Majchrzak-Hong S, Faurot K, Suchindran C, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ*. (2013) 346:e8707. doi: 10.1136/bmj.e8707
44. DiNicolantonio J, O'Keefe J. Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis. *Open Heart*. (2019) 6:e001011. doi: 10.1136/openhrt-2019-001011

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Longitudinal Association of Nut Consumption and the Risk of Cardiovascular Events: A Prospective Cohort Study in the Eastern Mediterranean Region

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Background and Aim: There are few pieces of evidence on the association between nut consumption and the risk of cardiovascular disease (CVD) in the Eastern Mediterranean Region. This study investigated the relationship of nut consumption with the risk of CVD and all-cause mortality in the Iranian population.

Methods and Results: This population-based prospective cohort study was carried out in 6,504 randomly selected participants aged ≥35 years in central Iran (2001–2013) in the framework of the Isfahan Cohort Study. Dietary data were collected by a validated 48-item food frequency questionnaire. Subjects or their next of kin were interviewed biannually, looking for the possible occurrence of cardiovascular events and all-cause mortality. During the median follow-up of 135 months and 52,704.3 person-years, we found a total of 751 CVD events. In unadjusted model, participants in the highest quartile of nut intake had a lower CVD risk {hazard ratio (HR) [95% confidence interval (CI)]: 0.57(0.47–0.70); *P* for trend <0.001}, CVD mortality [HR (95% CI): 0.54 (0.33–0.72); *P* for trend <0.001], and all-cause mortality [HR (95% CI): 0.24 (0.14–0.42); *P* for trend < 0.001]. In the fully adjusted model, the association was diluted, and no significant relationship was found between nut intake and CVD events and all-cause mortality, except for CVD mortality in the highest quartile vs. the lowest one [HR (95% CI): 0.55 (0.30–0.98)].

Conclusion: Nut intake had an inverse association with the risk of CVD mortality. It is suggested to perform studies to examine the association of individual types of nuts and different preparation methods on CVD risk and mortality.

Keywords: nut, cardiovascular disease, myocardial infarction, stroke, ischemic heart disease, chronic, mortality

INTRODUCTION

Globally, cardiovascular diseases (CVDs) are the leading cause of death and one of the major health concerns (1, 2). It is well-established that dietary factors are of great importance in developing, preventing, and managing CVD (3). Healthy dietary patterns are associated with lowered cardiovascular morbidity and mortality (4), and fats are one of the dietary factors that have been the focus of several studies. Replacing saturated fat with polyunsaturated fatty acid (PUFA) and monounsaturated fatty acid (MUFA) has been consistently reported to lower the incidence of CVD (5).

Nuts are a good source of unsaturated fatty acids with low amounts of saturated fats. They also contain many other components that may reduce CVD risk (6). These compounds include protein, minerals (calcium, magnesium, and potassium), vitamins (folic acid, niacin, tocopherols, and vitamin B-6), fiber, phytosterols, and polyphenols (7). The presence of nuts in the diet may decrease the CVD mortality rates through possible anti-inflammatory, antioxidant, and antiatherogenic mechanisms (7). Epidemiological studies have consistently shown that nut consumption is associated with a reduced risk of ischemic heart disease (IHD) and CVD incidence and mortality, and also total mortality in developed countries (8).

Several studies indicated the inverse association between nut consumption and CVD risk factor occurrence among the Iranian population (9, 10). However, to our best knowledge, few studies have evaluated the frequency of nut intake and the risk of CVD in Iran and the other countries in the Eastern Mediterranean region. Thus, we investigated whether there is an association between the frequency of nut consumption and the risk of cardiovascular events as well as cardiovascular and all-cause mortality among the Iranian population in this prospective cohort study.

SUBJECTS AND METHODS

Design and Study Population

The study sample consisted of 6,504 adults aged ≥35 years at baseline, living in urban and rural areas in central Iran (Isfahan, Arak, and Najafabad) from January to September 2001 (11). Subjects were chosen using stratified cluster random sampling. Firstly, the population was stratified based on the living area (urban and rural) in each county. The next step was the random selection of censuses from each county. The probability of selection was proportional to the expected number of households and divided into clusters of ∼1,000 households. Randomly 5–10% of households in each cluster were selected and counted, and from each household, one eligible individual (Iranian, mentally competent, and not pregnant) was selected randomly.

The home-interviews had a response rate of 98%, but 95% attended the examination clinic. For the present study, the individuals with a previous history of CVD ($n = 181$) and also those who missed before the first follow-up ($n = 891$) were excluded from the study. Eventually, the analysis was conducted on the data collected from 5,432 (84%) participants. At baseline, data were collected through face-to-face interviews, which included information about dietary intake. Afterward, follow-up surveys were carried out every 2 years by telephone interviews. In case of unsuccessful attempts by telephone, home-interviews were done. Also, we carried out repeated measurements similar to the baseline for all participants every 6 years in 2007 and 2013. The study was approved by the Ethics Committee of the Research Council of Isfahan Cardiovascular Research Center, a World Health Organization (WHO) collaborating center in Isfahan, Iran. The study design and details of subjects' recruitment and data collection methods were presented elsewhere (11).

Dietary Assessment

At baseline, data on dietary intake were collected by a Block-format validated 48-item food frequency questionnaire (FFQ) (12). The FFQs were completed by trained interviewers in a face-to-face manner. The participants, in an open-ended format, reported the frequency of the consumption of the food items during the last preceding year on daily, weekly, or monthly basis. Nut consumption was calculated by questions on walnut, almond, pistachio, and hazelnut consumption. Trained nutritionists rechecked and computed nut intake. The data on portion sizes of food items were not reported, as studies have shown that for most foods, portion size varies less among individuals than do frequencies of consumption. We examined dietary intake at baseline and during repeated measurement in 2007 and 2013 years.

Ascertainment of Cardiovascular Disease Events

The follow-up of participants continued until the occurrence of CVD events or their last successful interview, mostly before 2013, whichever happened first. The median duration of follow-up was 135 (interquartile range: 93–147) months. Over the 13 years of follow-up, subjects or their families had six biannual telephone interviews. Trained nurses performed structured primary interviews with three main questions: "is he/she alive?" has he/she been hospitalized for any reason? Specifically, focus on cardiovascular and cerebrovascular events. In the occurrence of death or hospitalization, the nurses obtained the date of the events, physician diagnosis, and the hospital's name during the interviews. If the death occurred out of the hospital, death certificates were attained from the provincial mortality database, and a trained expert nurse conducted verbal autopsy including medical history and signs and symptoms before death through a secondary interview with surviving family members. In the case of hospitalization events, trained nurses obtained related documents about reported hospitalization events through medical records and hospital records.

The documents related to each event were evaluated by the specialists' outcome adjudication panel consisted of four cardiologists and two neurologists (11). In the present study, cardiovascular events were defined as fatal and non-fatal myocardial infarction (MI), fatal and non-fatal stroke (which was defined as death from cerebrovascular disease), unstable angina, and sudden cardiac death, using modified criteria of WHO Expert Committee (13). Our definition for MI was based on the presence of at least two of the following criteria: (1) typical chest pain lasting more than 30 min, (2) ST elevation > 0.1 mV in at least two adjacent electrocardiograph leads, and (3) an increase in serum level of cardiac biomarkers. Death within 1 h of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by >1 h of symptoms were considered as sudden cardiac death. Moreover, the WHO stroke definition was used, i.e., stroke was defined as a rapid-onset focal neurological disorder persisting at least 24 h that had a probable vascular origin.

Assessment of Covariates

Trained health professionals conducted detailed home interviews at the baseline of the study for obtaining the required information about participants' general characteristics (socioeconomic and demographic information, data on dietary behaviors, smoking, and physical activity) (14). Participants were categorized into three groups based on their smoking status: smoker, ex-smoker, and non-smoker. Smokers were smoking at least one cigarette per day at the time of the study; those who previously smoked at least one cigarette per day were defined as ex-smokers and others as non-smokers. A validated physical activity questionnaire was used to assess physical activity (15). Total daily physical activity was calculated in metabolic equivalents of task-minute/day. Medical interviews and physical examinations, including a history of CVD and its risk factors, observations regarding heart rate, blood pressure, and electrocardiography, were obtained by trained physicians and nurses.

Blood pressure was measured according to standard protocols, using a calibrated sphygmomanometer twice after 5 min resting, and the mean was calculated as individual blood pressure. Height was measured without shoes to the nearest 0.5 cm, and weight was measured without shoes and with light clothing with a precision of 0.1 kg using a Seca scale. Body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters (kilograms per square meter). Fasting blood samples were taken and centrifuged immediately in each county; samples obtained in Isfahan and Najafabad were transported to the central laboratory within ∼1 h. In Arak, fasting blood glucose and 2-h post-prandial glucose test were measured immediately, and serum was frozen at −20°C, then by a 3-h ground transport with cold chain (−20°C), they were transported to the Isfahan Cardiovascular Research Center central laboratory, which has external national and international quality controls. Serum total cholesterol and fasting blood glucose were measured enzymatically, using an autoanalyzer (Eppendorf, Hamburg, Germany). Those individuals with fasting plasma glucose levels of ≥126 mg/dL or the 2-h post-load plasma glucose ≥200 mg/dl or on insulin or oral hypoglycemic agents were considered as having diabetes mellitus. Having a blood pressure ≥ 140/90 mmHg (based on an average of two measurements) or the use of antihypertensive medications was defined as hypertension. Hypercholesterolemia was defined as having serum total cholesterol levels ≥ 200 mg/dl or statin use.

Statistical Analysis

Energy-adjusted nut intake was calculated based on BMI as a surrogate measure (16) using the residual method due to the lack of data on energy intake in this study. Individuals were categorized based on the quartiles of nuts-BMI adjusted intake. Quantitative variables were expressed as mean ± SD, and qualitative variables were expressed as a percent. A Chi-square test was applied to compare the distribution of categorical variables across quartiles of nut intake. In terms of continuous variables, we applied the Kruskal–Wallis or Brown–Forsyth tests to evaluate means across quartiles of nut intake when the assumptions of one-way analysis of variance were not met. Analysis of covariance was applied to obtain age- and sex-adjusted intakes of food and food groups across quartiles of nut intake.

Cox regression models were fitted to examine the association between nut intake and cardiovascular events, with time to events as the time variable and the nut intake as the independent variable. The model was stratified on sex—that is, separate Cox regression was applied for men and women. The HRs and 95% CI for cardiovascular events across quartiles of nut intake were estimated based on four modeling processes: (1) crude model; (2) adjusted model by age (continuous) and also sex (male/female) in total population; (3) additionally adjusted by education (illiterate, primary school, and higher than primary school), residence area (urban/rural), smoking status (never, ex-smoker, current smoker), daily physical activity (continuous, metabolic equivalents of task-min/day), family history of CVD (yes/no), diabetes mellitus (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no) and aspirin use (yes/no), and menopausal status in females (yes/no); (4) further adjustment for BMI and dietary factors including red meat, fish, fruit and vegetable, hydrogenated and non-hydrogenated vegetable oil, fast food, cereals, legumes, animal fats, sweets, soft drink, and beverages.

The Schoenfeld residuals were used for the testing of the proportional hazards (PH) assumption. Further evaluation was applied to check the PH assumption graphically with the log-cumulative hazard plots against survival time and comparing Kaplan–Meier survival estimates and Cox adjusted estimated plotted on the same graph. If the graphical approaches suggested that there is some violation with PH assumption, extended Cox model was run based on an appropriate function of survival time by defining product term involving time-independent variable with some function of time [g(t) or Heaviside function] and testing the coefficient of the product term. In our analysis, there was not any violation of the PH assumption.

To determine the linear trend of relative risks across quartiles of nut intake, we considered the nut intake as a continuous variable in Cox regression models.

Statistical analyses were performed, using SAS software, version 9.4 (SAS Institute Inc.), and STATA software, version 14. $P < 0.05$ (two-tailed) were considered as statistically significant.

RESULTS

The baseline characteristics of participants according to the quartiles of nut intake was demonstrated in **Table 1**. Compared with those in the first quartile of nut intake, individuals in the top quartile had a lower mean of age and BMI and more physically active. They were less likely to be urbanization,

TABLE 1 | Baseline characteristics of study participants across nuts quartiles.

	Nut intake				
	Q1	**Q2**	**Q3**	**Q4**	***P*-value**
Age (year)	52.9 ± 11.2	54.47 ± 12.9	48.8 ± 10.8	46.6 ± 9.6	< 0.001[a]
Body mass index (kg/m^2)	30.1 ± 3.4	23.9 ± 3.6	26.30 ± 4.2	26.5 ± 4.2	< 0.001[b]
Daily physical activity (METs- min/day)	754.4 ± 480.4	839.3 ± 543.1	937.02 ± 573.8	958.74 ± 568.1	< 0.001[a]
Men (%)	35	56	54.1	49.9	< 0.001[c]
Urbanization (%)	75.5	65.3	77	71.6	< 0.001[c]
Illiterate (%)	46.4	47.3	27.1	24.8	< 0.001[c]
Family history of CVD (%)	5.9	4.5	5.1	6	0.26[c]
Current smoker (%)	9.7	19.9	15.9	19.4	< 0.001[c]
Obese (BMI ≥ 30) (%)	42.6	6.5	18.8	20	< 0.001[c]
Diabetes mellitus (%)	17	9.9	7.8	9.3	< 0.001[c]
Hypertension (%)	41.6	29	27	19	< 0.001[c]
Hypercholesterolemia (%)	67	56.1	55.6	53.6	< 0.001[c]
Post-menopausal women (%)	56.2	56.3	38.9	30.4	< 0.001[c]

Quantitative variables were expressed as Mean ± SD and qualitative variables were expressed as percent.
[a]*Obtained from Kruskal-Wallis test.*
[b]*Obtained from Brown-Forsyth test.*
[c]*Obtained from Chi-Square test.*

illiterate, obese, hypertensive, diabetic, hypercholesterolemic, and postmenopausal women, and more being male and smokers ($P < 0.001$).

Analyzing the participants' dietary intake indicated that those at the top quartile of nut intake had a higher mean intake of non-hydrogenated vegetable oil, fish, fruits and vegetables, legumes, hydrogenated vegetable oil, red meat, fast foods, animal fats, sweets, soft drinks and beverages (all $P < 0.001$), and cereals ($P = 0.002$) (**Table 2**).

During the median follow-up of 135 (interquartile range: 93–147) months and 52,704.3 person-years, we found a total number of 751 CVD events. Multivariable-adjusted HRs for MI, IHD, stroke, CVD incidents, all-cause mortality, and CVD mortality across quartiles of nut intake are presented in **Table 3**. In crude model, participants who ate more nuts had a lower risk of MI [HR (95% CI): 0.50 (0.31–0.81); *P* for trend = 0.002], IHD [HR (95% CI): 0.61 (0.48–0.77); *P* for trend <0.001], stroke [HR (95% CI): 0.49 (0.31–0.77); *P* for trend < 0.001], CVD [HR (95% CI): 0.57(0.47–0.70); *P* for trend < 0.001], all-cause mortality [HR (95% CI): 0.24 (0.14–0.42); *P* for trend < 0.001], and CVD mortality [HR (95% CI): 0.24 (0.14–0.42); *P* for trend < 0.001] in full adjusted model (**Table 3**).

After adjustment for age and sex, those in highest nut quartiles were significantly less likely to have CVD [HR (95% CI): 0.78 (0.63–0.96); *P* for trend = 0.013] events and also CVD mortality [HR (95% CI): 0.41 (0.23–0.73); *P* for trend = 0.003]. In the other two adjusted models, the association was diluted, and no significant relationship was found between nut intake and MI, IHD, stroke, CVD incidents, and all-cause mortality. However, there was a lower risk of CVD mortality in those with the most frequent of nut consumption, compared to the lowest quartile [HR (95% CI): 0.54 (0.30–0.97) in model 2 and 0.55 (0.30–0.98) in full adjustment model], however the trend was not significant ($P = 0.08$) (**Table 3**).

Sensitivity analysis based on sex illustrated a significant inverse relationship between frequency of nut intake and risk of MI [HR (95% CI): 0.42 (0.20–0.85); *P* for trend = 0.004], IHD [HR (95% CI): 0.61 (0.44–0.86); *P* for trend = 0.002], stroke [HR (95% CI): 0.46 (0.25–0.85); *P* for trend = 0.003], CVD [HR (95% CI): 0.56 (0.42–0.76); *P* for trend < 0.001], all-cause mortality [HR (95% CI): 0.48 (0.31–0.76); *P* for trend < 0.001], and CVD mortality [HR (95% CI): 0.28 (0.11–0.67); *P* for trend = 0.002] in women. However, these associations disappeared after adjustment for all potential confounders (**Table 4**). **Table 5** shows that, in men, there was a significant relationship between more frequent consumption of nut and lower risk of IHD [HR (95% CI): 0.54 (0.39–0.74); *P* for trend < 0.001], CVD [HR (95% CI): 0.53 (0.40–0.71); *P* for trend < 0.001], all-cause mortality [HR (95% CI): 0.37 (0.24–0.56); *P* for trend < 0.001], and CVD mortality [HR (95% CI): 0.18 (0.09–0.38); *P* for trend = 0.002]. After full adjustment, we only found a significant inverse association between nut intake and risk of all-cause [HR (95% CI): 0.60 (0.38–0.96); *P* for trend = 0.05] and CVD mortality [HR (95% CI): 0.37 (0.17–0.83); *P* for trend = 0.01].

DISCUSSION

We found that higher nut consumption was inversely related to MI, IHD, stroke, and major CVD events as well as all-cause and CVD mortality in Iranians after 13 years of follow-up in unadjusted model. After adjustment for age and sex, the lower major CVD events, and CVD mortality were still significant among the participants in the highest quartile of nut intake. After full adjustment for potential confounders, nut consumption had

TABLE 2 | Adjusted mean of food intake of study participants across nuts intake quartiles.

	Nut intake				
	Q1	**Q2**	**Q3**	**Q4**	***P*-value***
HVO	8.02 ± 0.027	8.16 ± 0.027	8.15 ± 0.027	8.20 ± 0.027	< 0.001
NHVO	2.55 ± 0.027	2.38 ± 0.024	2.53 ± 0.027	2.63 ± 0.031	< 0.001
Cereals	23.52 ± 0.027	23.58 ± 0.027	23.61 ± 0.027	23.67 ± 0.028	0.002
Red meat	4.03 ± 0.026	4.13 ± 0.028	4.19 ± 0.026	4.30 ± 0.029	< 0.001
Fish	0.43 ± 0.029	0.29 ± 0.023	0.43 ± 0.027	0.57 ± 0.032	< 0.001
Fruits & vegetables	13.10 ± 0.027	13.03 ± 0.028	13.09 ± 0.025	13.38 ± 0.029	< 0.001
Nuts	0.64 ± 0.004	0.66 ± 0.003	0.96 ± 0.004	2.28 ± 0.04	< 0.001
Legumes	2.98 ± 0.027	3.07 ± 0.028	3.03 ± 0.025	3.22 ± 0.029	< 0.001
Fast foods	0.45 ± 0.028	0.42 ± 0.021	0.54 ± 0.023	0.83 ± 0.033	< 0.001
Animal fats	2.42 ± 0.023	2.57 ± 0.028	2.64 ± 0.024	2.89 ± 0.032	< 0.001
Sweets, soft drink, & beverages	3.16 ± 0.022	3.21 ± 0.024	3.38 ± 0.024	3.78 ± 0.034	< 0.001

HVO, Hydrogenated vegetable oil; NHVO, Non-hydrogenated vegetable oil.
*Data are expressed as Mean ± SE; all values are adjusted by age and sex. *Obtained from ANCOVA.*

an inverse association with CVD mortality. Moreover, sensitivity analysis based on sex showed an inverse association between frequent consumption of nuts and risk of CVD mortality and all-cause death, only in men after full adjustment.

Our results are consistent with some other studies. In a meta-analysis of 20 prospective cohort studies, there was an inverse association between nut consumption and incident CVD, IHD, and all-cause mortality. Nevertheless, this study found no relationship between nut intake and stroke events (6). The results of the large prospective cohort of the Nurses' Health Study showed that the frequency of nut consumption had an inverse association with CVD. IHD and all-cause mortality but not with stroke mortality (17). The Physicians' Health Study showed an inverse association between nut consumption and CVD mortality but not with stroke (18). Other studies reported that nut consumption reduced the risk of CVD and stroke (8, 19, 20). In agreement to our finding, a recent cohort study of prospective urban rural epidemiological in 16 countries from five continents indicated that higher nut intake was associated with a lower risk of all-cause, CVD and non-CVD mortality but not MI, stroke, and major CVD risk in low-, middle-, and high-income countries (21). Similar to our results in men, some meta-analysis studies also showed that higher nut consumption lowered the risk of all-cause and/or CVD mortality (7, 8, 22). In line with our finding, the Iowa Women's Health Study in postmenopausal women showed no significant relationship between nut intake and risk of mortality from CHD but a weak association with all-cause death (23). Different results in men and women might be due to increased CVD and its risk factors in postmenopausal years (24). The possible mechanism may be because of losing the protective effect of estrogen on vasomotor tone regulation and its beneficial effects on CVD risk factors in postmenopausal women (25, 26). Pregnancy-related complications and more prevalence of systemic autoimmune diseases in women than men can accelerate the future risk of CVDs (27–29), and therefore, the effect of a healthy diet may be less in women than in men.

Nuts, either a particular type or in general, are beneficial to health and improve various cardiovascular risk factors (9, 10, 30–33). However, it is not exactly clear through which mechanisms nuts affect cardiovascular health (18). Nuts are nutrient-dense foods, and various studies have suggested different compounds, especially α-tocopherol, selenium, phenolic compounds, fiber, carotenoids, and phytosterols, for their health benefits (34).

The nuts' healthy fat profile can be protective against CVD (6). Fat accounts for 45.2–74.7% of the weight of different nuts. The fat content mostly consists of MUFA (mainly oleic acid) and PUFA, mainly alpha-linoleic acid (ALA), with < 4–5% of saturated fatty acids. Compared with marine n-3 PUFAs, plan sources of ALA have less price and more global availability. The review of Fleming and Kris–Etherton indicated a beneficial effect of ALA for the primary and secondary prevention of CVD (35). It has been established that lowering the intake of saturated fatty acids accompanied by higher intakes of MUFA and PUFA reduces CVD risk and mortality (36). It has also been suggested that the favorable effects of nuts on cardiovascular health are due to their anti-inflammatory properties (37). Nevertheless, the studies have not reported consistent results, whereas some studies found no significant relation between nut consumption and inflammatory biomarkers (38, 39); others have found that nut intake improves inflammatory biomarkers (40, 41).

Nuts are also a good source of vegetable protein. Bernstein and colleagues reported that consumption of nuts instead of red meat had an inverse association with the risk of coronary disease after 26 years of follow-up in women (42). Nuts are important sources of amino acid L-arginine, a substrate for endothelium-derived nitric oxide synthesis in the blood vessel wall that acts as a vasodilator and regulates vascular tone (43). It has been shown that nut consumption improves endothelial function (38). Nut fiber content is also notable (4–11 g/100 g). Moreover, nuts are considered as one of the favorable sources of dietary magnesium (44). Guasch-Ferré and colleagues reported an inverse association between CVD and all-cause mortality

TABLE 3 | Multiple adjusted hazard ratios of cardiovascular events according to quartiles of nut intake (time per week).

	Events rate		Crude model	Model 1[a]	Model 2[b]	Model 3[c]
	N	Person-year	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
MI						
MI						
Q1	50	13711.9	1	1	1	1
Q2	45	13198.9	0.94 (0.63–1.40)	0.74 (0.49–1.12)	0.92 (0.61–1.41)	0.98 (0.61–1.59)
Q3	35	13907.8	0.69 (0.45–1.06)	0.73 (0.47–1.14)	0.89 (0.57–1.40)	0.90 (0.56–1.46)
Q4	26	14198.5	0.50 (0.31–0.81)	0.61 (0.38–1)	0.75 (0.46–1.23)	0.77 (0.45–1.30)
P for trend			0.002	0.05	0.28	0.31
PH assumption			0.69	0.81	0.99	0.82
IHD						
Q1	180	13201.3	1	1	1	1
Q2	166	12807.1	0.95 (0.77–1.18)	0.81 (0.66–1.01)	0.98 (0.78–1.21)	1.07 (0.84–1.37)
Q3	133	13518.9	0.72 (0.57–0.90)	0.83 (0.66–1.04)	0.96 (0.76–1.21)	1.01 (0.79–1.28)
Q4	115	13785.5	0.61 (0.48–0.77)	0.80 (0.63–1.02)	0.93 (0.73–1.19)	0.98 (0.76–1.27)
P for trend			<0.001	0.07	0.56	0.81
PH assumption			0.90	0.80	0.65	0.67
Stroke						
Q1	57	13711.5	1	1	1	1
Q2	44	13187.9	0.81 (0.55–1.20)	0.72 (0.48–1.07)	0.91 (0.60–1.36)	1.15 (0.72–1.82)
Q3	27	13950.8	0.46 (0.29–0.73)	0.59 (0.37–0.93)	0.73 (0.46–1.17)	0.86 (0.53–1.41)
Q4	29	14198.1	0.49 (0.31–0.77)	0.72 (0.45–1.13)	0.95 (0.59–1.51)	1.13 (0.68–1.87)
P for trend			<0.001	0.07	0.52	0.96
PH assumption			0.48	0.28	0.35	0.19
CVD						
Q1	237	13008.6	1	1	1	1
Q2	210	12612.9	0.92 (0.76–1.11)	0.79 (0.65–0.95)	0.97 (0.80–1.17)	1.11 (0.89–1.38)
Q3	160	13425.4	0.65 (0.53–0.79)	0.77 (0.63–0.94)	0.91 (0.74–1.11)	0.98 (0.79–1.22)
Q4	144	13657.4	0.57 (0.47–0.70)	0.78 (0.63–0.96)	0.93 (0.75–1.16)	1.02 (0.81–1.28)
P for trend			<0.001	0.013	0.41	0.86
PH assumption			0.84	0.73	0.89	0.79
All-cause mortality						
Q1	129	13899.8	1	1	1	1
Q2	181	13353	1.47 (1.17–1.84)	1.12 (0.89–1.42)	1.21 (0.95–1.53)	1.05 (0.79–1.39)
Q3	88	14039.5	0.67 (0.51–0.88)	0.89 (0.68–1.18)	0.99 (0.75–1.31)	0.91 (0.67–1.22)
Q4	60	14326.1	0.45 (0.33–0.61)	0.77 (0.56–1.05)	0.84 (0.61–1.16)	0.79 (0.56–1.12)
P for trend			<0.001	0.06	0.23	0.12
PH assumption			0.56	0.58	0.60	0.27
CVD mortality						
Q1	60	13899.8	1	1	1	1
Q2	68	13353	1.19 (0.84–1.68)	0.88 (0.61–1.26)	1.11 (0.77–1.60)	1.04 (0.67–1.60)
Q3	36	14039.5	0.59 (0.39–0.89)	0.77 (0.50–1.17)	0.97 (0.63–1.48)	0.91 (0.58–1.44)
Q4	15	14326.1	0.24 (0.14–0.42)	0.41 (0.23–0.73)	0.54 (0.30–0.97)	0.55 (0.30–0.98)
P for trend			<0.001	0.003	0.08	0.08
PH assumption			0.37	0.69	0.48	0.58

Q, Quartile; HR (95% CI), Hazard ratio (95% confidence interval); MI, Myocardial Infraction; IHD, Ischemic heart disease (MI + Sudden cardiac death+ Unstable angina); CVD, Cardiovascular disease.

[a]Adjusted for age(year) and sex (men/women).

[b]Additionally, adjusted for education (illiterate/primary school/more than primary school), residency (urban/rural), smoking status (never/past/current smoker), daily physical activity (METs-min/day), family history of cardiovascular disease (yes/no), diabetes mellitus (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), and aspirin use.

[c]Additionally, adjusted for body mass index (kg/m^2), dietary factor including red meat, fish, fruit and vegetable, hydrogenated and non-hydrogenated vegetable oil, fast food, cereals, legumes, animal fats, sweets, soft drink, and beverages.

TABLE 4 | Multiple adjusted hazard ratios of cardiovascular events according to quartiles of nut intake (time per week) for women.

	Events rate		Crude model	Model 1[a]	Model 2[b]	Model 3[c]
	N	**Person-year**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
MI						
Q1	30	8975.1	1	1	1	1
Q2	10	5823.1	0.52 (0.25–1.06)	0.49 (0.24–1.01)	0.55 (0.27–1.15)	0.52 (0.22–1.21)
Q3	8	6393.6	0.37 (0.17–0.82)	0.49 (0.22–1.08)	0.59 (0.27–1.32)	0.56 (0.24–1.30)
Q4	10	7172.9	0.42 (0.20–0.85)	0.62 (0.30–1.30)	0.80 (0.37–1.72)	0.72 (0.31–1.67)
P for trend			0.004	0.08	0.33	0.31
PH assumption			0.61	0.85	0.81	0.55
IHD						
Q1	100	8655.2	1	1	1	1
Q2	64	5666.7	0.98 (0.72–1.34)	0.95 (0.69–1.30)	1.13 (0.82–1.55)	1.26 (0.87–1.80)
Q3	52	6211.9	0.72 (0.51–1.01)	0.97 (0.69–1.37)	1.10 (0.78–1.55)	1.15 (0.80–1.65)
Q4	50	6948.2	0.61 (0.44–0.86)	0.96 (0.67–1.36)	1.18 (0.83–1.69)	1.22 (0.83–1.79)
P for trend			0.002	0.80	0.36	0.34
PH assumption			0.46	0.37	0.37	0.24
Stroke						
Q1	38	8940.2	1	1	1	1
Q2	16	5791.4	0.65 (0.36–1.17)	0.64 (0.35–1.14)	0.75 (0.42–1.36)	1.14 (0.59–2.17)
Q3	12	6384.1	0.44 (0.23–0.84)	0.54 (0.28–1.05)	0.67 (0.35–1.31)	0.86 (0.43–1.71)
Q4	14	7147.4	0.46 (0.25–0.85)	0.62 (0.33–1.17)	0.74 (0.38–1.44)	0.95 (0.46–1.93)
P for trend			0.003	0.06	0.24	0.77
PH assumption			0.40	0.37	0.21	0.16
CVD						
Q1	138	8511.2	1	1	1	1
Q2	80	5609.1	0.88 (0.67–1.16)	0.85 (0.65–1.12)	1.01 (0.77–1.34)	1.23 (0.90–1.69)
Q3	65	6182.2	0.63 (0.47–0.85)	0.84 (0.62–1.13)	0.97 (0.71–1.31)	1.08 (0.78–1.48)
Q4	64	6880	0.56 (0.42–0.76)	0.86 (0.63–1.16)	1.06 (0.78–1.46)	1.15 (0.82–1.62)
P for trend			<0.001	0.24	0.81	0.48
PH assumption			0.76	0.71	0.84	0.67
All-cause mortality						
Q1	67	9084.2	1	1	1	1
Q2	76	5847.1	1.78 (1.28–2.47)	1.65 (1.19–2.30)	1.73 (1.24–2.41)	1.44 (0.96–2.17)
Q3	28	6409	0.59 (0.38–0.91)	0.95 (0.61–1.48)	1.02 (0.65–1.60)	0.95 (0.58–1.54)
Q4	26	7215.5	0.48 (0.31–0.76)	0.99 (0.62–1.58)	1.17 (0.73–1.87)	1.17 (0.69–1.95)
P for trend			<0.001	0.85	0.61	0.92
PH assumption			0.73	0.86	0.99	0.51
CVD mortality						
Q1	27	9084.2	1	1	1	1
Q2	27	5847.08	1.57 (0.92–2.67)	1.44 (0.84–2.46)	1.68 (0.98–2.90)	1.59 (0.83–3.02)
Q3	14	6409	0.73 (0.38–1.39)	1.18 (0.61–2.27)	1.45 (0.75–2.83)	1.62 (0.78–3.33)
Q4	6	7215.5	0.28 (0.11–0.67)	0.58 (0.23–1.41)	0.84 (0.33–2.12)	1.03 (0.39–2.72)
P for trend			0.002	0.49	0.71	0.53
PH assumption			0.52	0.76	0.55	0.82

Q, Quartile; HR (95% CI), Hazard ratio (95% confidence interval); MI, Myocardial Infraction; IHD, Ischemic heart disease (MI + Sudden cardiac death); CVD, Cardiovascular disease.
[a]Adjusted for age(year).
[b]Additionally, adjusted for education (illiterate/primary school/more than primary school), residency (urban/rural), smoking status (never/past/current smoker), daily physical activity (METs–min/day), family history of cardiovascular disease (yes/no), diabetes mellitus (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), aspirin use, and post-menopause (yes/no).
[c]Additionally, adjusted for body mass index (kg/m^2), dietary factor including red meat, fish, fruit and vegetable, hydrogenated and non–hydrogenated vegetable oil, fast food, cereals, legumes, animal fats, sweets, soft drink, and beverages.

TABLE 5 | Multiple adjusted hazard ratios of cardiovascular events according to quartiles of nut intake (time per week) for men.

	Events rate		Crude model	Model 1[a]	Model 2[b]	Model 3[c]
	N	Person-year	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
MI						
Q1	20	4736.8	1	1	1	1
Q2	35	7375.8	1.12 (0.65–1.95)	0.99 (0.57–1.74)	1.27 (0.72–2.26)	1.47 (0.76–2.81)
Q3	27	7514.2	0.85 (0.48–1.52)	0.98 (0.55–1.75)	1.19 (0.66–2.16)	1.26 (0.67–2.37)
Q4	16	7025.6	0.54 (0.28–1.04)	0.68 (0.35–1.33)	0.82 (0.42–1.62)	0.88 (0.43–1.81)
P for trend			0.03	0.29	0.57	0.60
PH assumption			0.80	0.85	0.79	0.96
IHD						
Q1	80	4546.1	1	1	1	1
Q2	102	7140.3	0.81 (0.61–1.09)	0.72 (0.53–0.96)	0.88 (0.65–1.20)	0.95 (0.67–1.35)
Q3	81	7307	0.63 (0.46–0.85)	0.72 (0.53–0.98)	0.85 (0.62–1.16)	0.89 (0.64–1.25)
Q4	65	6837.3	0.54 (0.39–0.74)	0.68 (0.49–0.95)	0.79 (0.56–1.11)	0.84 (0.59–1.21)
P for trend			<0.001	0.03	0.18	0.31
PH assumption			0.54	0.63	0.69	0.62
Stroke						
Q1	19	4771.2	1	1	1	1
Q2	28	7396.5	0.96 (0.53–1.71)	0.78 (0.43–1.40)	1.05 (0.57–1.95)	0.98 (0.49–2.00)
Q3	15	7566.7	0.50 (0.25–0.98)	0.64 (0.32–1.25)	0.81 (0.41–1.63)	0.80 (0.38–1.69)
Q4	15	7050.7	0.53 (0.27–1.05)	0.83 (0.42–1.64)	1.15 (0.57–2.33)	1.29 (0.59–2.79)
P for trend			0.01	0.44	0.98	0.75
PH assumption			0.94	0.58	0.74	0.50
CVD						
Q1	99	4497.4	1	1	1	1
Q2	130	7003.8	0.85 (0.65–1.10)	0.73 (0.56–0.95)	0.93 (0.71–1.23)	0.99 (0.73–1.36)
Q3	96	7243.2	0.60 (0.45–0.79)	0.71 (0.53–0.94)	0.85 (0.63–1.13)	0.89 (0.65–1.21)
Q4	80	6777.4	0.53 (0.40–0.71)	0.70 (0.52–0.95)	0.86 (0.63–1.16)	0.92 (0.66–1.28)
P for trend			<0.001	0.02	0.24	0.47
PH assumption			0.54	0.43	0.48	0.38
All-cause mortality						
Q1	62	4815.5	1	1	1	1
Q2	105	7505.9	1.09 (0.79–1.49)	0.81 (0.59–1.11)	0.89 (0.63–1.24)	0.80 (0.54–1.19)
Q3	60	7630.5	0.61 (0.42–0.86)	0.77 (0.54–1.10)	0.89 (0.62–1.28)	0.81 (0.55–1.20)
Q4	34	7110.6	0.37 (0.24–0.56)	0.59 (0.39–0.90)	0.64 (0.41–0.98)	0.60 (0.38–0.96)
P for trend			<0.001	0.02	0.06	0.05
PH assumption			0.85	0.76	0.63	0.59
CVD mortality						
Q1	33	4815.5	1	1	1	1
Q2	41	7505.9	0.80 (0.51–1.27)	0.59 (0.37–0.94)	0.78 (0.47–1.28)	0.71 (0.39–1.30)
Q3	22	7630.5	0.42 (0.24–0.72)	0.54 (0.32–0.93)	0.70 (0.40–1.23)	0.61 (0.33–1.11)
Q4	9	7110.6	0.18 (0.09–0.38)	0.30 (0.14–0.63)	0.38 (0.18–0.82)	0.37 (0.17–0.83)
P for trend			<0.001	0.001	0.01	0.01
PH assumption			0.55	0.69	0.70	0.55

Q, Quartile; HR (95% CI), Hazard ratio (95% confidence interval); MI, Myocardial Infraction; IHD, Ischemic heart disease (MI + Sudden cardiac death); CVD, Cardiovascular disease.
[a]*Adjusted for age (year).*
[b]*Additionally, adjusted for education (illiterate/primary school/more than primary school), residency (urban/rural), smoking status (never/past/current smoker), daily physical activity (METs–min/day), family history of cardiovascular disease (yes/no), diabetes mellitus (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), and aspirin use.*
[c]*Additionally, adjusted for body mass index (kg/m^2), dietary factor including red meat, fish, fruit and vegetable, hydrogenated and non–hydrogenated vegetable oil, fast food, cereals, legumes, animal fats, sweets, soft drink, and beverages.*

risk and magnesium intake (19). However, in the Physicians' Health Study, after additional adjustment for magnesium and fiber intake, the inverse association between nut consumption and mortality did not change, leading the authors to suggest that the favorable effects of nuts on mortality may be exerted through other mechanisms (18).

A newer but less investigated hypothesis is the nut–microbiome interaction in the human gut. On the one hand, it has been suggested that some harmful microbial species in the gut microbiome may play a role in the pathogenesis of atherosclerosis through producing a pro-atherogenic agent, trimethylamine-N-oxide, from foods such as red meat and eggs (45). On the other hand, nuts are considered as potential prebiotics. Thus, nut consumption ameliorates the growth of health beneficial microbial species (46). Studies have shown favorable effects of nut consumption on the gut microbiome and also on cardiometabolic health as a result of nut–microbiome interaction (47). However, only a limited number of studies have investigated the nut–microbiome interaction, and for a better understanding, further studies are needed.

Strengths and Limitations

Our study had some strength. To the best of our knowledge, it was the first study in the Middle East that investigated the relationship between nut consumption and CVD events. The prospective design of the present study strengthened the causal inference because the assessment of dietary intake of nuts was conducted before the incidence of the events and had three measurements. The study population was from three districts in Iran that offered us a heterogeneous socioeconomic status and a wide range of dietary intakes.

The limitations of this study should be considered. Although a validated FFQ was used for dietary data collection, we cannot exclude the existence of misclassification, similar to all epidemiologic studies. Moreover, our FFQ did not provide us with data on portion sizes. Therefore, we did not have any data about the total energy intake. Ideally, 24-h recalls should have also been acquired and the data combined for ideal nutritional intake ascertainment. Despite controlling for several confounders, we cannot ignore the effect of residual confounding. Finally, there were no data of other comorbidities responsible for well-known causes of death such as cancer and cerebral stroke and a comparison with the incidence of CVD.

CONCLUSION

We concluded an inverse association between nut intake (including walnuts, almonds, pistachios, and hazelnuts) and lower risk of CVD events through an unadjusted model; however, it disappeared after full adjustment for potential confounders except for CVD mortality in men and total population and all-cause mortality only in men. To investigate the effect of individual types of nuts, such as walnuts, pistachios, almonds, etc., and different preparation methods (raw, roasted, and/or salted) on CVD risk and mortality, we need studies with longer follow-up periods.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Isfahan Cardiovascular Research Center, WHO Collaborating Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NM, NS, MS, and HR designed research. FS and NG conducted research. NM and NG wrote the paper. JS-S provided major changes in the paper. RH analyzed data. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol.* (2017) 70:1–25. doi: 10.1016/j.jacc.2017.04.052
2. Jousilahti P, Laatikainen T, Peltonen M, Borodulin K, Mannisto S, Jula A, et al. Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years: population based observational study. *BMJ.* (2016) 352:i721. doi: 10.1136/bmj.i721
3. Martin N, Germano R, Hartley L, Adler AJ, Rees K. Nut consumption for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* (2015) 9:Cd011583. doi: 10.1002/14651858.CD011583
4. Patnode CD, Evans CV, Senger CA, Redmond N, Lin JS. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults without known cardiovascular disease risk factors: updated evidence report and systematic review for the us preventive services task force. *JAMA.* (2017) 318:175–93. doi: 10.1001/jama.2017.3303
5. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American heart association. *Circulation.* (2017) 136:e1–23. doi: 10.1161/CIR.0000000000000510
6. Mayhew A J dSRJ, Meyre D, Anand S S, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. *Br J Nutr.* (2016) 115:212–25. doi: 10.1017/S0007114515004316

7. Grosso G, Yang J, Marventano S, Micek A, Galvano F, Kales SN. Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies. *Am J Clin Nutr.* (2015) 101:783–93. doi: 10.3945/ajcn.114.099515
8. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med.* (2016) 14:207. doi: 10.1186/s12916-016-0730-3
9. Askari G, Yazdekhasti N, Mohammadifard N, Sarrafzadegan N, Bahonar A, Badiei M, et al. The relationship between nut consumption and lipid profile among the Iranian adult population; Isfahan healthy heart program. *Eur J Clin Nutr.* (2013) 67:385–9. doi: 10.1038/ejcn.2013.21
10. Yazdekhasti N, Mohammadifard N, Sarrafzadegan N, Mozaffarian D, Nazem M, Taheri M. The relationship between nut consumption and blood pressure in an Iranian adult population: Isfahan healthy heart program. *Nutr Metab Cardiovasc Dis.* (2013) 23:929–36. doi: 10.1016/j.numecd.2013.04.014
11. Sarrafzadegan N, Talaei M, Sadeghi M, Kelishadi R, Oveisgharan S, Mohammadifard N, et al. The Isfahan cohort study: rationale, methods and main findings. *J Hum Hypertens.* (2011) 25:545–53. doi: 10.1038/jhh.2010.99
12. Yu E, Malik VS, Hu FB. Cardiovascular disease prevention by diet modification: JACC health promotion series. *J Am Coll Cardiol.* (2018) 72:914–26. doi: 10.1016/j.jacc.2018.02.085
13. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA council on epidemiology and prevention; AHA statistics committee; world heart federation council on epidemiology and prevention; the European society of cardiology working group on epidemiology and prevention; centers for disease control and prevention; and the national heart, lung, and blood institute. *Circulation.* (2003) 108:2543–9. doi: 10.1161/01.CIR.0000100560.46946.EA
14. Mohammadifard N, Talaei M, Sadeghi M, Oveisegharan S, Golshahi J, Esmaillzadeh A, et al. Dietary patterns and mortality from cardiovascular disease: Isfahan cohort study. *Eur J Clin Nutr.* (2017) 71:252–8. doi: 10.1038/ejcn.2016.170
15. Talaei M, Rabiei K, Talaei Z, Amiri N, Zolfaghari B, Kabiri P, et al. Physical activity, sex, and socioeconomic status: a population based study. *ARYA Atheroscler.* (2013) 9:51–60.
16. Jakes RW, Day NE, Luben R, Welch A, Bingham S, Mitchell J, et al. Adjusting for energy intake–what measure to use in nutritional epidemiological studies? *Int J Epidemiol.* (2014) 33:1382–6. doi: 10.1093/ije/dyh181
17. Bao Y, Han J, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, et al. Association of nut consumption with total and cause-specific mortality. *New Engl J Med.* (2013) 369:2001–11. doi: 10.1056/NEJMoa1307352
18. Hshieh TT, Petrone AB, Gaziano JM, Djousse L. Nut consumption and risk of mortality in the physicians' health study. *Am J Clin Nutr.* (2015) 101:407–12. doi: 10.3945/ajcn.114.099846
19. Guasch-Ferre M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, et al. Nut consumption and risk of cardiovascular disease. *J Am Coll Cardiol.* (2017) 70:2519–32. doi: 10.1016/j.jacc.2017.09.035
20. Zhou D, Yu H, He F, Reilly KH, Zhang J, Li S, et al. Nut consumption in relation to cardiovascular disease risk and type 2 diabetes: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr.* (2014) 100:270–7. doi: 10.3945/ajcn.113.079152
21. de Souza RJ, Dehghan M, Mente A, Bangdiwala SI, Ahmed SH, Alhabib KF, et al. Association of nut intake with risk factors, cardiovascular disease, and mortality in 16 countries from 5 continents: analysis from the prospective urban and rural epidemiology (PURE) study. *Am J Clin Nutr.* (2020) 112:208–19. doi: 10.1093/ajcn/nqaa108
22. van den Brandt PA, Schouten LJ. Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis. *Int J Epidemiol.* (2015) 44:1038–49. doi: 10.1093/ije/dyv039
23. Ellsworth JL, Kushi LH, Folsom AR. Frequent nut intake and risk of death from coronary heart disease and all causes in postmenopausal women: the Iowa Women's health study. *Nutr Metab Cardiovasc Dis.* (2001) 11:372–7.
24. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *Am Coll Cardiol.* (2009) 54:1561–75. doi: 10.1016/j.jacc.2009.04.098
25. Bittner V. Menopause, age, and cardiovascular risk: a complex relationship. *J Am Coll Cardiol.* (2009) 54:2374–5. doi: 10.1016/j.jacc.2009.10.008
26. Westerman S, Wenger NK. Women and heart disease, the underrecognized burden: sex differences, biases, and unmet clinical and research challenges. *Clin Sci.* (2016) 130:551–63. doi: 10.1042/CS20150586
27. Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the avon longitudinal study of parents and children. *Circulation.* (2012) 125:1367–80. doi: 10.1161/CIRCULATIONAHA.111.044784
28. Intapad S, Alexander BT. Future cardiovascular risk: interpreting the importance of increased blood pressure during pregnancy. *Circulation.* (2013) 127:668–9. doi: 10.1161/CIRCULATIONAHA.112.000677
29. Shoenfeld Y, Gerli R, Doria A, Matsuura E, Cerinic MM, Ronda N, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation.* (2005) 112:3337–47. doi: 10.1161/CIRCULATIONAHA.104.507996
30. Hassannejad R, Mohammadifard N, Kazemi I, Mansourian M, Sadeghi M, Roohafza H, et al. Long-term nuts intake and metabolic syndrome: a 13-year longitudinal population-based study. *Clin Nutr.* (2019) 38:1246–52. doi: 10.1016/j.clnu.2018.05.006
31. Micha R, Shulkin ML, Penalvo JL, Khatibzadeh S, Singh GM, Rao M, et al. Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: systematic reviews and meta-analyses from the nutrition and chronic diseases expert group (NutriCoDE). *PLoS ONE.* (2017) 12:e0175149. doi: 10.1371/journal.pone.0175149
32. Mohammadifard N, Yazdekhasti N, Stangl GI, Sarrafzadegan N. Inverse association between the frequency of nut consumption and obesity among Iranian population: Isfahan healthy heart program. *Eur J Nutr.* (2015) 54:925–31. doi: 10.1007/s00394-014-0769-x
33. Mohammadifard N, Haghighatdoost F, Mansourian M, Hassannejhad R, Sadeghi M, Roohafza H, et al. Long-term association of nut consumption and cardiometabolic risk factors. *Nutr Metab Cardiovasc Dis.* (2019) 29:972–82. doi: 10.1016/j.numecd.2019.04.014
34. de Souza RGM, Schincaglia RM, Pimentel GD, Mota JF. Nuts and human health outcomes: a systematic review. *Nutrients.* (2017) 9:1311. doi: 10.3390/nu9121311
35. Fleming JA, Kris-Etherton PM. The evidence for α-linolenic acid and cardiovascular disease benefits: comparisons with eicosapentaenoic acid and docosahexaenoic acid. *Adv Nutr.* (2014) 5:863S−76S. doi: 10.3945/an.114.005850
36. Clifton PM, Keogh JB. A systematic review of the effect of dietary saturated and polyunsaturated fat on heart disease. *Nutr Metab Cardiovasc Dis.* (2017) 27:1060–80. doi: 10.1016/j.numecd.2017.10.010
37. Salas-Salvado J, Casas-Agustench P, Murphy MM, Lopez-Uriarte P, Bullo M. The effect of nuts on inflammation. *Asia Pac J Clin Nutr.* (2008) 17(Suppl. 1):333–6.
38. Neale EP, Tapsell LC, Guan V, Batterham MJ. The effect of nut consumption on markers of inflammation and endothelial function: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open.* (2017) 7:e016863. doi: 10.1136/bmjopen-2017-016863
39. Sauder KA, McCrea CE, Ulbrecht JS, Kris-Etherton PM, West SG. Effects of pistachios on the lipid/lipoprotein profile, glycemic control, inflammation, and endothelial function in type 2 diabetes: a randomized trial. *Metabolism.* (2015) 64:1521–9. doi: 10.1016/j.metabol.2015.07.021
40. Gulati S, Misra A, Pandey RM, Bhatt SP, Saluja S. Effects of pistachio nuts on body composition, metabolic, inflammatory and oxidative stress parameters in Asian Indians with metabolic syndrome: a 24-wk, randomized control trial. *Nutrition.* (2014) 30:192–7. doi: 10.1016/j.nut.2013.08.005
41. Yu Z, Malik VS, Keum N, Hu FB, Giovannucci EL, Stampfer MJ, et al. Associations between nut consumption and inflammatory biomarkers. *Am J Clin nutr.* (2016) 104:722–8. doi: 10.3945/ajcn.116.134205
42. Bernstein AM, Sun Q, Hu FB, Stampfer MJ, Manson JE, Willett WC. Major dietary protein sources and risk of coronary heart disease in women. *Circulation.* (2010) 122:876–83. doi: 10.1161/CIRCULATIONAHA.109.915165

43. Lorin J, Zeller M, Guilland JC, Cottin Y, Vergely C, Rochette L. Arginine and nitric oxide synthase: regulatory mechanisms and cardiovascular aspects. *Mol Nutr Food Res.* (2014) 58:101–16. doi: 10.1002/mnfr.201300033
44. Ros E. Nuts CVD. *Br J Nutr.* (2015) 113:S111–20. doi: 10.1017/S0007114514003924
45. Vinke PC, El Aidy S, van Dijk G. The role of supplemental complex dietary carbohydrates and gut microbiota in promoting cardiometabolic and immunological health in obesity: lessons from healthy non-obese individuals. *Front Nutr.* (2017) 4:34. doi: 10.3389/fnut.2017.00034
46. Lamuel-Raventos RM, Onge MS. Prebiotic nut compounds and human microbiota. *Crit Rev Food Sci Nutr.* (2017) 57:3154–63. doi: 10.1080/10408398.2015.1096763
47. Hernandez-Alonso P, Canueto D, Giardina S, Salas-Salvado J, Canellas N, Correig X, et al. Effect of pistachio consumption on the modulation of urinary gut microbiota-related metabolites in prediabetic subjects. *J Nutr Biochem.* (2017) 45:48–53. doi: 10.1016/j.jnutbio.2017.04.002

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Dietary Diversity and Its Contribution in the Etiology of Maternal Anemia in Conflict Hit Mount Cameroon Area: A Cross-Sectional Study

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Background: In the Mount Cameroon area, maternal anemia remains a major public health concern. We hypothesized that nutrient inadequacy may account for the level of anemia in pregnancy. Thus, this study examined the relative effect of dietary diversity on maternal anemia in the study area.

Methods: A total of 1,014 consenting pregnant women were enrolled in this cross-sectional study. Information on socio-demographic, antenatal characteristics, malaria and anemia control measures were documented. Dietary diversity (DD) was evaluated using the 24-h recall method and hemoglobin (Hb) levels (g/dl) measured using a portable Hb meter. Malaria parasitaemia was diagnosed by blood microscopy. Anemia status was trimester specific. Logistic regression analysis was used determine predictors of maternal anemia.

Results: Among the pregnant women enrolled, the mean DD score was 3.5±0.8 SD and only 10.4% had adequate dietary diversity. Anemia prevalence was 40.9%. Majority of the women consumed starchy staples (99.3%) while least consumed foods were dairy (4.5%), eggs (8.3%), fruits and vegetable (vitamin A-rich) (8.6%). A significant lower prevalence of anemia was associated with intake of dairy ($P < 0.001$), animal protein ($P = 0.006$), vitamin A-rich fruits and vegetables ($P < 0.001$). Furthermore, mean Hb levels were higher ($P < 0.001$) among women with diverse diets (12.39 ± 1.34) than in those with less diverse diets (10.85 ± 1.33). Predictors of anemia were as follows: study setting [Odd Ratio (OR) = 1.4, 95% CI: 1.07-1.94], occupation (OR = 1.9, 95% CI: 1.16-3.43), number of clinic visits (OR = 1.9, 95% CI: 1.27-2.91), trimester of pregnancy (OR = 3.2, 95% CI: 1.45-7.38), malaria parasitaemia (OR = 1.8, 95% CI: 1.33-2.68), out of home eating (OR = 1.4, 95% CI: 1.03-2.13), and DD (OR = 9.8, 95% CI: 4.56-20.80). The attributable risk of anemia due to dietary diversity was 82.9%.

Conclusion: In the study area, DD is a major risk factor for maternal anemia. This finding underscores the importance of content specific nutrition education during clinic visits to improve intake of protein and iron-rich food in anemia prevention.

Keywords: dietary diversity, anemia, pregnant women, Mount Cameroon area, cross-sectional study

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INTRODUCTION

Pregnancy is characterized by anatomical, physiological, and biochemical changes in the woman's body. These changes are accompanied by an increase in dietary energy and nutrient requirement to support these maternal adaptations during pregnancy as well as for nutrient delivery to the fetus. Thus, for adequate nutrient uptake, a pregnant woman's diet should composed of carbohydrates, protein, vitamins, minerals, and water (1). Notwithstanding, in low- and middle-income countries (LMICs) many women living in under resourced environments, suffer from undernutrition and pregnancy presents an additional burden on the women's nutritional requirement to meet the needs of both mother and the developing fetus. Consequences of inadequate nutrient intake in pregnancy include; low birth weight, intrauterine growth restriction as well as increased risk of maternal morbidity and mortality (2). More so, inadequate consumption of energy or specific nutrients during this "critical period" may contribute to deficits in the child's development as well as compromise survival later in adult life (3).

Dietary diversity is defined as increase in the variety of foods consumed over a specific reference period (4). A diverse diet not only ensures adequate intake of essential nutrients (5), it is known to boost the immune system thereby decreasing susceptibility to malaria parasitaemia in endemic areas (6, 7). Minimum dietary diversity for women (MDD-W) is a proxy indicator of dietary nutrient adequacy. This dichotomous indicator is the consumption of five or more food out of ten food groups (4, 8, 9). In LMICs, insufficient nutrient uptake and anemia among pregnant women are associated with monotonous starchy based diets with infrequent consumption of animal products and seasonal consumption of fruits and vegetables (8, 10). Foods rich in iron and vitamin A are known to reduce maternal anemia (11–13). Socioeconomic and cultural practices of the society in which individuals live may influence their dietary behavior (14). During antenatal care (ANC) clinics, pregnant women are educated on the health benefit of good nutrition practice in reducing anemia. Although each pregnant woman is given iron/folic acid (IFA) supplementation, they are encouraged to consume diverse food groups for adequate nutrient uptake to support pregnancy. However, this is not often the case, as financial constraints may delay early commencement of antenatal care and uptake of hematinics as well as hinder affordability of a diet rich in digestible forms of iron (15).

Globally, anemia is a major threat, affecting ∼38.2 % of pregnant women (16) with those in LMICs accounting for 43% of the burden (17). Anemia causes are multi-factorial and contributing factors vary with geographical setting, season and dietary practice (18). A diet deficient in essential nutrients (iron, folate, vitamins A and B12) is the major cause of nutritional anemia (19) with the most prevalent being iron deficiency anemia (20). Hemoglobinopathies may increase risk of maternal anemia (21). Besides nutrient intake, other factors associated with anemia include maternal age, trimester of pregnancy (22), parity levels and ANC visit (23).

In Cameroon, antenatal care interventions such as health and nutrition-related education, screening and treatment of anemia, intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP), IFA supplementation and distribution of insecticide treated nets (ITNs) have been intensified to reduce anemia and malaria in pregnancy. In spite of these interventions, anemia severity (41–53.3%) has not significantly decreased over the years in semi-urban and urbanized towns in the Mount Cameroon area (24, 25). Findings from a baseline study in the area suggest nutrient deficiency as a major contributor of anemia among pregnant women (26). Thus, we hypothesized that inadequate dietary intake may play a critical role in anemia in our setting. In this study, we described diet diversity characteristics and evaluated its contribution to anemia among pregnant women reporting for antenatal care in some medical facilities located in semi-urban and urbanized settings in the Mount Cameroon area. Findings of this study will identify contributory factors of maternal anemia and hence the designing of sustainable intervention strategies targeted at reducing anemia in pregnancy.

MATERIALS AND METHODS

Study Area

The study was carried out at ANC units in four medical facilities from two health districts: Tiko health district; Tiko Holforth health center (THHC) and Mutengene Medical Center (MMC) and Buea Health District; Buea Integrated Health Center (BIHC) and Mount Mary Hospital (MMH). These antenatal clinics were selected based on the type of locality; semi-urban (Mutengene and Tiko) and urbanized (Buea) settings.

Tiko is a semi-urban settlement located at 18 to 80 m above sea level (asl) between latitude 009°21′57.3″N and longitude 04°04′22.0″E with a population size of 147,423 inhabitants (27). The town has daily mean temperature ranging between 28° and 33°C, a relative humidity of 83.1% and an mean rainfall of 4,524 mm (28). This area is characterized by the presence of a local seaport that allows for fishing, import, and export of goods between neighboring countries. The rich volcanic soil encourages farming activities and industrial agriculture. This Health District hosts the Cameroon Development Corporation (CDC) plantations where banana, rubber and oil palm are cultivated and exported.

Mutengene is a road junction, semi-urban town located at 240 meters above sea level (asl) between latitude 009°18′52.8″N and longitude 04°05′37.2″E with 40,000 inhabitants. Farming and business constitute the mainstay of the town. The mean temperature and relative humidity are 25.08°C and 83%, respectively [Cameroon Development Corporation (CDC) weather record].

Buea is an urbanized town located at 896 m asl between latitude 4°9′9.72″N and longitude 9°14′27.6″E with a population of 43,000 inhabitants. Buea is characterized by mean temperature range of 18–27°C, relative humidity of 80% and rainfall of 4,000 mm (29). Common occupational activities in this area include teaching in the public and private educational institutions, civil servants, and business owners (30).

The Mount Cameroon area has two distinct seasons: a rainy season, which spans from March to October with maximum rainfall (2000–10,000 mm) in August and September. The dry season lasts for 4 months (November-February) (31). *Plasmodium falciparum* is the major plasmodium species in the area (32, 33).

THHC, MMC, BIHC and MMH offer services for antenatal care, preventive, curative, and delivery at low costs (34). In the study area, nearly all pregnant women attend ANC clinic at least once, but only 62% complete the recommended four or more ANC visits, with majority (73%) registering for ANC initiation in the second trimester of pregnancy (25). Pregnant women living in the Mount Cameroon area are commonly exposed to *P. falciparum* infection (peripheral blood infection) with prevalence range of 13.4–22.4% (24, 35). In Cameroon, the transition from a two to three doses of IPTp-SP policy took place in 2012 (36). Recent findings revealed a significant improvement in the uptake of ≥3 doses of SP in this area with a coverage of 47% (25). Additional benefits of repeated doses of SP in combination with ITNs use in reducing peripheral malaria parasitaemia and maternal anemia have been reported in the area (24). Though malaria-related anemia has decreased over the years, about 75% of the anemic cases are non-malaria related (26).

Sampling Design, Population, and Sampling Procedure

A descriptive and analytical cross-sectional study comprising of pregnant women attending ANC visit in four health facilities in semi-urban and urbanized settings in the Mount Cameroon area was carried out from July, 2018 to September, 2019.

The population sample size was determined using the Cochrane formulae for cross-sectional studies (37)

$$N = \frac{Z^2 P(1-P)}{d^2}$$

The sample size N was calculated based on the maternal anemia prevalence (p) of ∼40% (24), a margin of error of 5%, 95% confidence interval (CI), and an attrition rate of 10%. The minimum sample size per health district was 408. A non-probability sampling technique was used to enroll consenting pregnant women between the ages 15–49 years reporting for ANC initiation or follow-up. Recruitment involved approaching participants who were available (convenience) and after informing them of the study, those who met the eligibility criteria and gave their consent were enrolled consecutively. Pregnant women with reported history of hypertensive disorders, diabetes, or preeclampsia were excluded from the study.

Questionnaire Survey

An interview-guided structured questionnaire was used to record information pertaining to maternal socio-demographic characteristics, obstetric data, IPTp-SP, IFA uptake, ITN usage, medical history as well as dietary intake 24-h prior to survey. Adequate IPTp-SP uptake was defined as uptake of at least 3 or more SP doses as stipulated by the World Health Organization (36). Complete ANC attendance was defined as four or more clinic visits during pregnancy (38). The questionnaire on MDD-W guided obtention of data on dietary diversity (4).

Dietary Assessment

Minimum dietary diversity was assessed qualitatively using the 24-h recall method. This reference period was considered appropriate because it is less prone to recall error, less cumbersome for the respondents and corresponds with the time period used in several studies on DD (39). Each study participant was asked to list and describe the exact composition of all food items and drinks consumed (day or night) prior to survey (40). Foods consumed out of the home during the specified period were assessed.

Dietary diversity scores were estimated using 10 food groups which include; (1) grains, white roots, tubers and plantains (starchy staples), (2) pulses (beans, peas and lentils), (3) nuts and seeds, (4) dairy products, (5) meat, poultry and fish, (6) eggs, (7) dark green leafy vegetables, (8) vitamin A-rich food group (fruits and vegetables), (9) vegetables and (10) fruits. Consumption of food within any food group, equivalent to one tablespoon, was assigned a score (4, 39). Furthermore, the total score per participant was calculated as the sum total of the scores for the different food groups consumed (41). Women who consumed < 5 food groups were considered to have a poor DD (score range: 1–4) and those who consumed at least 5 food groups were considered to have a good DD (score range: 5–10) (4).

Sample Collection and Laboratory Analysis

Venous blood sample (2 ml) was collected from each pregnant woman by a licensed laboratory technician using standard procedures. Hemoglobin (Hb) levels were determined using a portable Urit12® Hb meter (URIT Medical Electronics Co., Ltd. Guangxi, China) and values documented to the nearest 0.1 g/dl. Anemia status was trimester specific and defined as follows; Hb <11.0 g/dl for women in the first (1–13 weeks of gestation) and third (≥27 weeks of gestation) trimesters and Hb <10.5 g/dl for those in the second trimester (14–26 weeks of gestation) (38, 42, 43). Blood films were prepared for the detection of malaria parasitaemia (44). Briefly, two drops of whole blood were placed on a labeled glass slide, thick and thin blood smears were prepared and air-dried. The thin blood films were fixed in absolute methanol for 30 s and later both films were stained with 10% Giemsa for 15 min and examined under a light microscope by two independent microscopists. A smear was declared positive for malaria parasitaemia if any asexual forms of *P. falciparum* were identified after examining 100 high power fields (44).

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Review Board of the University of Buea (Ref No: 2019/967-05/UB/SG/IRB/FHS). Administrative authorization was obtained from the South West Regional Delegation of Public Health, Buea. Participation in the study was voluntary and individuals who gave their consent signed a written consent form.

Data Analysis

Data was analyzed using IBM SPSS statistics software version 20. For continuous variables, the Kolmogorov-Smirnov test was used to check for normality and variables summarized into mean and standard deviation (SD). Proportions were used to describe categorical variables. Student *t*-test was used to compare the mean Hb levels per MDD-W categories. Pearson Chi-square test (χ^2) was used to evaluate differences in proportions.

The main outcome (dependent) variable was anemia. Covariates (independent variables) included; maternal age, setting, marital status, occupation, educational level, climatic season of enrolment, gravidity status, trimester of pregnancy, number of ANC visits, malaria parasite status, SP doses, ITN usage, out of home eating, and MDD-W. Prior to multivariable regression analysis, confounders were checked for collinearity by examining the variance inflation factor (VIF). Multicollinearity was absent with all covariates having a VIF < 2. Binary logistic regression model (enter method) was run to examine the independent effect of covariates on anemia status. All 1,014 participants were included in the model. The attributable risk (AR%) of anemia due to dietary diversity was calculated using an established method (45). Significant levels were set at 95% confidence interval (CI); $P < 0.05$.

RESULTS

Characteristics of the Study Population

Of the 1,014 consenting pregnant women enrolled, 79 were from THHC, 430 from MMC, 163 from MMH and 342 from BIHC. In general, 50.2 and 49.8% of the participants were from Tiko health district (THD) and Buea health district (BHD), respectively. With respect to gestational age, majority of these women were in their second (41.2%) and third (55.4%) trimesters of pregnancy (**Table 1**). Mean (±SD) maternal age was 26.7 ± 5.48 (range;15-46 years). Trading (business) was the most common occupational activity (43.6%), while only 14.6% were civil servants. About 42% were housewives, farmers, or students. More than half (62.2%) of the women were married. The highest level of education attained by most (53.1%) of the women was secondary education. Unexpectedly, majority of women attended < 4 ANC visits (77.3%) and only 12.2% had adequate IPTp-SP uptake (≥3 SP doses). Maternal age, educational level, occupational status, gravidity, trimester of pregnancy, IPTp-SP uptake and ITN usage varied between the two health districts. Meanwhile, marital status, ANC attendance and malaria parasite status were comparable between health districts (**Table 1**).

TABLE 1 | Baseline characteristics of the study population per study setting.

Variables	Categories	THD % (*n*)	BHD % (*n*)	Total % (*N*)	*P* value
Age (15-46 years)	≤20	19.6 (100)	8.9 (45)	14.3 (145)	<0.001
	21-25	29.7 (151)	28.5 (144)	29.7 (295)	
	>25	50.7 (258)	62.6 (316)	56.6 (574)	
Marital Status	Single	39.7 (202)	35.8 (181)	37.8 (383)	0.207
	Married	60.3 (307)	64.2(324)	62.2 (631)	
Educational level	Primary	28.3 (144)	11.9 (60)	20.1 (204)	<0.001
	Secondary	58.0 (295)	48.1 (243)	53.1 (538)	
	Tertiary	13.8 (70)	40.0 (202)	26.8 (272)	
Occupation status	Housewife	18.7 (95)	14.3 (72)	16.5 (167)	<0.001
	Farmer	9.4 (48)	2.2 (11)	5.8 (59)	
	Business	47.2 (240)	40.0 (202)	43.6 (442)	
	Students	14.9 (76)	24.2 (122)	19.5 (198)	
	Civil servants	9.8 (50)	19.4 (98)	14.6 (14.8)	
No of ANC	<4 clinic visits	77.6 (395)	77.0 (389)	77.3 (784)	0.827
	≥4 clinic visits	22.4 (114)	23.0 (116)	22.7 (230)	
Gravidity	Primigravid	31.2 (159)	38.0 (192)	34.6 (351)	0.047
	Secundigravid	25.3 (129)	25.1 (127)	25.2 (256)	
	Multigravid	43.4 (221)	36.8 (186)	40.1 (407)	
Trimester of pregnancy	First trimester	2.0 (10)	5.0 (25)	3.5 (35)	0.033
	Second trimester	41.7 (212)	40.8 (206)	41.2 (418)	
	Third trimester	56.4 (287)	54.3 (274)	55.3 (561)	
IPTp-SP dose uptake	1 dose	64.6 (329)	70.7 (357)	67.7 (686)	0.003
	2 doses	19.6 (100)	20.6 (104)	20.1 (204)	
	≥3 doses	15.7 (80)	8.7 (44)	12.2 (124)	
Women who own ITN	No	28.7 (146)	28.9 (146)	28.8 (292)	0.936
	Yes	71.3 (363)	71.1 (359)	71.2 (722)	
ITN usage	No	53.2 (271)	68.7 (347)	60.9 (618)	<0.001
	Yes	46.8 (238)	31.3 (158)	39.1 (396)	
IFA uptake	No	29.5 (150)	27.5 (139)	28.5 (289)	0.493
	Yes	70.5 (359)	72.5 (366)	71.5 (725)	
Malaria status	Negative	81.9 (417)	82.6 (417)	82.2 (834)	0.787
	Positive	18.1 (92)	17.4 (88)	17.8 (180)	
MDD-W	< 5 food groups	91.0 (463)	88.3 (446)	89.6 (909)	0.167
	≥ 5 food groups	9.0 (46)	11.7 (59)	10.4 (105)	

ANC, antenatal clinic; IPTp-SP, intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine; ITN, insecticide treated net; IFA, iron folic acid; MDD-W, minimum dietary diversity for women of reproductive age.

Dietary Diversity

The mean (±SD) MDD score of the study population was 3.57± 0.82 (score range: 1–7). Of the 1,014 women, 10.4% (95% CI: 8.6–12.4; $n = 105$) met the FAO criteria for MDD-W, whereas, 89.6% (95% CI: 87.7-91.4; $n = 909$) of the participants consumed diets with < 5 food groups. Considering the different foods consumed 24-h prior to study, nearly all women (99.3%) ate starchy staples, more than three-quarters (86.2%) consumed animal products (meat, poultry, fish), two-third (67.5%) of the women consumed other vegetables. Green leafy vegetables, fruits, pulses, nuts and seeds were consumed by 29.5, 21.4, 17.9, and 13.7% of the participants, respectively. Intake of dairy products (4.5%), eggs (8.3%), and vitamin A-rich fruits and vegetables (8.6%) was minimal (**Table 2**).

Prevalence of Maternal Anemia

Mean Hb concentration among the women in the first, second and third trimester was 11.43 ± 1.50 g/dl, 10.95 ± 1.50 g/dl, and 11.03 ± 1.33 g/dl, respectively. The overall prevalence of anemia was 40.9% (95% CI: 37.9-44.0; $n = 415$) (**Figure 1**).

Association Between Dietary Diversity, Maternal Anemia Status, and Hemoglobin Levels

The distribution of respondents according to the different food groups in relation to their anemic status are presented in **Figure 2**. Intake of dairy products ($P < 0.001$), meat, fish and poultry ($P = 0.006$), eggs ($P = 0.004$), dark green leafy vegetables ($P = 0.022$), vitamin A-rich fruits and vegetables ($P < 0.001$), consumption of vegetables ($P < 0.001$), fruits ($P < 0.001$) was significantly associated with lower prevalence of anemia (**Figure 2**).

Overall, the mean Hb levels were higher ($P < 0.001$) among women with good DD (12.39 ± 1.34) when compared with those with poor DD (10.85 ± 1.33). This observation was similar across the different trimesters of pregnancy except for the first trimester of pregnancy (**Figure 3**).

TABLE 2 | Proportion of the different food groups consumed by the study participants 24-h prior to survey.

Food groups	Frequency (*n*)	Percentage (%)
Grains, white roots, tubers and plantains	1007	99.3
Pulses (beans, peas and lentils)	181	17.9
Nuts and seeds	139	13.7
Meat, poultry and fish (iron rich foods)	874	86.2
Dairy products	46	4.5
Eggs	84	8.3
Dark green leafy vegetables	299	29.5
Other vitamin A-rich fruits and vegetables	87	8.6
Other vegetables	684	67.5
Other fruits	217	21.4

Factors Associated With Maternal Anemia

Binary logistic regression was performed to ascertain the determinants associated with the risk of maternal anemia. The predictor variables of anemic status were; study setting, level of education, occupation status, number of ANC clinic visits, trimester of pregnancy, malaria parasitaemia, MDD-W, and out of home eating (**Table 3**). Considering the odd ratios, BHD (OR = 1.4, 95% CI: 1.07-1.94), secondary level of education (OR = 1.5, 95% CI: 1.07-2.31), civil service status (OR = 1.9, 95% CI: 1.16-3.43), <4 ANC visits (OR = 1.9, 95% CI: 1.27-2.91), third trimester of pregnancy (OR = 3.2, 95% CI: 1.45-7.38), malaria parasitaemia (OR = 1.8, 95% CI: 1.33-2.68), poor DD (OR = 9.8, 95% CI: 4.65-20.80), and out of home eating (OR = 1.4, 95% CI: 1.03-2.13) were associated with increased odds of

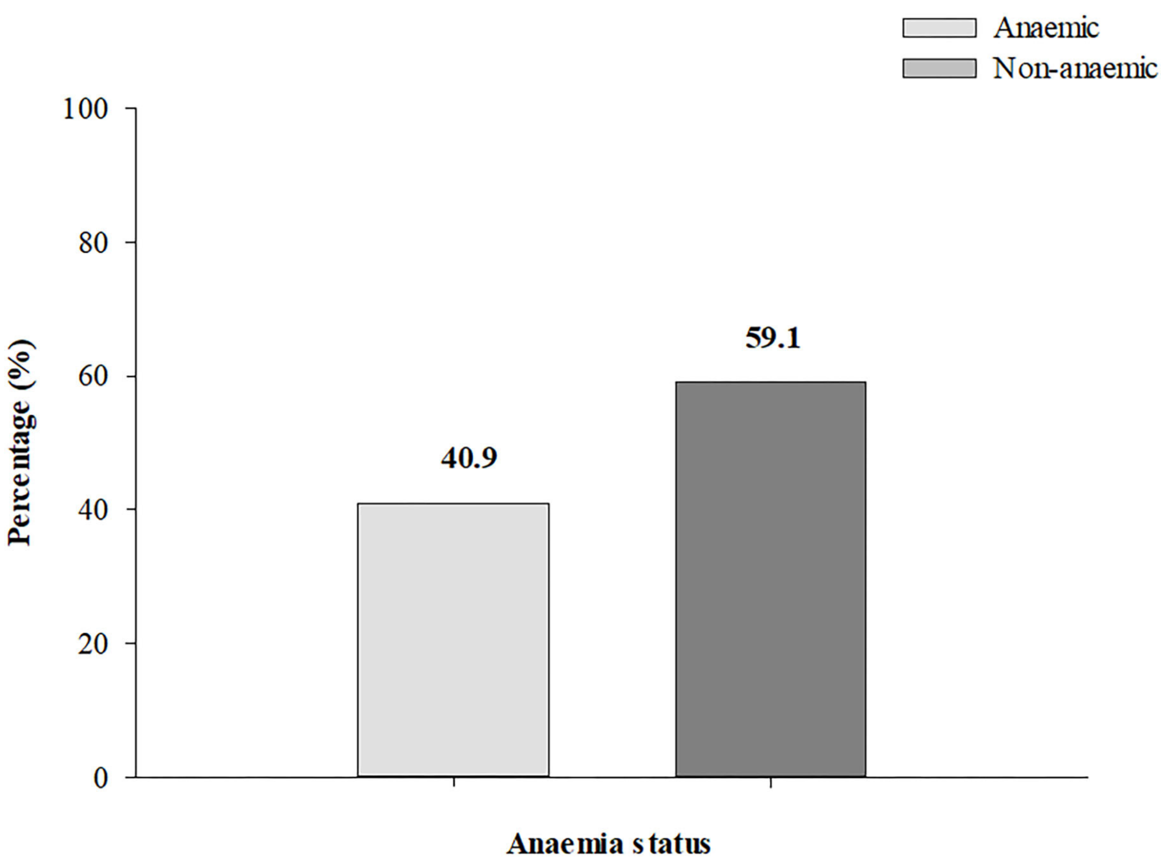

FIGURE 1 | Prevalence of anemia among pregnant women.

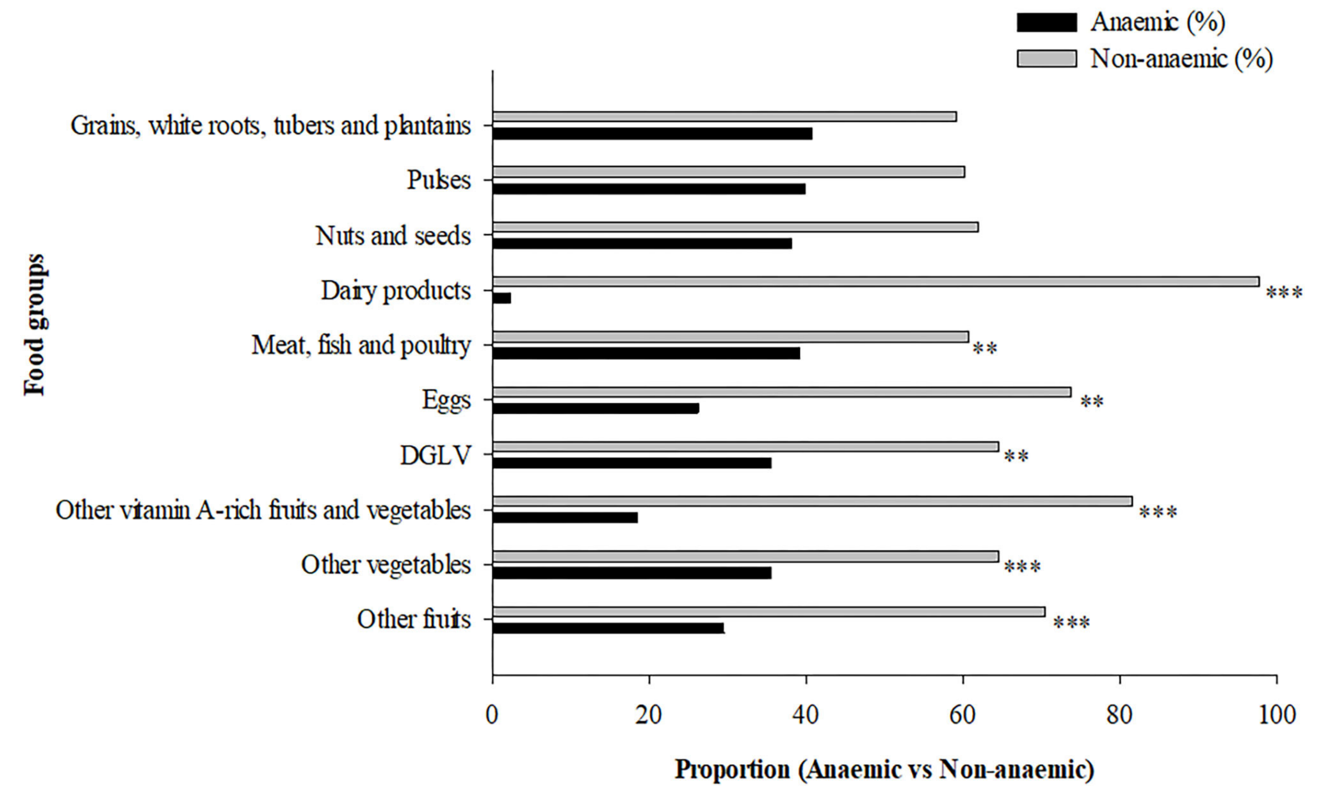

FIGURE 2 | Maternal dietary diversity during pregnancy and anemia status. $^{**}P < 0.01$, $^{***}P < 0.001$, Pearson Chi-square test. DGLV, dark green leafy vegetable.

anemia compared with their respective counterparts (**Table 3**). In addition, the attributable risk (AR%) of maternal anemia due to dietary diversity was 82.9% (95% CI: 60.8-105.2).

DISCUSSION

The causes of anemia are multi-factorial and the contribution of each of the factors may vary with dietary practice, geographical setting, sociodemographic, and season. This study determined the dietary diversity status of pregnant women and assessed its attribution in maternal anemia in the Mount Cameroon area. Extensive studies on DD has been conducted in several African settings, however, this is the first report on DD and its association with anemia in pregnant Cameroonian women.

The mean DD score of the pregnant women in this study was 3.5 ± 0.8 SD and only 10.4% of the pregnant women had adequate dietary diversity. Most (89.6%) of the pregnant women were not consuming adequate food (below the MDD-W score recommended for pregnant women) (4). A similar finding has been reported from Oromia region, Central Ethiopia (46). Contrarily, the mean DDS in this study is less than values reported by Yeneabat et al. (47) in Northwest Ethiopia and Ayensu et al. (48) in rural and urban areas of Ghana. These variations may be attributed to socio-demographic, socio-economic, geographical, and seasonal differences (46). Higher dietary diversity or variety of foods ensures adequate intake of essential nutrients that improves the probability of good health (49). In contrast with the present study, the pregnant women consumed less than the expected classes of food, which may be linked to micronutrient deficiencies.

In this study, the diet of pregnant women in the previous 24 h was composed mainly of starchy food group (grains, white roots, tubers and plantains) (99.3%), meat, poultry and fish group (86.2%), and vegetables (67.5%). Conversely, dairy products, eggs, fruits, and vegetables (vitamin A-rich) were least consumed foods. Comparable findings have been reported by authors in Tanzania (50), Ethiopia (46), and Kenya (51). The low socio-economic status of women resident in the study area may be associated with the inability to afford animal products. Moreover, many women in this study setting, on average, rely on a monthly income of <30.000 FCFA (franc des Communautés Financières d'Afrique) (~60 USD) (35). Also, pregnant women may have missed scheduled ANC opportunities to be sensitized or educated on healthy lifestyle and fight against malnutrition (52). It worth noting that, more than 75% of the pregnant women attended <4 ANC visits. In Cameroon, averagely 65% of women in each time period receives antenatal care four or more times from any health provider (53). Since 2017, the Anglophone crisis in the English-speaking regions of Cameroon has affected particularly rural and peri-urban communities. These areas have been hit hardest by violence and its indigenes have become internally displaced and also making it difficult for pregnant women to attend ANC clinic in some of these areas.

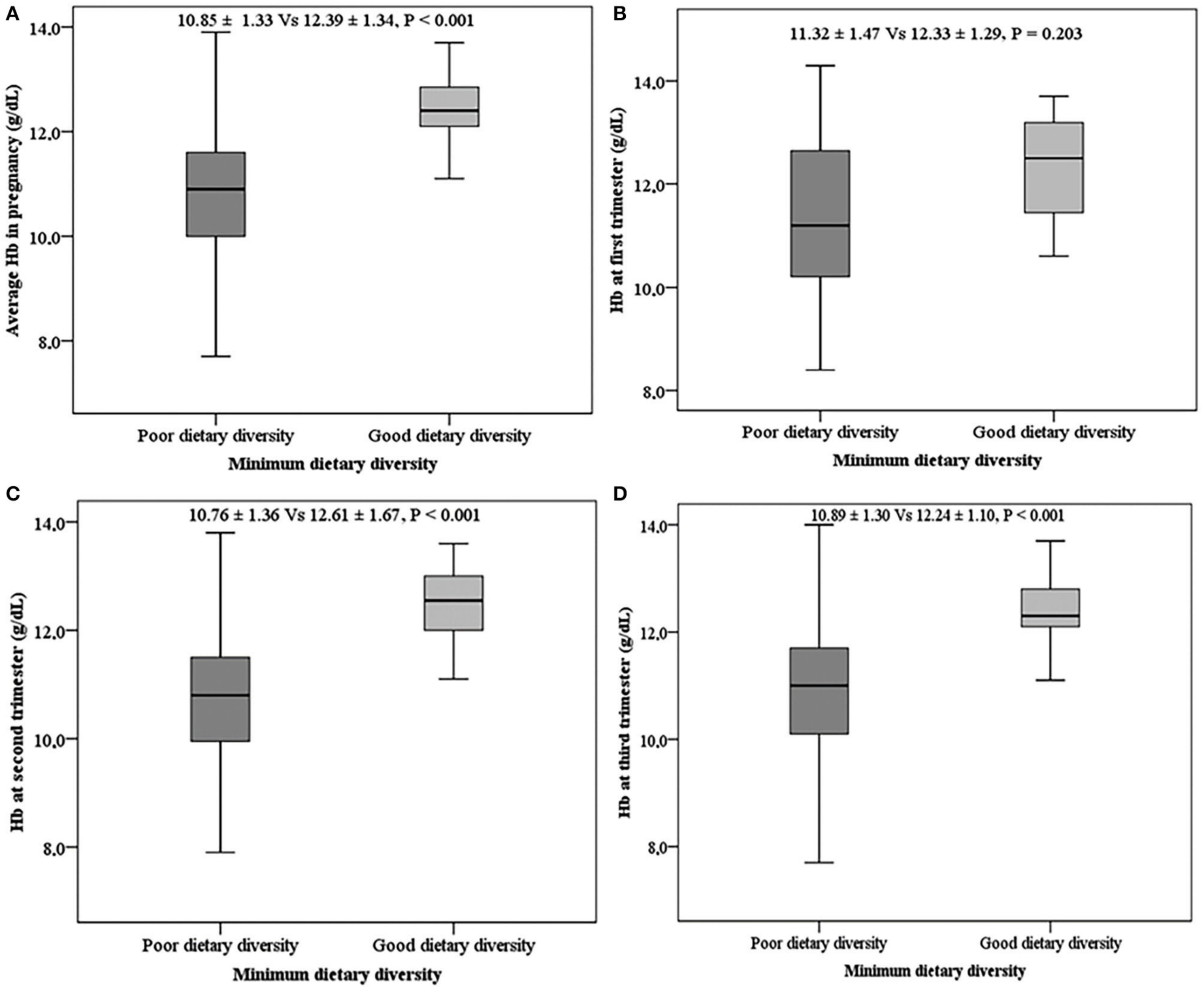

FIGURE 3 | Mean hemoglobin levels with respect to dietary diversity. **(A)** Mean Hb during pregnancy, **(B)** mean Hb in the first trimester, **(C)** mean Hb in the second trimester, **(D)** mean Hb in the third trimester.

Our findings confirm that anemia is a severe public health problem (40.9%) in this region of the country (16). The level of anemia revealed by this study is comparable with the national prevalence (39.7%) (range: 23.7–53.9) (53) but higher than the global average of 38.2% (16). On the other hand, the finding of this study is below the prevalence of anemia (52.5%) in the Northern region of Cameroon (54) and in Ghana (56.5%) (48). This demonstrates variation in the prevalence of anemia within different settings in the same country. This may be attributed specifically to geographical variations, differences in socio-economic status, cultural and dietary patterns (55).

The results of this study showed that study setting, maternal educational level, occupation status, number of ANC visits, gestational age, malaria parasitaemia, DD, and out of home eating were predictors of maternal anemia. These identified factors are discussed as follows.

Although DD is not the only contributing factor of anemia in pregnancy, the present study revealed that DD is the most pressing constraint. Low DD score (<5 food groups) increased the odds of anemia by ∼10 folds when compared with high DD score (≥5 food groups). In addition, DD had a positive effect on Hb levels regardless of the gestational age. More so, more than 80% of anemia was attributable to dietary diversity. These findings corroborate studies by Lebso et al. (13) and Delil et al. (56) in Southern Ethiopia. However, in Northern Ghana, diet was not one of the protective factors against anemia (57). Suboptimal dietary intake increases the risk of anemia which has negative effects on the growth and development of the fetus (21, 58) and lactation (57). A diverse diet composed of different food groups rich in micronutrients particularly, iron, vitamin A, vitamin B_{12}, and folic acid functions to promote red blood cell production thus preventing anemia among women of reproductive age (59,

TABLE 3 | Factors associated with maternal anemia.

Factors	Categories	Total *N*	Anemic % (*n*)	COR (95% CI)	*P* value	AOR (95%CI)	*P* value
Climatic seasons	Dry	213	46.0 (98)	1.3 (0.95-1.76)	0.090	1.2 (0.96-1.75)	0.169
	Rainy	801	39.6 (317)	REF		REF	
Health district	THD	509	38.7 (197)	REF	0.148	REF	
	BHD	505	43.2 (218)	1.2 (0.93-1.54)		1.4 (1.07-1.94)	0.015
Age (15-46 years)	≤20	145	45.5 (66)	1.2 (0.86-1.80)	0.477	1.4 (0.82-2.41)	0.215
	21-25	295	40.3 (119)	1.0 (0.75-1.34)		1.1 (0.79-1.66)	0.447
	>25	574	40.1 (230)	REF		REF	
Marital status	Single	383	39.2 (150)	REF	0.374	REF	
	Married	631	42.0 (265)	1.1 (0.86-1.45)		1.1 (0.87-1.61)	0.269
Education level	Primary	204	38.7 (79)	1.1 (0.79-1.68)	0.030	1.1 (0.68-1.91)	0.594
	Secondary	538	44.6 (240)	1.4 (1.09-1.99)		1.5 (1.07-2.31)	0.020
	Tertiary	272	35.3 (96)	REF		REF	
Occupation status	Housewives	167	40.1 (67)	1.1 (0.75-1.75)		1.2 (0.75-1.98)	0.422
	Farmers	59	44.1 (26)	1.3 (0.74-2.43)		1.3 (0.63-2.78)	0.454
	Business	442	41.4 (183)	1.2 (0.85-1.70)	0.645	1.2 (0.77-1.87)	0.417
	Civil servants	198	44.6 (66)	1.3 (0.89-2.12)		1.9 (1.16-3.43)	0.012
	Students	148	36.9 (73)	REF		REF	
ANC attendance	<4 clinic visits	784	43.8 (343)	1.7 (1.24-2.33)	0.001	1.9 (1.27-2.91)	0.002
	≥4 clinic visits	230	31.3 (72)	REF		REF	
Gravidity	Primigravid	351	39.3 (138)	0.8 (0.62-1.12)		0.8 (0.56-1.34)	0.530
	Secundigravid	256	39.1 (100)	0.8 (0.60-1.14)	0.397	0.8 (0.58-1.24)	0.407
	Multigravid	407	43.5 (177)	REF		REF	
Trimester of pregnancy	First trimester	35	31.4 (11)	REF		REF	
	Second trimester	418	36.6 (153)	1.2 (0.60-2.64)	0.019	1.4 (0.64-3.07)	0.396
	Third trimester	561	44.7 (251)	1.7 (0.84-3.67)		3.2 (1.45-7.38)	0.004
IPTp-SP uptake	First dose	686	42.6 (292)	1.5 (1.03-2.33)		1.5 (0.89-2.57)	0.121
	Second dose	204	40.7 (83)	1.4 (0.90-2.30)	0.099	1.2 (0.73-2.09)	0.420
	≥ three doses	124	32.3 (40)	REF		REF	
ITN usage	Yes	396	40.9 (162)	REF	0.993	REF	
	No	618	40.9 (253)	1.0 (0.77-1.29)		0.9 (0.73-1.29)	0.849
IFA uptake	Yes	725	40.8 (296)	REF	0.919	REF	
	No	289	41.2 (119)	1.0 (0.76-1.33)		1.1 (0.81-1.63)	0.408
Malaria status	Positive	180	53.9 (97)	1.8 (1.37-2.62)	0.000	1.8 (1.33-2.68)	<0.001
	Negative	834	38.1 (318)	REF		REF	
MDD-W	<5 food groups	909	44.8 (407)	9.8 (4.72-20.45)		9.8 (4.56-20.80)	<0.001
	≥5 food groups	105	7.6 (8)	REF	0.000	REF	
Out of home eating	Yes	173	46.8 (81)	1.3 (0.96-1.85)	0.083	1.4 (1.03-2.13)	0.032
	No	841	39.7 (334)	REF		REF	

ANC, antenatal clinic; IPTp-SP, intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine; ITN, insecticide treated net; IFA, iron folic acid uptake; MDD-W, minimum dietary diversity for women; COR crude odd ratio; AOR adjusted odd ratio.

60). This study demonstrated that women who ate out of their homes were 1.4 times more likely to be anemic. Eating out of home is associated with poor dietary quality and a predisposing factor for higher energy and fats relative to lower micronutrient intake (61). In addition, out of home foods are limited in essential nutrients especially, vitamin C, calcium, and iron (57, 62, 63).

It is well established that malaria parasitaemia causes and/or aggravates anemia (31, 64, 65). The occurrence of malarial anemia (23.4%) among pregnant women is not an uncommon finding in the Mount Cameroon Area (26, 31). Although, *P. falciparum* infection plays a role in the pathophysiology of anemia, however, it is not the major contributing factor of anemia in our endemic setting.

Our results showed that women who attended ANC clinic less than four times were more likely (OR = 1.9) to be anemic. Regular ANC visits permits increase uptake of prophylactic measures against malarial infection, iron and folic acid supplementation as well as enables the pregnant woman acquire knowledge on adequate nutrition and health education (57). The number of ANC visits was seen as a strong predictor of anemia among pregnant women in Ghana (57, 66). Pregnant women in their third trimester of gestation were 3.2 times more likely to be anemic than those in their first and second trimester. The association between gestational age and anemia agrees with findings by El Aishiry et al. (67) in Egypt, Lebso et al. (13) in Ethiopia and Wemakor (68) in Ghana. During the third trimester of gestation, the haemo-dilutional effect of pregnancy and increase in nutritional demand for the mother and growing fetus are maximal (69).

Socio-demographic factors associated with the occurrence of anemia included educational status, occupation and residence. Women engaged in civil service were 1.9 times at increased risk of anemia when compared with other occupations. This could be related to missed meals, since they are busy throughout the day. Similarly, severe anemia was significantly more prevalent among women in waged labor in rural Nepali (70). Several studies have reported reduced risk of anemia in association with higher level of education (56, 71–73). On the contrary, this study demonstrated otherwise. This could be explained partly by bias as more than 50% of pregnant women in the study population have attained a secondary level of education. Education enable women to adopt better health seeking behaviors as well as utilization of information that are important to nutritional status. Residents in BHD were 1.4 times more affected by anemia than those of THD. This difference may be related to variation in dietary micronutrient profile and socio-demographics of these women. THD is characterized by mainly farming activities, industrial agriculture and business whereas common occupational activities in BHD include teaching in the public and private educational institutions and civil servants and business. Less anemia among residents in THD than in BHD is likely linked to availability and consumption of variety of farm produce (rich in iron) in THD. Nevertheless, further studies on dietary iron intake, iron bioavailability and maternal anemia are crucial.

STRENGTHS AND LIMITATIONS

This study confirms that anemia is an important public health problem among pregnant women in Africa and highlights the importance of simple preventive actions to increase dietary diversity by promoting nutritional education and the awareness about the importance of having a balanced diet for pregnant women. However, this study had some limitations. Only qualitative dietary assessment was done. Though quantitative methods are best for assessing nutrient adequacy, these methods are cumbersome and not affordable in limited resource settings like ours. Simple measures of dietary diversity such as MDD-W indicator, equally, has been shown to reflect micronutrient adequacy (4). We attest that temporality is the primary limitation of cross-sectional study design. However, we used both descriptive and analytical cross-sectional study designs, and sufficiently large sample size population.

CONCLUSION

In general, 40.9% of the pregnant women had anemia. Only 10.4% had adequate dietary diversity while 89.6% did not meet the FAO indicator of minimum dietary diversity for women. This study revealed that diets of these women are composed mainly of starchy staples, but less of dairy products, eggs, dark green leafy vegetables, fruits, and vegetables (vitamin A-rich) as well as fruits. Intake of iron-rich diets improved Hb levels. The predictors of anemia were: setting, educational level, occupation, number of ANC attendance, trimester of pregnancy, malaria parasitaemia, MDD-W and eating out of home. Poor DD was a key contributor of anemia (AR% = 82.9%). Nutritional education on the importance of a balanced diverse diet should be intensified during ANC to curb the risk of anemia in pregnancy in the Mt. Cameroon area.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study, involving human participants, was reviewed, and approved by Institutional Review Board of the University of Buea. Informed consent to participate in this study was provided by the participants and/or legal guardian.

AUTHOR CONTRIBUTIONS

VJ and JA-K conceived and designed the study. VJ and KM conducted the research including data collection. VJ and JA were responsible for data management and analysis. VJ interpreted the data and wrote the first draft of the manuscript. JA-K supervised and critically revised the manuscript for important and intellectual content. HK supervised and revised the manuscript for important and intellectual content. All authors read and approved the final manuscript.

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REFERENCES

1. El-Farrash RA, Ismail EAR, Nada AS. Cord blood iron profile and breast milk micronutrients in maternal iron deficiency anemia. *Pediatr Blood Cancer.* (2012) 58:233–8. doi: 10.1002/pbc.23184
2. Gernand AD, Schulze KJ, Stewart CP, West Jr KP, Christian P. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. *Nat Rev Endocrinol.* (2016) 12:274. doi: 10.1038/nrendo.2016.37
3. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al. Maternal and child undernutrition: consequences for adult health and

human capital. *Lancet.* (2008) 371:340–57. doi: 10.1016/S0140-6736(07)61692-4
4. FAO F. *Minimum Dietary Diversity for Women: A Guide for Measurement*. Rome: FAO (2016).
5. Ahmed AU, Hill RV, Smith LC, Wiesmann DM, Frankenberger T, Gulati K, et al. The world's most deprived: characteristics and causes of extreme poverty and hunger. *Intl Food Policy Res Inst.* (2007) 43:1–148. doi: 10.2499/0896297705
6. Katona P, Katona-Apte J. The interaction between nutrition and infection. *Clin Infect Dis.* (2008) 46:1582–8. doi: 10.1086/587658
7. Onukogu SC, Ibrahim J, Ogwuche RA, Jaiyeola TO, Adiaha MS. Role of nutrition in the management and control of malaria infection: a review. *World Sci News.* (2018) 107:58–71. Available online at: http://yadda.icm.edu.pl/yadda/element/bwmeta1.element.psjd-c9333114-5a34-4ecc-8580-61e8139e8648
8. Lee SE, Talegawkar S, Merialdi M, Caulfield LE. *What Are African Women Eating During Pregnancy?* Rockville, MD: Federation of American Societies for Experimental Biology (2011).
9. Kennedy G, Baye K, Powell B, Bailey A. *Connecting Diverse Diets With Production Systems: Measures and Approaches for Improved Food and Nutrition Security. Encyclopedia of Food Security and Sustainability*. Amsterdam: Elsevier (2018). p. 209–16. doi: 10.1016/B978-0-08-100596-5.21542-4
10. Rammohan A, Goli S, Singh D, Ganguly D, Singh U. Maternal dietary diversity and odds of low birth weight: empirical findings from India. *Women Health.* (2019) 59:375–90. doi: 10.1080/03630242.2018.1487903
11. Semba RD, Bloem M. The anemia of vitamin A deficiency: epidemiology and pathogenesis. *Eur J Clin Nutr.* (2002) 56:271–81. doi: 10.1038/sj.ejcn.1601320
12. Obwocha A, Mbagaya G, Were G. Dietary intake-among pregnant women attending ante-natal Clinic AtKisiiLevel 5 Hospital, Kenya. *IOSR J Environ Sci Toxicol Food Technol.* (2016) 10:77–82. doi: 10.9790/2402-1004017782
13. Lebso M, Anato A, Loha E. Prevalence of anemia and associated factors among pregnant women in Southern Ethiopia: A community based cross-sectional study. *PLoS ONE.* (2017) 12:e188783. doi: 10.1371/journal.pone.0188783
14. Mekonnen S, Endalamaw M. Dietary practice and associated factors among pregnant women in Gondar Town North West, Ethiopia. *Int J Nutrition and Food Sci.* (2015) 4:707–12. doi: 10.11648/j.ijnfs.20150406.27
15. Madhavi LH, Singh HKG. Nutritional status of rural pregnant women. *People's J Sci Res.* (2011) 4:20–23. Available online at: https://www.pjsr.org/July11_pdf/5-Dr.%20Madhavi%20LH.pdf
16. WHO. *The Global Prevalence of Anaemia in 2011*. Geneva: World Health Organization (2015).
17. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low-and middle-income countries: systematic review and meta-analysis, 2. *Am J Clin Nutr.* (2016) 103:495–504. doi: 10.3945/ajcn.115.107896
18. McClure EM, Meshnick SR, Mungai P, Malhotra I, King CL, Goldenberg RL, et al. The association of parasitic infections in pregnancy and maternal and fetal anemia: a cohort study in coastal Kenya. *PLoS Negl Trop Dis.* (2014) 8:e2724. doi: 10.1371/journal.pntd.0002724
19. Zerfu TA, Umeta M, Baye K. Dietary diversity during pregnancy is associated with reduced risk of maternal anemia, preterm delivery, and low birth weight in a prospective cohort study in rural Ethiopia. *Am J Clin Nutr.* (2016) 103:1482–8. doi: 10.3945/ajcn.115.116798
20. Khalafallah AA, Dennis AE. Iron deficiency anaemia in pregnancy and postpartum: pathophysiology and effect of oral versus intravenous iron therapy. *J Pregnancy.* (2012) 2012:630519. doi: 10.1155/2012/630519
21. Msuya SE, Hussein TH, Uriyo J, Sam NE, Stray-Pedersen B. Anaemia among pregnant women in northern Tanzania: prevalence, risk factors and effect on perinatal outcomes. *Tanzan J Health Res.* (2011) 13:33–9. doi: 10.4314/thrb.v13i1.60881
22. Nik Rosmawati N, Mohd Nazri S, Mohd Ismail I. The rate and risk factors for anemia among pregnant mothers in Jerteh Terengganu, Malaysia. *J Community Med Health Educ.* (2012) 2:2161. doi: 10.4172/2161-0711.1000150
23. Mondal B, Tripathy V, Gupta R. Risk factors of anemia during pregnancy among the Garo of Meghalaya, India. *J Hum Ecol.* (2006) 14:27–32. Available online at: http://www.krepublishers.com/02-Journals/JHE/JHE-00-Special%20Issues/JHE-14-Eco-Cul-Nut-Hlth-Dis-Web/JHE-SI-14-04-027-032-Mondal-B/JHE-SI-14-04-027-032-Mondal-B-Text.pdf
24. Fokam EB, Ngimuh L, Anchang-Kimbi JK, Wanji S. Assessment of the usage and effectiveness of intermittent preventive treatment and insecticide-treated nets on the indicators of malaria among pregnant women attending antenatal care in the Buea Health District, Cameroon. *Malar J.* (2016) 15:172. doi: 10.1186/s12936-016-1228-3
25. Anchang-Kimbi JK, Kalaji LN, Mbacham HF, Wepnje GB, Apinjoh TO, Sumbele IUN, et al. Coverage and effectiveness of intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP) on adverse pregnancy outcomes in the Mount Cameroon area, South West Cameroon. *Malar J.* (2020) 19:1–12. doi: 10.1186/s12936-020-03155-2
26. Anchang-Kimbi JK, Nkweti VN, Ntonifor HN, Apinjoh TO, Chi HF, Tata RB, et al. Profile of red blood cell morphologies and causes of anaemia among pregnant women at first clinic visit in the mount Cameroon area: a prospective cross sectional study. *BMC Res Notes.* (2017) 10:645. doi: 10.1186/s13104-017-2961-6
27. Tabi ESB, Eyong EM, Akum EA, Löve J, Cumber SN. Soil-transmitted Helminth infection in the Tiko Health District, South West Region of Cameroon: a post-intervention survey on prevalence and intensity of infection among primary school children. *Pan Afr Med J.* (2018) 30:15676. doi: 10.11604/pamj.2018.30.74.15676
28. Anguh E, Ako S, Numfor E, Josiah ZB, Ndassi V. Presence of an unmapped focus for urogenital schistosomiasis in the tiko health district in cameroon: Implications for control. *Internat J Trop Disease Health.* (2018) 32:1–8. doi: 10.9734/IJTDH/2018/43575
29. Nkuo-Akenji TK, Chi PC, Cho JF, Ndamukong KK, Sumbele I. Malaria and helminth co-infection in children living in a malaria endemic setting of mount Cameroon and predictors of anemia. *J Parasitol.* (2006) 92:1191–5. doi: 10.1645/GE-895R.1
30. Nlinwe NO. Effects of malaria on iron stores in the pregnant women of Buea and Tiko Health District, South West Region, Cameroon. *J Metab Syndr.* (2014) 3:4–9. doi: 10.4172/2167-0943.1000170
31. Achidi E, Kuoh A, Minang JT, Ngum B, Achimbom B, Motaze S, et al. Malaria infection in pregnancy and its effects on haemoglobin levels in women from a malaria endemic area of Fako Division, South West Province, Cameroon. *J Obstet Gynaecol.* (2005) 25:235–40. doi: 10.1080/01443610500060628
32. Wanji S, Kimbi HK, Eyong JE, Tendongfor N, Ndamukong JL. Performance and usefulness of the Hexagon rapid diagnostic test in children with asymptomatic malaria living in the Mount Cameroon region. *Malar J.* (2008) 7:89. doi: 10.1186/1475-2875-7-89
33. Sakwe N, Bigoga J, Ngondi J, Njeambosay B, Esemu L, Kouambeng C, et al. Relationship between malaria, anaemia, nutritional and socio-economic status amongst under-ten children, in the North Region of Cameroon: a cross-sectional assessment. *PLoS ONE.* (2019) 14:e0218442. doi: 10.1371/journal.pone.0218442
34. Anchang-Kimbi JK, Achidi EA, Apinjoh TO, Mugri RN, Chi HF, Tata RB, et al. Antenatal care visit attendance, intermittent preventive treatment during pregnancy (IPTp) and malaria parasitaemia at delivery. *Malar J.* (2014) 13:162. doi: 10.1186/1475-2875-13-162
35. Anchang-Kimbi JK, Nkweti VN, Ntonifor HN, Apinjoh TO, Tata RB, Chi HF, et al. Plasmodium falciparum parasitaemia and malaria among pregnant women at first clinic visit in the mount Cameroon Area. *BMC Infect Dis.* (2015) 15:439. doi: 10.1186/s12879-015-1211-6
36. World Health Organization. *WHO Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-Pyrimethamine (IPTp-SP)*. Geneva: World Health Organization. (2013).
37. Cochran W. *Sampling Techniques. 3rd edition*. New York, NY: John Wiley & Sons Inc. (1977).
38. World Health Organization. *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience*. Geneva: World Health Organization (2016).
39. Lander RL, Hambidge KM, Westcott JE, Tejeda G, Diba TS, Mastiholi SC, et al. Pregnant women in four low-middle income countries have a high prevalence of inadequate dietary intakes that are improved by dietary diversity. *Nutrients.* (2019) 11:1560. doi: 10.3390/nu11071560
40. Nguyen PH, Martin-Prevel Y, Moursi M, Tran LM, Menon P, Ruel MT, et al. Assessing dietary diversity in pregnant women: relative validity of the list-based and open recall methods. *Curr Dev Nutr.* (2020) 4:nzz134. doi: 10.1093/cdn/nzz134

41. Bukusuba J, Kikafunda JK, Whitehead RG. Food security status in households of people living with HIV/AIDS (PLWHA) in a Ugandan urban setting. *Br J Nutr.* (2007) 98:211–7. doi: 10.1017/S0007114507691806
42. Control CfD, Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR RR.* (1998) 47:1-29.
43. Hotez PJ. Empowering women and improving female reproductive health through control of neglected tropical diseases. *PLoS Negl Trop Dis.* (2009) 3:e559. doi: 10.1371/journal.pntd.0000559
44. Cheesbrough M. *District Laboratory Practice in Tropical Countries*. New York, NY: Cambridge University Press (2006). doi: 10.1017/CBO9780511543470
45. Handler A. *Analytic Methods in Maternal and Child Health*. Division of Science, Education, and Analysis, Health Resources and Services, Chicago, IL (1998).
46. Desta M, Akibu M, Tadese M, Tesfaye M. Dietary diversity and associated factors among pregnant women attending antenatal clinic in Shashemane, Oromia, Central Ethiopia: a cross-sectional study. *J Nutr Metab.* (2019) 2019:3916864. doi: 10.1155/2019/3916864
47. Yeneabat T, Adugna H, Asmamaw T, Wubetu M, Admas M, Hailu G, et al. Maternal dietary diversity and micronutrient adequacy during pregnancy and related factors in East Gojjam Zone, Northwest Ethiopia, 2016. *BMC Preg Childbirth.* (2019) 19:173. doi: 10.1186/s12884-019-2299-2
48. Ayensu J, Annan R, Lutterodt H, Edusei A, Peng LS. Prevalence of anaemia and low intake of dietary nutrients in pregnant women living in rural and urban areas in the Ashanti region of Ghana. *PLoS ONE.* (2020) 15:e0226026. doi: 10.1371/journal.pone.0226026
49. Hudson GJ. Food intake in a west African village. Estimation of food intake from a shared bowl. *Br J Nutr.* (1995) 73:551–69. doi: 10.1079/BJN19950058
50. Ochieng J, Afari-Sefa V, Lukumay PJ, Dubois T. Determinants of dietary diversity and the potential role of men in improving household nutrition in Tanzania. *PLoS ONE.* (2017) 12:e189022. doi: 10.1371/journal.pone.0189022
51. Kiboi W, Kimiywe J, Chege P. Determinants of dietary diversity among pregnant women in Laikipia County, Kenya: a cross-sectional study. *BMC Nutr.* (2017) 3:12. doi: 10.1186/s40795-017-0126-6
52. Bhutta ZA, Darmstadt GL, Hasan BS, Haws RA. Community-based interventions for improving perinatal and neonatal health outcomes in developing countries: a review of the evidence. *Pediatrics.* (2005) 115(Supplement 2):519–617. doi: 10.1542/peds.2004-1441
53. World Health Organization. *WHO Global Report on Traditional and Complementary Medicine 2019*. Geneva: World Health Organization (2019).
54. Monteh CT, Ndié J, Sobngwi JL, Nkoum BA. Risk factors of anaemia among pregnant women in Banyo Health District, Adamawa Region of Cameroon. *Central Afric J Public Health.* (2019) 5:221–6. doi: 10.11648/j.cajph.20190505.17
55. Gebreweld A, Tsegaye A. Prevalence and factors associated with anemia among pregnant women attending antenatal clinic at St. Paul's hospital millennium medical college, Addis Ababa, Ethiopia. *Adv Hematol.* (2018) 2018:3942301. doi: 10.1155/2018/3942301
56. Delil R, Tamiru D, Zinab B. Dietary diversity and its association with anemia among pregnant women attending public health facilities in South Ethiopia. *Ethiop J Health Sci.* (2018) 28:5. doi: 10.4314/ejhs.v28i5.14
57. Saaka M, Oladele J, Larbi A, Hoeschle-Zeledon I. Dietary diversity is not associated with haematological status of pregnant women resident in rural areas of northern Ghana. *J Nutr Metab.* (2017) 2017:8497892. doi: 10.1155/2017/8497892
58. Symington EA, Baumgartner J, Malan L, Zandberg L, Ricci C, Smuts CM. Nutrition during pregnancy and early development (NuPED) in urban South Africa: a study protocol for a prospective cohort. *BMC Preg Childbirth.* (2018) 18:308. doi: 10.1186/s12884-018-1943-6
59. Brooker S, Hotez PJ, Bundy DA. Hookworm-related anaemia among pregnant women: a systematic review. *PLoS Negl Trop Dis.* (2008) 2:e291. doi: 10.1371/journal.pntd.0000291
60. Hu S, Tan H, Peng A, Jiang H, Wu J, Guo S, et al. Disparity of anemia prevalence and associated factors among rural to urban migrant and the local children under two years old: a population based cross-sectional study in Pinghu, China. *BMC Public Health.* (2014) 14:601. doi: 10.1186/1471-2458-14-601
61. Lachat C, Nago E, Verstraeten R, Roberfroid D, Van Camp J, Kolsteren P. Eating out of home and its association with dietary intake: a systematic review of the evidence. *Obesity Rev.* (2012) 13:329–46. doi: 10.1111/j.1467-789X.2011.00953.x
62. Agbozo F, Abubakari A, Der J, Jahn A. Maternal dietary intakes, red blood cell indices and risk for anemia in the first, second and third trimesters of pregnancy and at predelivery. *Nutrients.* (2020) 12:777. doi: 10.3390/nu12030777
63. Anwar M, Hill E, Skujins J, Huynh K, Doss C, editors. Kalico: A Smartphone Application for health-smart menu selection within a budget. In: *International Conference on Smart Health*. Berlin: Springer (2013). p. 113–21. doi: 10.1007/978-3-642-39844-5_14
64. Bate A, Kimbi HK, Lum E, Lehman LG, Onyoh EF, Ndip LM, et al. Malaria infection and anaemia in HIV-infected children in Mutengene, Southwest Cameroon: a cross sectional study. *BMC Infect Dis.* (2016) 16:523. doi: 10.1186/s12879-016-1853-z
65. Sumbele IUN, Sama SO, Kimbi HK, Taiwe GS. Malaria, moderate to severe anaemia, and malarial anaemia in children at presentation to hospital in the Mount Cameroon area: a cross-sectional study. *Anemia.* (2016) 2016:5725634. doi: 10.1155/2016/5725634
66. Tibambuya BA, Ganle JK, Ibrahim M. Anaemia at antenatal care initiation and associated factors among pregnant women in West Gonja District, Ghana: a cross-sectional study. *Pan Afr Med J.* (2019) 33:17924. doi: 10.11604/pamj.2019.33.325.17924
67. El Ashiry A, El Ghazali S, Habil I. Prevalence and determinants of anaemia in third trimester pregnancy in Fayoum governorate-Egypt. *Acta Medica Mediterranea.* (2014) 30:1045–51. Available online at: https://www.actamedicamediterranea.com/archive/2014/medica-5/prevalence-and-determinants-of-anaemia-in-third-trimester-pregnancy-in-fayoum-governorate-egypt/document
68. Wemakor A. Prevalence and determinants of anaemia in pregnant women receiving antenatal care at a tertiary referral hospital in Northern Ghana. *BMC Preg Childbirth.* (2019) 19:495. doi: 10.1186/s12884-019-2644-5
69. Bukar M, Audu B, Sadauki H, Elnafaty A, Mairiga A. Prevalence of iron deficiency and megaloblastic anaemia at booking in a secondary health facility in north eastern Nigeria. *Nigerian Med J.* (2009) 50:33. Available online at: https://www.ajol.info/index.php/nmj/article/view/53263
70. Makhoul Z, Taren D, Duncan B, Pandey P, Thomson C, Winzerling J, et al. Risk factors associated with anemia, iron deficiency and iron deficiency anemia in rural Nepali pregnant women. *Southeast Asian J Trop Med Public Health.* (2012) 43:735. Available online at: https://www.tm.mahidol.ac.th/seameo/2012-43-3/23-4981-16.pdf
71. Sumbele IUN, Samje M, Nkuo-Akenji T. A longitudinal study on anaemia in children with Plasmodium falciparuminfection in the Mount Cameroon region: prevalence, risk factors and perceptions by caregivers. *BMC Infect Dis.* (2013) 13:123. doi: 10.1186/1471-2334-13-123
72. Melku M, Addis Z, Alem M, Enawgaw B. Prevalence and predictors of maternal anemia during pregnancy in Gondar, Northwest Ethiopia: an institutional based cross-sectional study. *Anemia.* (2014) 2014:108593. doi: 10.1155/2014/108593
73. Gudeta TA, Regassa TM, Belay AS. Magnitude and factors associated with anemia among pregnant women attending antenatal care in Bench Maji, Keffa and Sheka zones of public hospitals, Southwest, Ethiopia, 2018: a cross-sectional study. *PLoS ONE.* (2019) 14:e0225148. doi: 10.1371/journal.pone.0225148

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Intake of Fibre-Associated Foods and Texture Preferences in Relation to Weight Status Among 9–12 Years Old Children in 6 European Countries

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Plant foods, rich in fibre, can offer textures that children find difficult to orally manipulate, resulting in low preferences but are important for a healthy diet and prevention of overweight in children. Our aim was to investigate preferences for food texture, intake of fibre-associated foods and the relation to BMI. Three hundred thirty European children (9–12 years, 54% female) indicated their texture preferences using the Child-Food-Texture-Preference- Questionnaire (CFTPQ), and their parents responded on fibre-associated food consumption and anthropometric information. BMI was significantly lower for children with higher intake of wholegrain alternatives of common foods; in addition to being significantly influenced by country and the wearing of a dental brace. Overall BMI-for-age-percentiles (BMI_pct) were negatively associated with the consumption of wholegrain cereals, white pasta and wholemeal products and positively associated with the intake of legumes and white biscuits. In males, BMI_pct were negatively associated with wholegrain products and dried fruits, and in females, positively with legume consumption. A few country-related associations were found for BMI_pct and wholegrain biscuits, seeds and nuts and refined products. No overall correlation was found between BMI_pct and the texture preference of soft/hard foods by CFTPQ, except in Austria. We conclude that this study revealed evidence of a connection between fibre-associated foods and children's BMI at a cross-cultural level and that sex is an important determinant of fibre-associated food intake and the development of overweight in childhood.

Keywords: texture preferences, plant foods, high/low fibre foods, overweight, BMI-for-age percentiles

INTRODUCTION

Nowadays childhood overweight/obesity is one of the most significant health problems worldwide (1). The highest levels of children with overweight and obesity have been reported in Southern Europe (Greece, Italy, Spain), whereas the ratio tends to be lower in Western and Northern Europe (2). Overweight and obesity existing already in childhood and adolescence can lead to serious chronic diseases (3, 4) and when persisting into adulthood, cardiovascular disease, diabetes and certain cancers are serious consequences (5–7). Therefore, the evaluation and classification of weight status in children is important for health assessment and- monitoring the prevention of diseases (8).

Observational studies have consistently found a positive correlation between the consumption of plant foods and improved long-term health outcomes in children (9, 10) emphasising that dietary fibre-rich plant foods, such as grains, fruits, vegetables, potatoes and legumes have positive health effects. The main effects are weight loss (10) and reduced long term risk of metabolic syndrome (11). Studies conducted in Europe, though carried out with adults, confirmed that intake of fibre-rich wholegrain pasta compared to refined pasta increased satiety and reduced hunger without changing the energy intake at subsequent meals (12, 13).

However, the intake of fruits and vegetables in European children is low (14), suggesting that only 6–24% reach the WHO recommendations, where females show a higher consumption than males (15–18). Moreover, research confirms that children with overweight/obesity consume less fruits and vegetables than children with normal weight (19). A low consumption of fruits and vegetables is not only associated with a higher risk of becoming overweight (19, 20), but also with the development of chronic diseases (21, 22). It was found that many children, instead of a diet rich in fruits and vegetables, choose rather sugar- and fat-rich snacks (23–25), which could lead to a higher energy intake (26) and consequently to overweight/obesity (27–29). However, no difference in the number of daily snacks between overweight and children with normal weight was found (23).

Eating behaviours in childhood are also often affected by picky eating (30), whereas these factors may have an influence on the development of overweight/obesity. Picky eating is very common in childhood, because children often have an avoidance of certain foods (31) and therefore show a low variety of foods in their diet.

The reasons for picky eating may be due to infancy, because food texture and the acceptance of food were related to the development of chewing (32). It has been shown that children who have early experiences with texture in their life tend to show a broader acceptance of those textures later. Demonteil et al. found that children were able to accept most textures at the age of 12 month because their chewing behaviour was established, however this was not always reflected by parental feeding practices (33). Lukasewycz and Mennella showed in their study that adults prefer harder foods and those containing more particles and children's preferences are developing with increasing age so that they become more adult-like later on (32). Szczesniak found out that children prefer food that can be easily manipulated in mouth (34). Moreover, a study from Werthmann et al. showed that children's consumption of e.g., a yoghurt decreased when the texture was modified by adding pieces to it (31). In vegetables tactile properties play a particularly important role in the rejection or acceptance (35). Therefore, the consumption of vegetables in young people is strongly related to the sensory properties of the respective vegetable variety (36–39). The structure of plants is based upon fibre, therefore, the texture of fibre-rich foods have more intensive tactile properties which may lead some children to reject such foods (31, 35). Studies show that children often reject foods with slimy, grainy or hard textures (36–39).

Little is yet known about a possible correlation between food texture preferences and overweight in children. In one previous European study a correlation was found between the preference for foods with a soft texture and food neophobia (40), which is in turn linked to the increase in body weight in adults (41).

The present study aimed to explore the relationship between weight status of European children, the consumption frequency of foods with high and low fibre content and texture preferences (soft/hard). We hypothesised that; (1) A higher intake of high fibre foods would be correlated with a lower BMI in children, potentially due to increasing satiety and reducing the intake of energy-dense foods, and (2) A higher preference for soft textures and therefore a lower consumption of plant-based high fibre foods would be connected with a higher BMI in children.

MATERIALS AND METHODS

Study Design and Participants

A total response of 330 children (9–12 years, 151 males, 179 females) from six European countries (Austria, Finland, Italy, Spain, Sweden and UK) and their parents was reached in this study (see **Figure 1**). The number of participants from each country is summarised in **Table 1**. The study protocol was approved by the relevant research ethics committee of each country, and written consent was obtained from the parents according to the declaration of Helsinki (Austria: No. 30-200 ex. 17/18, Finland: No. 12/2018, Italy: No. 49/17, Spain: No. PI2017180, Sweden: No 2017/549, UK: No. UREC 18/15). Inclusion criteria were the parental consent and the willingness to participate within this study. In detail, parents were informed about the procedures and were asked to sign an informed consent and therefore, children without a signed parental informed consent were excluded from the study. Children received an information sheet and gave their verbal consent to participate, none of the children declined to participate to the study. Recruitment took place in both primary and secondary schools, as children with the age between 9 and 12 years are sufficiently evolved to understand and complete the selected sensory tests (see below) (42). The study design included tests with the children which were carried out directly at school during class, as one visit per class. The parents completed questionnaires relating to their children at home via on-line links, or on-paper, as preferred by the parent. These questionnaires included personal data of their children (e.g., age, sex, height, weight), eating habits of their children (food

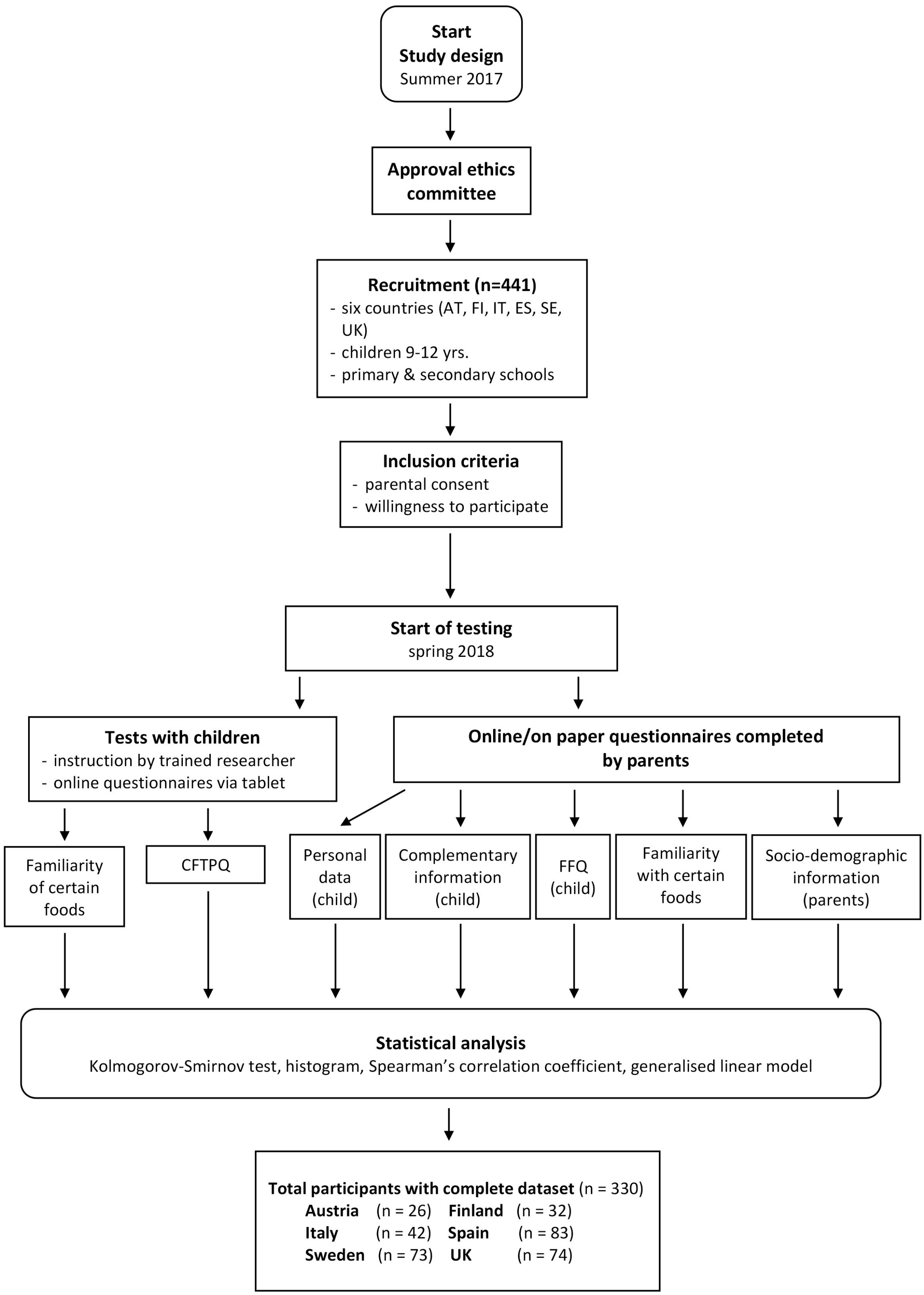

FIGURE 1 | Flow chart of the study.

TABLE 1 | Distribution of weight status.

BMI classification*	Total	Country						Sex	
		Austria	Finland	Italy	Spain	Sweden	UK	Males	Females
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Underweight <5 pct	23 (7.0)	3 (11.5)	3 (9.4)	4 (9.5)	6 (7.2)	4 (5.5)	3 (4.1)	9 (6.0)	14 (7.8)
Normal weight 5–84.9 pct	252 (76.4)	18 (69.2)	23 (71.9)	35 (83.3)	60 (72.3)	58 (79.5)	58 (78.4)	113 (74.8)	139 (77.7)
Overweight ≥ 85 pct	55 (16.7)	5 (19.2)	6 (18.8)	3 (7.1)	17 (20.5)	11 (15.1)	13 (17.6)	29 (19.2)	26 (14.5)
Overweight 85–94.9 pct	*40 (12.1)*	*4 (15.4)*	*5 (15.6)*	*2 (4.8)*	*12 (14.5)*	*9 (12.3)*	*8 (10.8)*	*23 (15.2)*	*17 (9.5)*
Obese ≥ 95 pct	*15 (4.6)*	*1 (3.8)*	*1 (3.1)*	*1 (2.4)*	*5 (6.0)*	*2 (2.7)*	*5 (6.8)*	*6 (4.0)*	*9 (5.0)*
Total	330 (100)	26 (100)	32 (100)	42 (100)	83 (100)	73 (100)	74 (100)	151 (100)	179 (100)

**Distribution of BMI categories according to CDC criteria in participating countries, pct=BMI-for-age-percentiles.*

frequency questionnaire, FFQ, mainly on fibre-rich and fibre-low foods), complementary information on their children (e.g., dental status), their familiarity with certain food items, and gave information on socio-demographic information (e.g., economic situation, education). Questionnaires and procedures for both children and parents were translated in English, reviewed by a native English speaker, and then translated in every language by two independent native speakers. The two translated versions were compared to identify discrepancies and reach consensus for an updated version. To improve comparability of the data collected in different cultures (43), procedures, experimental design and instructions to children and parents were the same in all countries and all tests were carried out within a 3-month period in the spring of 2018. After a team of trained researchers gave instructions, children worked on their own answering the questionnaires online via tablets. Children were tested by class or in smaller groups (4–5 children) on their own and were not influenced by their classmates. Tablets/computers were used by the children to complete the online questionnaire on familiarity with certain food items and the child food texture preference questionnaire (CFTPQ).

The data presented in this paper were collected as part of a wider study that developed and validated the child food preference questionnaire (CFTPQ), and further details of the overall study design are reported in Laureati et al. (40).

Anthropometric Measurements

In all six countries, the weight and the height of the children were self-reported by the parents within an online questionnaire. In addition, in Austria and the United Kingdom, the weight in kg (nearest to 0.1 kg) of the children was obtained with a portable scale (SECA). To determine children's height in cm (nearest to 0.1 cm) a portable stadiometer (SECA) in Austria and a tape measure mounted on the wall in the United Kingdom were used. The BMI was calculated by dividing the body weight in kg by the square of the height in m. High correlation coefficients of self-reported vs. measured BMI-data were obtained in UK ($r = 0.82$, $p < 0.01$) and Austria ($r = 0.94$, $p < 0.01$). This self-report validity could only be checked for UK and Austria, as there were no measured data in the other four countries. In addition to reporting numerical BMI data, BMI-for-age percentiles (BMI_pct) data are also reported in this paper. This accounts for the fact that children are individually and rapidly growing, hence the classification of weight status during childhood is complex (8). The Centers for Disease Control and Prevention (CDC), the International Obesity Task Force (IOTF) and the World Health Organisation (WHO) have developed suitable methods for BMI classification in children (44–46). CDC BMI_pct, suitable for comparing the BMI-data from different countries were used and for each participant the percentile was calculated. Furthermore, the BMI of participants was grouped into underweight (<5th percentile), normal weight (5th–84.9th percentile) or overweight (85th−94.9th percentile)/obesity (≥95th percentile) according to age- and sex-specific BMI percentiles cut-offs (46).

Child Food Texture Preference Questionnaire

The detailed procedure for data collection and calculation of the CFTPQ index was previously described elsewhere (40). In brief, a questionnaire with pictures of 17 pairs of soft/smooth and hard/particulate food were presented to the child, e.g., yoghurt with pieces/yoghurt without pieces, apple/apple sauce, orange/orange juice, or toasted bread/soft bread. Of each pair, the child chose the preferred one. The children also reported their familiarity with each item. When both food pictures of a pair were also reported familiar by the child, this pair was considered as valid an included within the analysis. Children with <8 valid pairs were excluded from analysis resulting in 309 datasets from 330 children. For each time choosing the soft/smooth version a value of 1, or for choosing the hard/particulate version a value of 2 was given. Individual CFTPQ indices were calculated. The score ranged from 0 to 100 with higher scores representing a preference for the hard/particulate food items.

Food Frequency Questionnaire for High/Low Fibre Foods

A 17-item questionnaire (40) of the frequency consumption of 12 fibre-rich (e.g., wholegrain products) and 5 low-fibre (e.g., refined "white" products) foods was completed by the parents for their children. Unreturned and incomplete questionnaires could not be included from the analysis ($n = 111$), resulting in $n = 330$ valid answers. Data were collected using a 6-point-category scale with answering options, less than once a month or never, 1–3 times per month, 1–3 times a week, 4–6 times a week, once a day, multiple times per day; in addition to category, I don't know. Parents were asked to recall their child's intake in the aforementioned categories over the previous 4—week period, and images were provided with the name of each food item. For each food item, the daily frequency equivalents (DFE) were calculated, so that the daily consumption quantity of all foods can be compared. DFE of 0= less than once a month or never, DFE of 0.07 = 1–3 times a month, DFE of 0.28 = 1–3 times a week, DFE of 0.71 = 4–6 times a week, DFE of 1 = once a day, DFE of 2.5 = multiple times a day, as published elsewhere (40).

Furthermore, the following scores were calculated from the FFQ Items:

Total consumption of high fibre foods (12 items, DFE): DFE sum of high fibre foods

$\sum$ [wholegrain versions of bread, porridge, cereals, biscuits, rice and pasta; fresh fruits, dried fruits, nuts/seeds, vegetables, potatoes, legumes]

Total consumption of wholemeal foods (5 items, DFE): DFE sum of wholegrain foods

$\sum$ [wholegrain versions of bread, cereals, biscuits, rice, pasta]

Total consumption of refined foods (5 items, DFE): DFE sum of refined foods

$\sum$ [refined versions of bread, cereals, biscuits, rice, pasta]

Wholegrain (%):

$$\frac{\textit{wholemeal alternatives}}{\textit{refined alternatives}} \times 100$$

Statistical Analysis

Distribution of data was tested with one sample Kolmogorov-Smirnov tests and histograms. Outlier analysis confirmed there were no outliers in BMI nor CFTPQ variables. As expected there were outliers in reported FFQ data, as the majority of children having low wholegrain consumption. However, this reflects current dietary habits and, therefore, as consumption of higher levels of wholegrain foods is of interest in this study the outliers were not removed in the primary analysis. Where significant effects relating consumption frequency to BMI were found secondary analysis was carried out excluding outliers and subsequently reported in the limitations section.

The association between BMI_pct and the consumption frequencies of specific food items and the CFTPQ index were tested with Spearman's correlation coefficient (**Table 2**). To assess the related effect of independent factors and covariates, the generalised linear model (GsLM, BMI_pct as dependent variable) was included in the analyses. As the BMI-for-age percentiles are important in the consideration of children's BMI and considering most of data were not normally distributed, including any transformation of BMI_pct, the generalised linear model analysis using the Tweedie model was carried out. Included (significant) factors and covariates were the country of participation, currently wearing a dental brace and total consumption of wholemeal foods (section Relationship between BMI-for-age percentiles and all other factors) whereas sex, age of introducing solids, whether parents went to university, economic situation, CFTPQ, total consumption of refined alternatives, high fibre foods and wholegrain (%) were excluded. Subsequently, single food items that significantly correlated with BMI_pct were tested within (wholegrain cereals, white biscuits, white pasta, and legumes). Four final models with one or more factor/covariate were built (models 1–4).

Effects showing a $p \leq 0.05$ were considered significant, while $p \leq 0.10$, although not significant but at a borderline level (47), were marked and reported as observed differences that may be worthy of additional investigation. The analysis was performed with SPSS V24 Software (IBM Analytics, USA).

RESULTS

Weight Status Across Country and Sex

Out of the 330 participating children with completed parental questionnaire, 76.4% had normal weight, 7.0% had underweight, 16.7% had overweight, whereof 4.6% had obesity (**Table 1**).

Taking children with overweight and obesity together, the highest proportions were reported for Spain (20.5%), followed by Austria (19.2%), Finland (18.8%), UK (17.6%). The countries with the lowest proportion of children with overweight and obesity were Sweden (15.1%) and Italy (7.1%). Partly, due to low subject numbers in many groups the differences between countries could not revealed significant.

Almost 6.0% of males and 7.8% of females had underweight, whereas 19.2% of males had overweight or obesity compared to 14.5% of females. The differences between males and females were only borderline significant (difference between males and females with overweight was $p = 0.087$).

Relationships Between BMI_pct and Texture Preference

Preference for softer (smooth) or harder (particulate) textures concluded from the CFTPQ index was not significantly correlated with the BMI_pct ($r = 0.056$, $p = 0.998$, $n = 309$). Austria was the only country showing a significant positive correlation between preference for harder/particulate textures (higher CFTPQ) and BMI_pct ($r = 0.441$, $p = 0.040$, $n = 22$); the positive correlation in males between texture preferences (CFTPQ) and BMI_pct was borderline significant ($r = 0.144$, $p = 0.086$, $n = 143$) (**Table 2**).

Associations of BMI_pct and Consumption of High/Low Fibre Foods

Parental responses on the 17-item food frequency questionnaire were completed and returned for 330 of the 441 participating children (**Table 2**). BMI_pct across the overall group correlated negatively with the reported consumption of wholegrain cereals ($r = -0.127$, $p = 0.021$), white pasta ($r = -0.122$, $p = 0.027$) and wholemeal products ($r = -0.113$, $p = 0.04$). Furthermore, BMI_pct correlated positively with the consumption frequency of white biscuits ($r = 0.119$, $p = 0.03$) and legumes ($r = 0.145$, $p = 0.008$). In summary, children with higher weight consumed less wholegrain cereals, white pasta and wholemeal products, whereas they consumed more white biscuits and legumes.

TABLE 2 | Spearman's correlation coefficient of the BMI-for-age percentiles (CDC) with texture preference and eating frequency.

	Total (*n* = 309)	**Austria** (*n* = 22)	**Finland** (*n* = 32)	**Italy** (*n* = 40)	**Spain** (*n* = 74)	**Sweden** (*n* = 69)	**UK** (*n* = 72)	**Males** (*n* = 143)	**Females** (*n* = 166)
CFTPQ-Index (by children)	0.056	0.441*	−0.104	0.029	0.163	−0.022	0.039	0.144(*)	−0.013
Food items and Indices (by adults)	Total (*n* = 330)	Austria (*n* = 26)	Finland (*n* = 25)	Italy (*n* = 42)	Spain (*n* = 83)	Sweden (*n* = 73)	UK (*n* = 74)	Males (*n* = 150)	Females (*n* = 173)
White bread (DFE)	−0.001	−0.101	−0.305	−0.091	0.183 (*)	0.081	−0.041	0.077	−0.062
Wholegrain bread (DFE)	−0.054	0.024	−0.050	0.103	−0.035	−0.045	−0.138	−0.158(*)	0.061
Wholegrain porridge (DFE)	0.010	0.231	−0.049	−0.125	0.045	0.064	0.031	−0.115	0.135
Cornflakes (DFE)	−0.041	−0.265	−0.118	0.010	0.029	−0.106	−0.087	−0.065	−0.028
Wholegrain cereals (DFE)	−0.127*	0.130	−0.181	−0.289(*)	−0.099	−0.160	−0.176	−0.225**	−0.031
Biscuits white (DFE)	0.119*	−0.258	−0.172	0.151	0.099	0.084	0.088	0.123	0.116
Wholegrain biscuits (DFE)	−0.001	−0.007	−0.431*	0.028	0.028	0.252*	0.107	−0.065	0.069
Fresh fruits (DFE)	−0.032	−0.048	0.010	−0.251	−0.037	0.003	−0.035	−0.036	−0.018
Dried fruits (DFE)	−0.089	0.052	−0.292	−0.009	−0.105	−0.062	−0.154	−0.229**	0.048
Total fruits (fresh and dried) (DFE)	−0.032	−0.050	−0.129	−0.261	−0.073	−0.029	−0.077	−0.100	0.003
Seeds and nuts (DFE)	−0.002	−0.182	−0.201	0.177	−0.226*	0.276*	−0.025	−0.069	0.065
Vegetables (DFE)	−0.027	−0.099	0.022	−0.206	0.121	0.055	−0.045	−0.041	0.015
Potatoes (DFE)	−0.020	0.027	0.077	0.055	−0.078	0.019	−0.117	−0.060	−0.007
Legumes (DFE)	0.145**	0.036	0.235	−0.066	0.203(*)	0.066	0.210(*)	0.043	0.227**
Rice white (DFE)	−0.016	−0.169	−0.370(*)	−0.005	0.110	−0.135	0.074	−0.042	0.013
Wholegrain rice (DFE)	−0.042	0.149	−0.101	0.068	−0.079	0.080	−0.182	−0.106	0.034
Pasta white (DFE)	−0.122*	−0.118	−0.180	−0.249	−0.030	−0.089	−0.046	−0.106	−0.145(*)
Wholegrain pasta (DFE)	−0.028	−0.005	−0.224	0.089	−0.028	0.110	0.059	−0.096	0.068
Vegetables and fruits (DFE)	−0.049	−0.080	−0.007	−0.246	−0.004	0.018	−0.068	−0.063	−0.022
TC of high fibre foods (DFE)†	−0.048	0.072	−0.089	−0.240	−0.077	0.076	−0.034	−0.111	0.048
TC of wholemeal foods (DFE)‡	−0.113*	0.160	−0.231	−0.075	−0.146	0.006	−0.126	−0.229**	0.022
TC of refined foods (DFE)§	0.014	−0.164	−0.321	−0.073	0.239*	−0.090	−0.025	0.041	−0.018
Wholegrain (%)‖	−0.067	0.305	0.107	−0.041	−0.188(*)	0.089	−0.084	−0.201*	0.086

*Comparison of texture preference (CFTPQ, child food texture preference questionnaire) and correlation of frequency consumption (daily frequency equivalents, DFE) of certain fibrerich/poor foods and Scores of fibrerich/poor foods reported by adults, TC, Total consumption; (DFE), daily frequency equivalents, (*) only borderline significant, but maybe worthy of an additional investigation $p \leq 0.1$, *$p \leq 0.05$, **$p \leq 0.01$.*

† *Total consumption of high fibre foods (12 items, DFE): Sum of daily consumption of high fibre foods (wholegrain: bread, porridge, cereals, biscuits, fresh fruit, dried fruit, seeds, vegetables, potatoes, legumes, rice, pasta).*

‡ *Total consumption of wholemeal foods (5 items, DFE): Sum of daily consumption of whole meal foods (bread, cereals, biscuits, rice, pasta).*

§ *Total consumption refined foods (5 items, DFE): Sum of refined foods (bread, cereals, biscuits, rice, pasta).*

‖ *Wholegrain (%): (whole-meal alternatives/refined alternatives) × 100.*

Country-Related Differences

There were a number of significant, mostly weak correlations of consumption frequency and BMI_pct that were found in the data from specific countries (**Table 2**).

In **Austria** ($n = 26$), there was no specific correlation with the BMI_pct and any food item.

Regarding **Finland** ($n = 25$), there was a negative correlation with whole grain biscuits ($r = -0.431$, $p = 0.032$) and a negative correlation for white rice with borderline significance ($r = -0.370$, $p = 0.069$).

For **Italy** ($n = 42$) it was revealed that the consumption of wholegrain cereals was negatively associated with BMI_pct, but not significantly ($r = -0.289$, $p = 0.064$).

In **Spain** ($n = 77$), there was a significant positive correlation between BMI_pct and the consumption of refined products ($r = 0.239$, $p = 0.029$), although this only reached borderline significance for white bread ($r = 0.183$, $p = 0.097$) and legume consumption ($r = 0.203$, $p = 0.066$). Furthermore, a significant negative correlation was found between BMI_pct and consumption of seeds and nuts (r =-0.226, $p = 0.040$), although the negative correlation with wholegrain (%) was only borderline significant ($r = -0.188$, $p = 0.088$).

Within the data of **Sweden** ($n = 72$), two positive correlations between BMI_pct and the consumption of whole grain biscuits ($r = 0.252$, $p = 0.031$) and seeds and nuts ($r = 0.276$, $p = 0.018$) was found.

Finally, in the **UK** ($n = 74$) a positive correlation but only borderline significant was found for the consumption of legumes and BMI_pct ($r = 0.210$, $p = 0.073$).Sex-related differences

Males with higher BMI_pcts consumed less **dried fruits** ($r = -0.229$, $p = 0.005$). Furthermore, the consumption of wholegrain products decreased with increasing BMI_pct (**wholemeal products** ($r = -0.229$, $p = 0.005$), wholegrain cereals ($r = -0.225$, $p = 0.006$), and only borderline significantly wholegrain bread ($r = -0.158$, $p = 0.054$) and wholegrains (%) ($r = -0.201$, $p = 0.014$).

In females, the BMI_pct positively correlated with the consumption of legumes ($r = 0.227$, $p = 0.003$) and negatively but only borderline significantly with the consumption of **white pasta** ($r = -0.145$, $p = 0.069$). No further sex-related correlations were revealed.

Relationship Between BMI_pct and All Other Factors

Additional analysis was carried out to investigate relationships between BMI_pct, socio-demographic, texture preference, and food intake. GsLM found that country had no significant effect on BMI_pct ($p = 0.095$, model 1), however, both wearing braces ($p = 0.045$, $B = -10.75$) and total consumption of wholemeal foods were significantly related to lower BMI_pct ($p = 0.037$, $B = -4.56$, model 2). The median BMI_pct for those wearing a dental brace was 37 compared to 55 for those without. There was no overall significant effect of texture preference (CFTPQ) on BMI_pct. Separate models were performed to check the effects of reported consumption of individual foods, each model considering groups of food items which did not correlate with one another. In model 3 a significant relationship was found between BMI_pct and wholegrain cereals ($p = 0.034$, $B = -10.17$), white pasta ($p = 0.020$, $B = -8.698$) but not for white biscuits ($p = 0.347$) and in model 4 between BMI_pct and legumes ($p = 0.041$, $B = 16.05$) and wholegrain cereals ($p = 0.034$, $B = -9.93$).

Once the outlying data were removed, secondary analysis (regression and GsLM) found no significant relationship between wholegrain consumption and BMI_pct.

DISCUSSION

This study aimed to explore the relationship between the weight status of 9–12 years old children across Europe, their consumption of fibre rich foods and their preference for soft or hard food textures. The main findings are:

- The **proportion of** overall children with overweight or obesity was 16.7% and with underweight 7.0%.
- BMI_pct had significant negative associations with **the overall consumption frequency** of wholegrain cereals, white pasta and wholemeal products, and was positively associated with consumption frequency of legumes and white biscuits.
- **Country-related associations** were found for BMI_pct and wholegrain biscuits (negative, Finland; positive, Sweden), seeds and nuts (negative, Spain; positive Sweden) and refined products (positive, Spain).
- BMI_pct had a significantly negative association with frequency of consuming wholemeal (-products) and dried fruits, but only **in males**.
- The BMI_pct was significantly higher with a higher consumption of legumes, but only **in females**.
- No differences in texture preference (CFTPQ) for hard/particulate or soft/smooth food pairs according to BMI_pct were found, except a significant positive correlation for Austria.

Weight Status and Covariates

The prevalence of children with overweight (including obesity) was found from highest to lowest in Spain (20.5%), Finland (18.8%), Austria (19.2%), the UK (17.6%), Sweden (15.1%), and by far lowest in Italy (7.1%). With the exception of Spain, our study found lower counts of children with overweight compared to literature (Spain: 19.2%, Finland: 23%, Austria: 25.2%, UK: 28%, Sweden: 17.7%, Italy: 20.8%) (48–51).

We assume that the lower reported distribution of overweight in these countries in our study might be explained by underreporting (52, 53) and/or the fact that the data were recorded in defined regions and are not representative for the whole country. For example, previous data has shown that inhabitants of Northern Italy have lower weight compared to people in the South (54, 55), and in line with this, children in our study were recruited in Northern Italy (Milano, Lombardy region). In England, the proportion of children with obesity has been found to be higher in areas of deprivation, significantly so for females (51). In the UK, part of the children in our study were recruited from urban areas in the South East which is not a region of high deprivation in England (56).

In Austria and the UK, measured and reported parental data of the children's height and weight (calculated BMI) had a very high agreement (respectively, 0.94 and 0.82, both $p < 0.001$). Furthermore, the use of different criteria in classification of weight status might limit the comparison between study results. In children, BMI for age and sex specific cut-off points are used according to population specific data e.g., WHO (45), CDC (46), or IOTF (44, 57). In our case, the CDC BMI-for-age percentiles were used. This classification is slightly different compared to the WHO criteria (57). There are high contrasts across different studies, as in an Italian sample only 2.7% children with underweight and 20.9% children with overweight were reported using WHO criteria (58).

There is less information on the proportion of children with underweight from studies in Europe compared to studies revealing overweight. Our study found rates of >7% in 4 out of 6 countries, in Italy (9.5%), Finland (9.4%), Austria (11.5%), and Spain (7.2%) still considering that these were self-reported data. In Spain, for 6–14 years old children, a mean prevalence of 10.2% for underweight was reported (59) using IOTF criteria, which is comparable to the present results.

Interestingly, we did not observe a tendency towards a lower BMI in southern compared to northern countries which was also noted in two recent epidemiological studies (2, 60). One might speculate, that diet styles might be changing, from the traditional southern Mediterranean diet, that is considered rich in fruits, vegetables and olive oil (61), towards more snacking and consumption of highly processed foods (62). This issue was addressed in recent studies found that a large part of the population of children and adolescents in the Southern countries have poor adherence to their traditional diet (63, 64). On the other hand, non-Mediterranean populations have been the major benefactors, since during the same period they have adopted a Mediterranean dietary pattern (65).

Another interesting result was that wearing a dental brace was accounting for a lower BMI (GsLM models; section 3.6) and this issue was already addressed elsewhere (66, 67). It is assumed that manipulating food is more difficult (68) and total food consumption might be lower (67) compared to children without wearing a dental brace. One previous study has reported mean body weight to significantly decrease during orthodontic treatment (from pre-treatment to 1 month into treatment), predominantly due to discomfort, however the study was of a limited size ($n = 30$) and in adults rather than children (66) Furthermore, a previous study found that increasing leptin-levels were reported in adults with orthodontic appliances, which might also lead to lower appetite and therefore to reduced food intake (69) and might contribute to a reduced BMI. In this context previous orthodontic research has found that adolescents with obesity had an increased initial tooth displacement and a higher rate of tooth movement compared to a normal-weight group, and it has been proposed that this may affect the treatment period (70–72), and therefore it is perhaps unsurprising that we found a difference in BMI related to wearing a dental brace.

Weight Status & Texture Preference

We did not find any association between children's weight status and the preference for soft/smooth or harder/particulate structure of foods reflected by the CFTPQ index, either across the study population as a whole or country wise, except for Austria. In Austria the correlation was significant and quite high ($r = 0.441$), however the number of children was low ($n = 22$) and should be interpreted carefully. So to speculate for Austria it is indicated that with increasing weight children do like the particulate/harder foods e.g., chocolate bar, crunchy cornflakes or whole carrots. This is an unexpected result as food requiring more oral processing (e.g., hard, crunchy, thick food) has previously been associated with lower eating rate, a consequent increase of satiety and reduced energy intake (73). One study of eating rate in children (4–5 years) found that those who ate faster had higher energy intake, and this was associated with increased BMI z-score and adiposity (74). It should be underlined that texture preferences were investigated with a picture-based questionnaire (CFTPQ) with items that were not necessarily representative of fibre-rich foods, and thus may only partially have captured the link between fibre consumption and texture-driven preferences. More research is needed to better understand this complex and interrelated association.

Weight Status & Consumption of High/Low Fibre Foods

Fibre consumption and consumption of fibre-rich foods in European countries does not meet current recommended daily intake guidelines (75–80), thus we anticipated that a consumption of high fibre foods would be negatively associated with BMI as indicated in literature (81, 82). In this study we found a weak, but significant association of increasing BMI_pct with a decreasing consumption frequency of wholegrain cereals and wholemeal products (bread, cereals, biscuits, pasta, rice). These results are mainly driven by Italy (cereals), Finland, Spain and the UK (wholemeal products) and by males (**Table 2**). Furthermore, both wholegrain products and wholegrain cereals were significant predictors of BMI percentiles, across the respective regression and GsLM models (section Relationship between BMI-for-age percentiles and all other factors). Koo et al. previously stated the importance of increasing wholegrain consumption on the management of childhood obesity (83), although studies show diverse results. In adults, within an intervention trial ($n = 316$) it was revealed that wholegrain consumption did not reduce body weight or fat (%) (10, 84). However, systematic reviews have concluded that the intake of high fibre cereals can lead to modest weight reduction in adults (10, 85). This was further confirmed by another survey ($n = 716$) on fibre intake in adolescents in schools. In one study it was revealed that fibre intake below the recommendations is associated with a higher risk of becoming overweight (81).

Furthermore, in the current study a lower consumption of dried fruits was associated with higher BMI_pct in males. It was reported that males eat less fruits than females and in this survey the preferences for fruit and vegetable was the main predictor (81%) of the sex difference here (16). Generally, independent of sex, a lower intake of fruits and vegetables which are high in fibre (and also vitamins and minerals) is associated with overweight in children (19) and also in adults (86, 87). In the survey on children's eating behavior ($n = 39$), it was shown that children with overweight and obesity ate significantly less fruits and vegetables than children with normal weight, but no sex differences for intake were found here (19). However, in the survey of Fogel and Blisserr ($n = 99$), the intake of fruits and vegetables did not show a significant correlation with BMI in 5–9 year old school children and again did not report on sex differences (88).

Legumes are fibre-rich and we hypothesised that the consumption would be lower in children with higher BMI_pct, as fibres are known to facilitate earlier satiation and improve diet quality (89). Moreover, intake of legumes in adults is associated with other health benefits such as reduced risk of cancer, cardiovascular disease (90) and metabolic syndrome (11). In contrast, we found that the legume consumption, especially in females, was positively associated with BMI (**Table 2**) and was further included within GsLM (section Relationship between BMI-for-age percentiles and all other factors) models. This result was mainly influenced by data from UK and Spain and we assume the result is related to typical preparation methods and combination with energy dense foods and ingredients. In Spain, the traditional way to prepare legume-dishes involves adding stewed vegetables and pork (chorizo, blood sausage, and ribs). Particularly, the combination with meat might increase the energy density in these dishes. In the UK, this higher legume intake may have been partly driven by a higher consumption of pre-prepared soft baked beans and/or cooked lentils as Dhal, very popular, easy and fast cooked affordable food (91, 92). Baked beans are generally high in sugar (91, 92) and Dhal high in fat. If used frequently in the diet in place of non-sugared/low-fat vegetables and legumes, it is perhaps more likely to contribute to higher rather than lower weight status. Moreover, our recent finding that children with higher legume consumption like softer texture fits here—as canned beans and boiled legumes are soft in their texture (40).

Limitations

A few limitations could have affected our results such as that we mainly analysed BMI from self-reported data. Here, to consider a qualitative procedure child's weight and height was asked via the same question in all countries. Therefore, correlation of self-reported BMI-data vs. measured ones could only be analysed for Austria and UK. We want to acknowledge that consistency in measurement is fundamental in clinical and epidemiological research and that discrepancy and bias might have effect our BMI data. Furthermore, different classification methods limit the comparability with other study results on BMI. The estimation of daily food intake in children is important and often performed by using a FFQ. This is a widely applied and relevant instrument in epidemiological investigations in assessing children nutrition (93). FFQs are simple to administer and cost-efficient, although have limited validity and reliability in the context of over- and underestimation and overly rely on subject's memory (94). Some of these limitations are exacerbated where the questionnaire incorporates a higher number of food items. The use of indices which summarise food items and groups are of interest to reduce complexity and have been shown to be valid in young children, as have FFQs which use shorter recall reporting periods (95). Furthermore, using pictures combined with portion sizes, clear instructions and question period (e.g., last month) are relevant in valid food questionnaire instruments, especially in epidemiological approaches (96, 97). Therefore, in this study we utilised a FFQ that was short be containing only 17 items of direct relevance to the study, it asked parents only to remember the last 4 week period, and it provided images of each food item. The item number might have been too few to determine more specific differences (e.g., for legumes) and information on preparation methods would have been helpful. A further improvement in future studies would be to add portion size. As exact fibre intake could not be calculated, we were only able to estimate the intake of foods by daily frequencies portions. Very few children in the study consumed a high proportion of wholegrain foods. Where significant relationships were found between consumption of wholemeal products and BMI_pct, it must be noted that the consumption data contained outliers. Whereas, half of the children in the study consumed less than half of a daily equivalent of wholemeal alternatives (wholegrain bread, cereals, biscuits, rice or pasta), there were only 23 children (7%) reported to consume 2 or more DFEs of these alternatives. Once the outlying data were removed, secondary analysis (GsLM) found no significant relationship between wholegrain consumption and BMI-pct. We suggest this justifies the need for intervention studies of children in this age group comparing high wholegrain diets to standard diets. Furthermore, as food high in fibre also contains minerals, vitamins, and phytochemicals which are known to have positive health effects, this might additionally influence to the BMI related outcomes. Finally, even though the sample size was appropriate overall (n=330), we acknowledge the fact that for some variables (e.g., country-related differences) a larger sample size would have been beneficial. Future studies should confirm and extend our findings, here, the parental compliance should be considered as we were faced with low response.

CONCLUSIONS

Significant associations between parent-reported intake of fibre rich and also fibre poor foods and the child BMI-for-age percentile were found, but were depended on specific foods and sex. Overall there was a weak, but significant, negative association between the total consumption of wholemeal products (wholegrain equivalent of bread, cereals, biscuits, rice, and pasta) and weight status. Furthermore, there was no direct evidence that texture preference for soft and hard food is associated with BMI_pct of 9–12-year-old children. Moreover, cultural differences and sex need to be considered as determinants of food preferences. Further research encompassing a wider range of single foods including preparation methods and full recipes could assist in gaining deeper insights in the relationship of weight status, fibre consumption, and texture preferences of children.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article may be made available by the authors pending a specific request at the discretion of the Data Access and Management Commission of the E3S - Working group on Children.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Austria: No. 30-200 ex. 17/18, Finland: No. 12/2018, Italy: No. 49/17, Spain: No. PI2017180, Sweden: No 2017/549, UK: No. UREC 18/15. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HJ, ML, VA, MS, PS, and GZ: conceptualisation. RK, BA, ML, MS, PS, GZ, and LM: data curation. MH-W, BA, ML, VA, MS, and PS: funding acquisition. MH-W, RK, and LM: writing–original draft. BA, HJ, ML, VA, MS, PS, and GZ: writing–review & editing. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet.* (2017) 390:2627–42. doi: 10.1016/S0140-6736(17)32129-3
2. Spinelli A, Buoncristiano M, Kovacs VA, Yngve A, Spiroski I, Obreja G, et al. Prevalence of severe obesity among primary school children in 21 European countries. *Obes Facts.* (2019) 12:244–58. doi: 10.1159/000500436
3. Biro FM, Wien M. Childhood obesity and adult morbidities. *Am J Clin Nutr.* (2010) 91:1499–505. doi: 10.3945/ajcn.2010.28701B
4. Whitaker RC, Wright JA, Pepe MS, Seidel KS, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med.* (1997) 337:869–73. doi: 10.1056/NEJM199709253371301
5. Guh DP, Zangh W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health.* (2009) 9:88. doi: 10.1186/1471-2458-9-88
6. Van Kruijsdijk RC, Van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev.* (2009) 18:2569–78. doi: 10.1158/1055-9965.EPI-09-0372
7. Nejat EJ, Polotsky AJ, Pal L. Predictors of chronic disease at midlife and beyond - the health risks of obesity. *Maturitas.* (2010) 65:106–11. doi: 10.1016/j.maturitas.2009.09.006
8. Li K, Haynie D, Lipsky L, Palla H, Iannotti RJ, Simons-Morton B. Assessment of adolescent weight status: similarities and differences between CDC, IOTF, and WHO references. *Prev Med.* (2016) 87:151–4. doi: 10.1016/j.ypmed.2016.02.035
9. Marlett JA, McBurney MI, Slavin JL. Position of the American dietetic association: health implications of dietary fiber. *J Am Diet Assoc.* (2002) 102:993–1000. doi: 10.1016/S0002-8223(02)90228-2
10. Brownlee IA, Chater PI, Pearson JP, Wilcox MD. Dietary fibre and weight loss: Where are we now? *Food Hydrocoll.* (2017) 68:186–91. doi: 10.1016/j.foodhyd.2016.08.029
11. Wei B, Liu Y, Lin X, Fang Y, Cui J, Wan J. Dietary fiber intake and risk of metabolic syndrome: A meta-analysis of observational studies. *Clin Nutr.* (2018) 37:1935–1942. doi: 10.1016/j.clnu.2017.10.019
12. Cioffi I, Ibrugger S, Bache J, Thomassen MT, Contaldo F, Pasanisi F, et al. Effects on satiation, satiety and food intake of wholegrain and refined grain pasta. *Appetite.* (2016) 107:152–8. doi: 10.1016/j.appet.2016.08.002
13. Martini D, Brusamolino A, Del Bo C, Laureati M, Porrini M, Riso P. Effect of fiber and protein-enriched pasta formulations on satiety-related sensations and afternoon snacking in Italian healthy female subjects. *Physiol Behav.* (2017) 185:61–9. doi: 10.1016/j.physbeh.2017.12.024
14. Yngve A, Poortvliet E, Elmadfa I, Brug J, Ehrenblad B, Franchini B, et al. Fruit and vegetable intake in a sample of 11-year-old children in 9 European countries: the pro children cross-sectional survey. *Ann Nutr Metab.* (2005) 49:236–45. doi: 10.1159/000087247
15. Dibsdall L, Lambert N, Bobbin R, Frewer L. Low-income consumers' attitudes and behaviour towards access, availability and motivation to eat fruit and vegetables. *Public Health Nutr.* (2003) 6:159–68. doi: 10.1079/PHN2002412
16. Bere E, Brug J, Klepp K-I. Why do boys eat less fruit and vegetables than girls? *Public Health Nutr.* (2008) 11:321–5. doi: 10.1017/S1368980007000729

17. Friel S, Newell J, Kelleher C. Who eats four or more servings of fruit and vegetables per day? Multivariate classification tree analysis of data from the 1998 survey of lifestyle, attitudes and nutrition in the republic of Ireland. *Public Health Nutr.* (2005) 8:159–69. doi: 10.1079/PHN2004670
18. Rasmussen M, Krølner R, Klepp K-I, Lytle L, Brug J, Bere E, et al. Determinants of fruit and vegetable consumption among children and adolescents: a review of the literature. Part I: quantitative studies. *Int J Behav Nutr Phys Act.* (2006) 3:1–19. doi: 10.1186/1479-5868-3-22
19. Miller P, Moore R, Kral T. Children's daily fruit and vegetable intake: associations with maternal intake and child weight status. *J Nutr Educ Behav.* (2011) 43:396–400. doi: 10.1016/j.jneb.2010.10.003
20. Guenther PM, Dodd KW, Reedy J, Krebs-Smith SM. Most Americans eat much less than recommended amounts of fruits and vegetables. *J Am Diet Assoc.* (2006) 106:1371–9. doi: 10.1016/j.jada.2006.06.002
21. Pryor WA, Stahl W, Rock CL. Beta carotene: from biochemistry to clinical trials. *Nutr Rev.* (2009) 58:39–53. doi: 10.1111/j.1753-4887.2000.tb07810.x
22. Steinmetz K, Potter J. Vegetables, fruits and cancer. I. Epidemiology. *Cancer Causes Control.* (1991) 2:325–57. doi: 10.1007/BF00051672
23. Ha A, Bae S, Urrutia-Rojas X, Singh KP. Eating and physical activity practices in risk of overweight and overweight children: compliance with US department of agriculture food guide pyramid and with national association for sport and physical activity guidelines for children. *Nutr Res.* (2005) 25:905–15. doi: 10.1016/j.nutres.2005.09.010
24. Jahns L, Siega-Riz AM, Popkin BM. The increasing prevalence of snacking among US children from 1977 to 1996. *J Pediatr.* (2001) 138:493–8. doi: 10.1067/mpd.2001.112162
25. Cross A, Babicz D, Cushman LF. Snacking patterns among 1,800 adults and children. *J Am Diet Assoc.* (1994) 94:1398–403. doi: 10.1016/0002-8223(94)92542-9
26. Samuelson G, Bratteby L, Enghardt H, Hedgren M. Food habits and energy and nutrient intake in Swedish adolescents approaching the year 2000. *Acta Paediatr Suppl.* (1996) 11:1651–2227. doi: 10.1111/j.1651-2227.1996.tb14268.x
27. Heald FP. Fast food and snakc fod: Beneficial or deleterious. *J Adolesc Health.* (1992) 13:380–3. doi: 10.1016/1054-139X(92)90033-8
28. Jeffery RW, French SA. Epidemic obesity in the United States: are fast foods and television viewing contributing? *Am J Public Health.* (1998) 88:277–80. doi: 10.2105/AJPH.88.2.277
29. Gortmaker S, Dietz W, Cheung L. Inactivity, diet, and the fattening of America. *J Am Diet Assoc.* (1990) 90:1247–1252.5.
30. Moding KJ, Bellows LL, Grimm KJ, Johnson SL. A longitudinal examination of the role of sensory exploratory behaviors in young children's acceptance of new foods. *Physiol Behav.* (2020) 218:112821. doi: 10.1016/j.physbeh.2020.112821
31. Werthmann J, Jansen A, Havermans R, Nederkoorn C, Kremers S, Roefs A. Bits and pieces. Food texture influences food acceptance in young children. *Appetite.* (2015) 84:181–187. doi: 10.1016/j.appet.2014.09.025
32. Lukasewycz LD, Mennella JA. Lingual tactile acuity and food texture preferences among children and their mothers. *Food Qual Prefer.* (2012) 26:58–66. doi: 10.1016/j.foodqual.2012.03.007
33. Demonteil L, Tournier C, Agnès M, Dusoulier M, Weenen H, Nicklaus S. Longitudinal study on acceptance of food textures between 6 and 18 months. *Food Qual Prefer.* (2019) 71:54–65. doi: 10.1016/j.foodqual.2018.05.010
34. Szczesniak A. Consumer awareness of and attitudes to food texture. *J Texture Stud.* (1972) 3:206–217. doi: 10.1111/j.1745-4603.1972.tb00624.x
35. Nederkoorn C, Jansen A, Havermans RC. Feel your food. The influence of tactile sensitivity on picky eating in children. *Appetite.* (2015) 84:7–10. doi: 10.1016/j.appet.2014.09.014
36. Cox DN, Melo L, Zabaras D, Delahunty CM. Acceptance of health-promoting *Brassica* vegetables: the influence of taste perception, information and attitudes. *Public Health Nutr.* (2012) 15:1474–82. doi: 10.1017/S1368980011003442
37. Dinehart ME, Hayes JE, Bartoshuk LM, Lanier SL, Duffy VB. Bitter taste markers explain variability in vegetable sweetness, bitterness, and intake. *Physiol Behav.* (2006) 87:304–13. doi: 10.1016/j.physbeh.2005.10.018
38. Dinnella C, Morizet D, Masi C, Cliceri D, Depezay L, Appleton KM, et al. Sensory determinants of stated liking for vegetable names and actual liking for canned vegetables: a cross-country study among European adolescents. *Appetite.* (2016) 107:339–47. doi: 10.1016/j.appet.2016.08.110
39. Krølner R, Rasmussen M, Brug J, Klepp K-I, Wind M, Due P. Determinants of fruit and vegetable consumption among children and adolescents: a review of the literature. Part II: qualitative studies. *Int J Behav Nutr Phys Act.* (2011) 8:1–38. doi: 10.1186/1479-5868-8-112
40. Laureati M, Sandvik P, Almli LV, Sandell M, Zeinstra GG, Methven L, et al. Individual differences in texture preferences among european children: development and validation of the child food texture preference questionnaire (CFTPQ). *Food Qual Prefer.* (2020) 80:103828. doi: 10.1016/j.foodqual.2019.103828
41. Proserpio C, Laureati M, Invitti C, Pagliarini E. Reduced taste responsiveness and increased food neophobia characterize obese adults. *Food Qual Prefer.* (2018) 63:73–9. doi: 10.1016/j.foodqual.2017.08.001
42. Laureati M, Pagliarini E, Toschi TG, Monteleone E. Research challenges and methods to study food preferences in school-aged children: a review of the last 15years. *Food Qual Prefer.* (2015) 46:92–102. doi: 10.1016/j.foodqual.2015.07.010
43. Ares G. Methodological issues in cross-cultural sensory and consumer research. *Food Qual Prefer.* (2018) 64:253–63. doi: 10.1016/j.foodqual.2016.10.007
44. Cole TJ, Bellizzi MC, Flegel KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ.* (2000) 320:1240. doi: 10.1136/bmj.320.7244.1240
45. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ.* (2007) 85:660–7. doi: 10.2471/BLT.07.043497
46. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat.* (2002) 246:1–190.
47. Hackshaw A, Kirkwood A. Interpreting and reporting clinical trials with results of borderline significance. *BMJ.* (2011) 343:d3340. doi: 10.1136/bmj.d3340
48. BMGF. *Childhood Obesity Surveillance Initiative (COSI) - Bericht Österreich 2017*. Vienna: BMGF (2017). 1–32p.
49. Börnhorst C, Siani A, Russo P, Kourides Y, Sion I, Molnár D, et al. Early life factors and inter-country heterogeneity in BMI growth trajectories of european children: the IDEFICS study. *PLOS ONE.* (2016) 11:e0149268. doi: 10.1371/journal.pone.0149268
50. Currie C, Zanotti C, Morgan A, Currie D, de Looze M, Roberts C, et al. *Social Determinants of Health and Well-Being Among Young People: Health Behaviour in School-Aged Children (HBSC) Study : International Report From the 2009-2010 Survey*. Copenhagen: World Health Organization, Regional Office for Europe (2012).
51. Conolly A, Craig S. *Health Survey for England 2018 Overweight and Obesity in Adults and Children*. London: Health and Social Care Information Centre (2019). 1–31p.
52. Rietmeijer-Mentink M, Paulis WD, van Middelkoop M, Bindels PJE, van der Wouden JC. Difference between parental perception and actual weight status of children: a systematic review. *Matern Child Nutr.* (2013) 9:3–22. doi: 10.1111/j.1740-8709.2012.00462.x
53. Karunanayake CP, Rennie DC, Hildebrand C, Lawson JA, Hagel L, Dosman JA, et al. Actual body weight and the parent's perspective of child's body weight among rural Canadian children. *Children.* (2016) 3:13. doi: 10.3390/children3030013
54. Brunello G, Labartino G. Regional differences in overweight rates: the case of Italian regions. *Econ Hum Biol.* (2014) 12:20–9. doi: 10.1016/j.ehb.2012.10.001
55. Cacciari E, Milani S, Balsamo A, Dammacco F, Luca FD, Chiarelli F, et al. Italian cross-sectional growth charts for height, weight and BMI (6–20 y). *Eur J Clin Nutr.* (2002) 56:171–80. doi: 10.1038/sj.ejcn.1601314
56. Noble S, McLennan D, Noble M, Plunkett E, Gutacker N, Silk M, et al. *English Indices of Deprivation 2019: Research Report.* London (2019). 1–87p. Available online at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/833947/IoD2019_Research_Report.pdf
57. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity: extended international BMI

cut-offs. *Pediatr Obes.* (2012) 7:284–94. doi: 10.1111/j.2047-6310.2012.00064.x

58. Ashi H, Campus G, Klingberg G, Forslund HB, Lingström P. Childhood obesity in relation to sweet taste perception and dental caries – a cross-sectional multicenter study. *Food Nutr Res.* (2019) 63:1682. doi: 10.29219/fnr.v63.1682
59. de Ruiter I, Olmedo-Requena R, Sánchez-Cruz JJ, Jiménez-Moleón JJ. Trends in child obesity and underweight in Spain by birth year and age, 1983 to 2011. *Rev Españ Cardiol.* (2017) 70:646–55. doi: 10.1016/j.rec.2016.12.013
60. Ahrens W, Pigeot I, Pohlabeln H, De Henauw S, Lissner L, Molnár D, et al. Prevalence of overweight and obesity in European children below the age of 10. *Int J Obes.* (2014) 38:S99–107. doi: 10.1038/ijo.2014.140
61. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the mediterranean diet: a literature review. *Nutrients.* (2015) 7:9139–53. doi: 10.3390/nu7115459
62. Fernández-Alvira JM, Bammann K, Eiben G, Hebestreit A, Kourides YA, Kovacs E, et al. Prospective associations between dietary patterns and body composition changes in European children: the IDEFICS study. *Public Health Nutr.* (2017) 20:3257–65. doi: 10.1017/S1368980017002361
63. Naska A, Trichopoulou A. Back to the future: The Mediterranean diet paradigm. *Nutr Metab Cardiovasc Dis.* (2014) 24:216–9. doi: 10.1016/j.numecd.2013.11.007
64. Rosi A, Paolella G, Biasini B, Scazzina F, Alicante P, De Blasio F, et al. Dietary habits of adolescents living in North America, Europe or Oceania: a review on fruit, vegetable and legume consumption, sodium intake, and adherence to the mediterranean diet. *Nutr Metab Cardiovasc Dis.* (2019) 29:544–60. doi: 10.1016/j.numecd.2019.03.003
65. da Silva R, Bach-Faig A, Raidó Quintana B, Buckland G, Vaz de Almeida MD, Serra-Majem L. Worldwide variation of adherence to the mediterranean diet, in 1961–1965 and 2000–2003. *Public Health Nutr.* (2009) 12:1676–84. doi: 10.1017/S1368980009990541
66. Ajwa N, Makhdoum L, Alkhateeb H, Alsaadoun A, Alqutub S, Alkhumayes H. The impact of orthodontic appliance on body weight changes, dietary habits, and self-perceived discomfort in early stages of orthodontic treatment. *Glob J Health Sci.* (2018) 10:11–7. doi: 10.5539/gjhs.v10n9p11
67. Schott TC, Ludwig B. Quantification of wear-time adherence of removable appliances in young orthodontic patients in relation to their BMI: a preliminary study. *Pat Prefer Adher.* (2014) 8:1587–95. doi: 10.2147/PPA.S69586
68. Farzanegan F, Zebarjad SM, Alizadeh S, Ahrari F. Pain reduction after initial archwire placement in orthodontic patients: a randomized clinical trial. *Am J Orthod Dentofacial Orthop.* (2012) 141:169–73. doi: 10.1016/j.ajodo.2011.06.042
69. Srinivasan B, Chitharanjan A, Kailasam V, Lavu V, Ganapathy V. Evaluation of leptin concentration in gingival crevicular fluid (GCF) during orthodontic tooth movement and its correlation to the rate of tooth movement. *J Orthod Sci.* (2019) 8:6. doi: 10.4103/jos.JOS_58_18
70. Saloom HF, Papageorgiou SN, Carpenter GH, Cobourne MT. Impact of obesity on orthodontic tooth movement in adolescents: a prospective clinical cohort study. *J Dent Res.* (2017) 96:547–54. doi: 10.1177/0022034516688448
71. Michelogiannakis D, Rossouw PE, Khan J, Akram Z, Menenakos E, Javed F. Influence of increased body mass index on orthodontic tooth movement and related parameters in children and adolescents: a systematic review of longitudinal controlled clinical studies. *J Orthod.* (2019) 46:323–34. doi: 10.1177/1465312519873669
72. von Bremen J, Lorenz N, Ludwig B, Ruf S. Increased BMI in children—an indicator for less compliance during orthodontic treatment with removable appliances. *Eur J Orthod.* (2018) 40:350–5. doi: 10.1093/ejo/cjy007
73. McCrickerd K, Lim CM, Leong C, Chia EM, Forde CG. Texture-based differences in eating rate reduce the impact of increased energy density and large portions on meal size in adults. *J Nutr.* (2017) 147:1208–17. doi: 10.3945/jn.116.244251
74. Fogel A, Goh AT, Fries LR, Sadananthan SA, Velan SS, Michael N, et al. Faster eating rates are associated with higher energy intakes during an *ad libitum* meal, higher BMI and greater adiposity among 4·5-year-old children: results from the growing up in Singapore towards healthy outcomes (GUSTO) cohort. *Br J Nutr.* (2017) 117:1042–51. doi: 10.1017/S0007114517000848
75. Elmadfa I, Institut für Ernährungswissenschaften (Wien), Österreich, Bundesministerium für Gesundheit. *Österreichischer Ernährungsbericht 2012.* Wien: Bundesministerium für Gesundheit (2012). 1–424p.
76. Public Health England. *National Diet and Nutrition Survey. Years 1 to 9 of the Rolling Programme (2008/2009 – 2016/2017): Time Trend and Income Analyses.* Public Health England (2019). 56p.
77. López-Sobaler AM, Aparicio A, Rubio J, Marcos V, Sanchidrián R, Santos S, et al. Adequacy of usual macronutrient intake and macronutrient distribution in children and adolescents in Spain: a national dietary survey on the child and adolescent population, ENALIA 2013–2014. *Eur J Nutr.* (2019) 58:705–19. doi: 10.1007/s00394-018-1676-3
78. Pietinen P, Paturi M, Reinivuo H, Tapanainen H, Valsta LM. FINDIET 2007 Survey: energy and nutrient intakes. *Public Health Nutr.* (2010) 13:920–4. doi: 10.1017/S1368980010001102
79. Moraeus L, Lemming EW, Hursti U-KK, Arnemo M, Sipinen JP, Lindroos A-K. Riksmaten adolescents 2016–17: a national dietary survey in Sweden – design, methods, and participation. *Food Nutr Res.* (2018) 62:1381. doi: 10.29219/fnr.v62.1381
80. Sette S, D'Addezio L, Piccinelli R, Hopkins S, Le Donne C, Ferrari M, et al. Intakes of whole grain in an Italian sample of children, adolescents and adults. *Eur J Nutr.* (2017) 56:521–33. doi: 10.1007/s00394-015-1097-5
81. De Carvalho ÉB, Vitolo MR, Gama CM, Lopez FA, Taddei JAC, de Morais MB. Fiber intake, constipation, and overweight among adolescents living in São Paulo city. *Nutrition.* (2006) 22:744–9. doi: 10.1016/j.nut.2006.05.001
82. Mann KD, Pearce MS, McKevith B, Thielecke F, Seal CJ. Whole grain intake in the UK remains low: results from the national diet and nutrition survey rolling programme years 1, 2 and 3. *Proc Nutr Soc.* (2015) 74:E60. doi: 10.1017/S0029665115000750
83. Koo HC, Poh BK, Ruzita AT. Intervention on whole grain with healthy balanced diet to manage childhood obesity (GReat-Child^{TM}trial): study protocol for a quasi-experimental trial. *Springerplus.* (2016) 5:840. doi: 10.1186/s40064-016-2431-y
84. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, et al. Markers of cardiovascular risk are not changed by increased whole-grain intake: the WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr.* (2010) 104:125–34. doi: 10.1017/S0007114510000644
85. Cho SS, Qi L, Fahey GC, Klurfeld DM. Consumption of cereal fiber, mixtures of whole grains and bran, and whole grains and risk reduction in type 2 diabetes, obesity, and cardiovascular disease. *Am J Clin Nutr.* (2013) 98:594–619. doi: 10.3945/ajcn.113.067629
86. Nour M, Lutze SA, Grech A, Allman-Farinelli M. The relationship between vegetable intake and weight outcomes: a systematic review of cohort studies. *Nutrients.* (2018) 10:1626. doi: 10.3390/nu10111626
87. Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A, et al. Critical review: vegetables and fruit in the prevention of chronic diseases. *Eur J Nutr.* (2012) 51:637–63. doi: 10.1007/s00394-012-0380-y
88. Fogel A, Blissett J. Effects of sucrose detection threshold and weight status on intake of fruit and vegetables in children. *Appetite.* (2014) 83:309–16. doi: 10.1016/j.appet.2014.09.003
89. Ahn CH, Bae JH, Cho YM. Premeal consumption of a protein-enriched, dietary fiber-fortified bar decreases total energy intake in healthy individuals. *Diabetes Metab J.* (2019) 43:879–92. doi: 10.4093/dmj.2018.0202
90. Mitchell D, Rumney J, Campbell J, Cai D, Curran J, Marinangeli C. Increasing pulse intake improves diet quality in adults in the US (P18-114-19). *Cur Dev Nutr.* (2019) 3:1677. doi: 10.1093/cdn/nzz039.P18-114-19
91. Statista. *Canned Beans: Weekly Consumption in the UK 2006-2016/17. Statista.* (2020). Available online at: https://www.statista.com/statistics/721177/weekly-uk-household-consumption-of-canned-beans-united-kingdom-uk/ (accessed February 3, 2020).
92. Rauber F, Da Costa Louzada ML, Steele EM, Millett C, Monteiro CA, Levy RB. Ultra-processed food consumption and chronic non-communicable diseases-related dietary nutrient profile in the UK (2008–2014). *Nutrients.* (2018) 10:587. doi: 10.3390/nu10050587

93. Vilela S, Severo M, Moreira T, Ramos E, Lopes C. Evaluation of a short food frequency questionnaire for dietary intake assessment among children. *Eur. J Clin Nutr.* (2019) 73:679–91. doi: 10.1038/s41430-018-0200-4
94. Bell LK, Golley RK, Magarey AM. Short tools to assess young children's dietary intake: a systematic review focusing on application to dietary index research. *J Obes.* (2013) 2013:709626. doi: 10.1155/2013/709626
95. Lovell A, Bulloch R, Wall CR, Grant CC. Quality of food-frequency questionnaire validation studies in the dietary assessment of children aged 12 to 36 months: a systematic literature review. *J Nutr Sci.* (2017) 6:e16. doi: 10.1017/jns.2017.12
96. Vuholm S, Lorenzen JK, Kristensen M. Relative validity and reproducibility of a food frequency questionnaire to assess dietary fiber intake in Danish adults. *Food Nutr Res.* (2014) 58:24723. doi: 10.3402/fnr.v58.24723
97. Shim JS, Oh K, Kim HC. Dietary assessment methods in epidemiologic studies. *Epidemiology and Health.* (2014) 36:e2014009. doi: 10.4178/epih/e2014009

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Dietary Inflammatory Index Is Related to Heart Failure Risk and Cardiac Function: A Case–Control Study in Heart Failure Patients

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Aims: Previous studies suggest that diet and inflammation are important risk factors for heart failure (HF); however, the associations remain unclear. The Dietary Inflammatory Index (DII®) was established to measure the inflammatory capacity of individuals' diet. This study aimed to explore the DII in HF subjects compared with controls.

Methods and Results: We conducted a case–control (116 cases and 113 controls) study that recruited in the similar clinics. DII scores were calculated based on dietary intakes. N-Terminal pro-brain natriuretic peptide (NT-proBNP) levels and ejection fraction (EF) were assessed in both groups. In order to analyze DII scores with HF as the outcome, we used conditional logistic regression. A linear regression was applied to explore the associations between the DII and left ventricular EF (LVEF).
There was statistically significant difference in DII scores in cases vs. controls (−0.16 ± 1.37 vs. −0.33 ± 1.67; $p = 0.040$). Conditional logistic regression has shown that subjects with higher DII scores had higher risk of HF. For every one-point rise in DII score, the odds of having HF increased by 30% (OR: 1.30; CI: 1.03, 1.69; $p = 0.047$). The EF was inversely associated with saturated fatty acid ($\beta = -0.34$, 95% CI: −0.61, −0.07; $p = 0.012$). Subjects with higher DII scores had higher NT-proBNP levels and had lower EF.

Conclusion: The DII score was associated with high probability of HF. It appears that consumption of anti-inflammatory diet may lead to the prevention of HF and therefore suggests that dietary modification with the goal of reducing DII scores could be a valuable strategy for improving clinical outcomes in these patients.

Keywords: dietary inflammatory index, dietary intake, inflammation, case–control studies, heart failure

BACKGROUND

Heart failure (HF) affects an estimated 23 million people worldwide (1) and leads to substantial numbers of hospitalizations and health-care costs. Therefore, prevention of HF has become a major public health concern, not just a major cause of its increasing prevalence but also because of its deleterious effect on quality of life (2). Low-grade inflammation is a principal factor leading to development of HF (3, 4). Furthermore, erythrocyte sedimentation rate (ESR), as a marker of inflammation, was a significant predictor of HF (3, 5). In particular, it has been shown that some environmental factors, such as dietary intake, are important in triggering an inflammatory response (6, 7).

The relationship between diet and HF is well-established. Healthy dietary patterns such as the Mediterranean diet are independently connected with a lower possibility of all-cause cardiovascular and cancer-related mortality (8, 9). Several studies have shown that certain nutrients can help alleviate diseases and modify systemic inflammation (9–12). On the other hand, diets with high sugar, refined starches, and saturated and trans-fatty acids and are poor in antioxidants and fibers may cause an activation of chronic inflammation (13). Undeniably, dietary patterns have long been known as potent factors leading to the acceleration of HF pathogenesis (14). Many dietary components have long been supposed to play a vital role in development of inflammation via both anti-inflammatory and pro-inflammatory mechanisms. Therefore, it is important to develop a scoring algorithm that takes into account these influences within an overall dietary pattern. Although most of the studies focus on whole diet in underlying mechanisms leading to HF development (15), knowledge about dietary components of that specific dietary components is still limited especially because the pathways leading to HF are not fully understood.

The dietary inflammatory index (DII®) has been designed to quantify the potential inflammatory properties of a diet (16). The association between DII and various inflammatory markers has been established by multiple cohorts (17, 18). A large growing body of data investigating the associations between DII and risk of a wide range of non-communicable diseases including obesity, diabetes, cancers, and cardiovascular disease (CVD) has emerged (18–21).

The DII is not just restricted to macronutrients and micronutrients; it also includes flavonoids and frequently consumed parts of the diet such as tea and spices. The potential interactions among nutrients also must be taken into account (22). Moreover, individuals with greater DII had more risk of metabolic disorders (19, 23). As start and development of HF is related to a chronic pro-inflammatory state (24), we hypothesized that higher DII scores (or higher DII quartiles) are associated with HF and worse clinical outcomes. Based on previous research with the DII and evidence linking inflammation with CVD, this study aimed to examine the relationship between the DII and HF in a case–control research conducted in Iran.

METHODS

Subjects

The current hospital-based matched case–control study was conducted from January 2017 through February 2018 in cardiac medical centers in Tabriz, East Azerbaijan Province, Iran. Subjects with HF were recruited by convenience sampling from the Madani Heart Center under the supervision of Tabriz University of Medical Sciences. The hospital is a single specialty heart hospital, which is the largest of its kind in the northwest of the country, with 330 administrative and clinical staff.

The sample size calculation has been explained before. Briefly, the sample size was designed by the following formula: $n = [(Z\alpha/2 + Z\beta)2 \times \{(p1\ (1{-}p1) + (p2\ (1{-}p2))\}]/(p1{-}p2)^2$, where p1 is the proportion of the subjects with low DII, α-error = 0.05, and power = 80% (1–β) (25). Consequently, a sample size of 120 patients was calculated for the study (120 in each group). We also assumed 5% loss (125 + 5), and the final sample size of 250 was included in this study.

Patients with HF clinically defined based on the European Society of Cardiology guidelines, who were established less than a year before enrolment, were involved in the study. Other inclusion criteria were subjects aged 30–70 years and did not announce modifications to their diets from the time during diagnosis. We included only new cases in the study with the intention of lessening the possibility that subjects altered their diet considerably in during diagnosis. Patients were diagnosed to have HF if they had had left ventricular ejection fraction (LVEF) ≤ 0.35, were in New York Heart Association (NYHA) functional classification class II to IV HF for ≥ 3 months before study, had a heart rate ≥ 68 bpm, and were receiving standard therapy of diuretics and an angiotensin-converting enzyme (ACE) inhibitor or digoxin. HF cases were patients who had two-dimensional echocardiography and confirmed by clinical symptoms. Also, the patients with preserved EF but with clinical symptoms were also considered in this study. Exclusion criteria in the case group included the following: (a) non-adherence to the study protocol, (b) reporting caloric intake >4,000 or <800 kcal/day, (c) inability to respond to the questions, and (d) supplement therapy for HF.

Controls ($n = 125$) were randomly selected from the same hospital who were admitted to the hospitals and underwent percutaneous coronary intervention (PCI) and no evidence of cardiomyopathy (EF ≥ 40) but who might have hyperlipidemia and hypertension ($n = 125$). Exclusion criteria for controls were prior diagnosis of inflammatory diseases of the peripheral nervous system; cancer; liver diseases and gastrointestinal, metabolic, and endocrine disorders; and immune system disorders and have a special diet (e.g., vegetarian or weight-loss diet) and low cardiac function (EF < 40). Patients with acute myocardial infarction (MI) and decreased cardiac function were excluded. Controls were coordinated to cases on age (±4 years) and sex. All of the patients were screened by an

Abbreviations: ANOVA, analysis of variance; CAD, coronary artery disease; CRP, C-reactive protein; CVD, cardiovascular disease; NT-proBNP, N-terminal (NT)-pro hormone BNP; LVEF, left ventricular ejection fraction; ESR, erythrocyte sedimentation rate; DII, Dietary Inflammatory Index; HF, heart failure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NYHA, New York Heart Association; TC, total cholesterol; TNF-α, tumor necrosis factor-α.

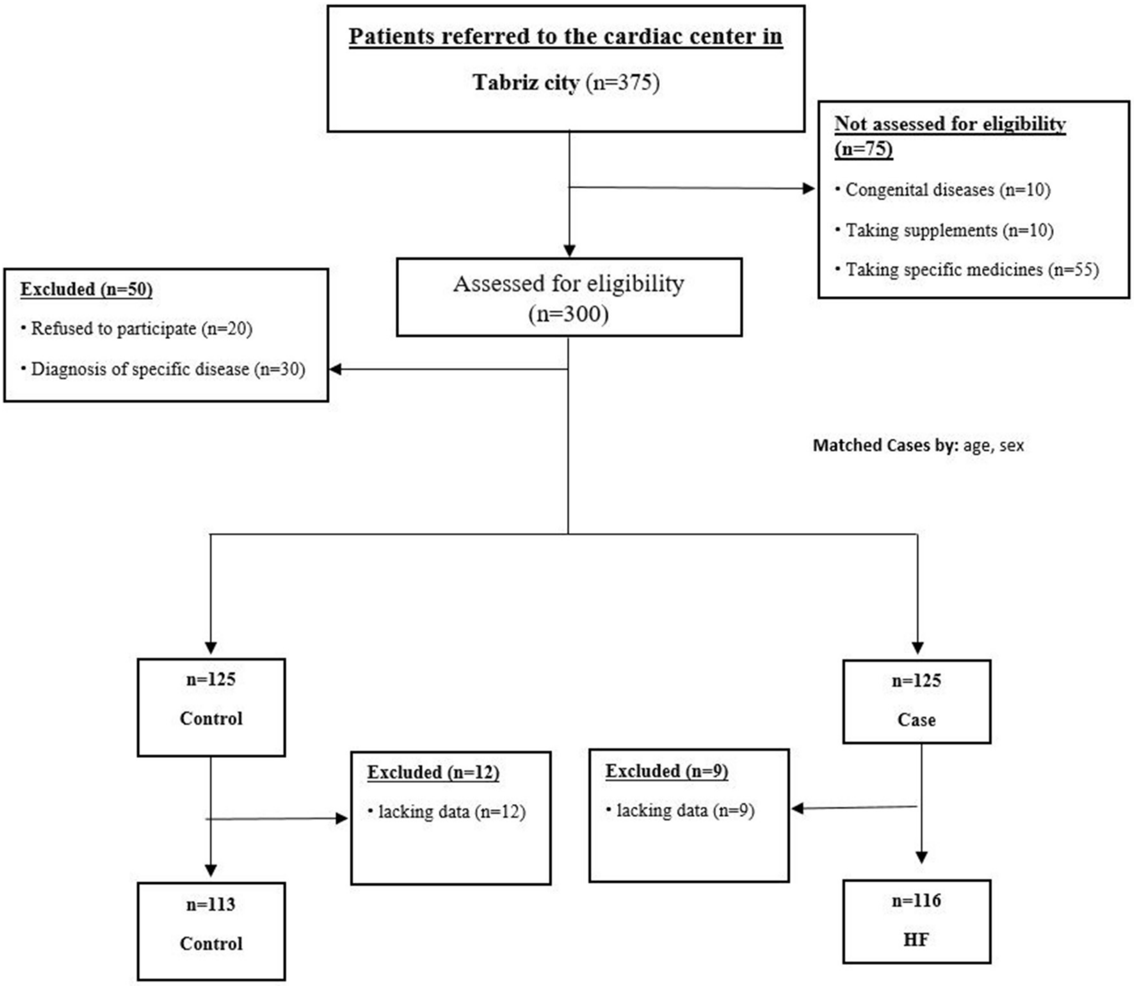

FIGURE 1 | Flowchart of study.

expert cardiologist for eligibility. Of joined cases and controls, nine HF and 12 controls were excluded because of lacking food frequency questionnaires (FFQs) or other data. The final sample comprised 116 cases and 113 controls, demonstrating a 90% response rate (**Figure 1**). Informed consent was obtained from all subjects. The research was approved by the research council of the Tabriz University of Medical Sciences (No. IR.TBZMED.REC.1397.184). Information on sociodemographic characteristics, anthropometric data, biochemical variables, and medical history was assessed using a standard questionnaire by a trained interviewer.

Assessment of Anthropometric Data

We used a scale (Seca 770; Seca GmbH & Co, Hamburg, Germany) with 0.5-kg accuracy while patients were wearing light clothing and no shoes in order to measure the subjects' body weight. We also utilized a tape with 0.5-cm accuracy in order to assess their height. We computed the body mass index (BMI) by weight-to-height ratio ($BMI = kg/m^2$).

N-Terminal pro-brain natriuretic peptide (NT-proBNP) levels was assessed by the quantitative electrochemiluminescence immunoassay (ELISA) method (Roche kite).

Determination of Ejection Fraction

EF was measured by two-dimensional echocardiography. The participants were divided into EFs $\geq$40% (controls) and $<$35% (HF case) subgroups. Furthermore, we used clinical symptoms, which confirmed classification.

Dietary Assessment

We obtained dietary intake by making use of a 138-item semi-quantitative FFQ involving of a list of a finite foods and beverages with standard serving sizes usually consumed by Iranians (26, 27). Patients were requested to state how often they consumed each of the food listed by the number of times (every day, weekly, once a month, and annually). According to a standard serving size for each nutrient item, and then each contributor's intake was transformed to weight equivalents (i.e., μg, g, and mg) per day. Then, dietary information was investigated for energy and nutrients, using revised Nutritionist IV software (Nutritional Database Manager 4.0.1, First Data Bank, USA). The development and validation of the DII are described in detail elsewhere (22). The greater the DII score, the more pro-inflammatory the diet. More negative values represent the more anti-inflammatory diets. The DII tertile cut points were categorized based on cut points: Tertile 1 ≤ -1.132; Tertile 2 $= -1.132$ to 0.467; Tertile 3 ≥ 0.467.

TABLE 1 | Characteristics of patients in the case and control groups ($n = 229$).

Characteristics	Cases ($n = 116$)	Controls ($n = 113$)	*p*-value
Age, years	56.34 ± 12.99	57.40 ± 13.43	0.547
Gender, n (%)			
Male	75 (64.66)	69 (61.06)	0.573
Female	41 (35.34)	44 (38.94)	
BMI, kg/m^2, mean ± SD	26.63 ± 5.75	26.73 ± 5.29	0.892
Smoking, n (%)			
Yes	35 (30.17)	22 (19.47)	0.061
No	81 (69.83)	91 (80.53)	
Hypertension, n (%)			
Yes	61 (52.59)	51 (45.13)	0.259
No	55 (47.41)	62 (54.87)	
EF (%)	25.34 ± 9.70	43.3 ± 19.5	0.001
LDL, mg/dl, mean ± SD	131.60 ± 30.14	120.37 ± 34.84	0.010
HDL mg/dl, mean ± SD	39.47 ± 7.26	44.81 ± 9.15	0.000
Cholesterol mg/dl, mean ± SD	180.89 ± 47.24	173.11 ± 46.43	0.210
TG, mg/dl, mean ± SD	151.34 ± 48.62	139.90 ± 48.26	0.075
DII, mean ± SD	−0.16 ± 1.37	−0.33 ± 1.67	0.040

Student t-test was used for continuous variables. Chi-square test was used for categorical variables. Significance was at $p < 0.05$. p-values are based on Mann–Whitney U-test. DII, dietary inflammatory index; BMI, body mass index; EF, ejection fraction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

Data Analysis

The data were examined by SPSS 16 software (SPSS Inc., Chicago, IL, USA). Data are presented as mean and standard deviation, frequency and percent, or median and interquartile range. The normality of data was assessed and proved by skewness and kurtosis test. For all statistical assessments, $p < 0.05$ was considered as significant. Independent samples *t*-test and Mann–Whitney *U*-test were used for between-group differences. *p*-values for trends were calculated for variables across DII tertiles. Conditional logistic regression was done to calculate odds ratio (OR) and 95% confidence intervals (CIs) for HF as the outcome. Multiple linear regressions via the enter method were used to evaluate the associations between EF as outcome and continuous outcomes such as DII, sex, age, and BMI.

RESULTS

Table 1 indicates the distribution of HF and controls with reference to some variables. DII scores in our study ranged from −3.3 (maximum anti-inflammatory score) to +2.82 (most pro-inflammatory score). By design, the demographic distributions were not different in cases and controls. Furthermore, the control group had higher values of high-density lipoprotein (HDL) ($p = 0.001$) and lower level of low-density lipoprotein (LDL) than the case groups ($p = 0.01$).

The results also indicated that the mean DII score for the HF group was higher than that of the control group (-0.16 ± 1.37 vs. -0.33 ± 1.67; $p = 0.040$). When DII scores were transformed toward tertiles (**Table 2**), cumulative trends across tertiles of DII were detected for total fat and saturated fat, whereas statistically substantial decreasing trends were perceived for some anti-inflammatory intake such as fiber and beta carotene. However, in the analysis via the DII shown as tertiles, we failed to find any significant trend of increasing risk ($p > 0.05$) for other cardiovascular risk

TABLE 2 | Characteristics of the participants according to the quartiles of dietary inflammatory index.

Variables	Tertile 1	Tertile 2	Tertile 3	p_{trend}
Demographic				
Age (years)	56.79 ± 10.44	56.89 ± 14.90	56.98 ± 14.13	0.995
Gender, n (%)				0.735
Male	46 (61.33)	48 (63.16)	48 (64.00)	
BMI (kg/m)	26.43 ± 4.71	27.09 ± 6.38	26.61 ± 5.42	0.752
Smoking, n (%)	24 (32.00)	17 (22.37)	15 (20.00)	0.090
Pro-inflammatory				
Total fat (g)	71.05 ± 30.13	84.75 ± 41.19	94.23 ± 44.92	< 0.001
Cholesterol (mg)	231.44 ± 155.77	202.39 ± 98.96	194.97 ± 108.23	0.198
Saturated fat (g)	19.00 (9.00, 23.19)	17.39 (9.74, 20.53)	30.70 (18.53, 33.41)	< 0.001
Anti-inflammatory				
Fiber (g)	18.41 ± 8.82	4.00 ± 1.44	13.35 ± 5.73	< 0.001
Beta carotene (μg)	267.17 (97.72, 451.10)	73.16 (23.49, 519.60)	146.00 (17.51, 296.66)	< 0.001

*For abbreviations, see **Table 1**. Values are presented as mean ± SD for variables with normal distribution or median (interquartile) for variables without normal distribution. Tertile 1 ≤ -1.132; Tertile 2 $= -1.132$ to 0.467; Tertile 3 ≥ 0.467.*

TABLE 3 | Micronutrient intake of the participants according to the tertiles of dietary inflammatory index.

Variables	Tertile 1	Tertile 2	Tertile 3	p_{trend}
Sodium (mg)	1115.00 (775.10, 2038.00)	1119.50 (499.00, 1973.00)	1999.00 (1367.00, 2131.00	0.020
Iron (mg)	14.51 (1,232, 14.94)	13.11 (9.20, 16.95)	12.87 (11.80, 17.88)	0.147
Zinc (mg)	7.91 (5.81, 10.75)	7.37 (5.17, 10.54)	9.15 (7.31, 1,032)	0.513
Magnesium (mg)	254.7 (181.27, 272.43)	195.50 (151.60, 232.70)	202.87 (183.70, 213.50)	0.006
Manganese (mg)	2.18 (1.88, 2.46)	1.93 (1.39, 2.48)	1.60 (1.26, 2.11)	0.401
Potassium (mg)	2728.00 (2375.00, 3636.00)	2067.00 (1696.50, 2466.67)	2588.5 (2318.00, 2676.00)	0.044
Calcium (mg)	694.67 (509.33, 1054.00)	663.30 (389.67, 817.50)	679.00 (526.30, 1077.00)	0.969
Phosphorus (mg)	1012.00 (785.40, 1255.00)	989.65 (611.87, 1,113.00)	1109.00 (1055.00, 1148.00)	0.589
Copper	1.34 (1.09, 1.47)	0.99 (0.77, 1.46)	1.09 (0.87, 1.22)	0.005
Selenium	0.10 (0.09, 0.14)	0.11 (0.08, 0.15)	0.08 (0.05, 0.17)	0.048
Chromium	0.05 (0.03, 0.08)	0.04 (0.02, 0.06)	0.05 (0.02, 0.07)	0.209
Vitamin A	802.67 (686.10, 922.70)	416.00 (271.80, 843.80)	422.30 (352.5, 502.33)	< 0.001
Vitamin E	4.79 (2.98, 7.24)	3.57 (2.09, 5.56)	3.57 (2.51, 6.08)	0.031
Vitamin K	70.28 (44.90, 114.40)	30.67 (18.29, 50.66)	40.48 (19.05, 74.33)	< 0.001
Vitamin D	1.00 (0.21, 1.99)	1.05 (0.04, 2.00)	0.79 (0.03, 2.11)	0.634
Thiamin	2.28 (1.65, 2.46)	1.63 (1.31, 2.07)	1.60 (1.48, 1.92)	< 0.001
Riboflavin	1.56 (1.11, 1.92)	1.42 (0.87, 1.56)	1.52 (1.48, 1.83)	0.268
Niacin	19.88 (17.21, 24.98)	16.78 (12.83, 21.00)	17.79 (14.34, 22.89)	0.060
Pantothenic acid	4.92 (4.09, 5.64)	3.83 (2.52, 4.81)	3.94 (3.83, 4.57)	< 0.001
Pyridoxine	1.38 (1.08, 2.27)	0.98 (0.80, 1.44)	1.11 (0.93, 1.45)	< 0.001
Folate	210.40 (186.13, 251.60)	135.00 (101.28, 245.20)	155.20 (131.67, 199.20)	< 0.001
Cobalamin	2.83 (2.31, 3.34)	2.83 (1.66, 3.70)	3.51 (1.98, 4.08)	0.474
Biotin	23.94 (17.11, 26.48)	15.37 (10.98, 21.95)	16.84 (11.52, 21.48)	< 0.001

Data are median (interquartile range).
Tertile 1 ≤ −1.132; Tertile 2 = −1.132 to 0.467; Tertile 3 ≥ 0.467.

factors including lipid profile. Also, when DII was transformed into tertiles according to DII, there are some differences observed between the micronutrient intake of the participants (**Table 3**).

Clinical markers by DII tertiles are presented in **Table 4**. Especially, members in tertiles 3 had higher NT-proBNP and had lower EF (**Table 4**). The present results led us to conclude that low DII score leads to better clinical outcome in HF patients. However, in the analysis via the DII shown as tertiles, we failed to find any significant trend ($p > 0.05$) for other cardiovascular risk factors including lipid profile.

Logistic regression analysis was done with HF as the outcome (**Table 5**), and the findings showed that each unit increase in DII score was associated with a 30% (OR: 1.30; CI: 1.03, 1.69; $p = 0.047$) increase in the odds of being diagnosed with HF. Significant OR also was perceived for triglyceride (TG), LDL, and HDL.

In a linear regression model including LVEF as the outcome, EF value was inversely associated with saturated fatty acid ($\beta = -0.34$, 95% CI: −0.61, −0.07; $p = 0.012$) (**Table 6**). No statistically significant relationship was established between the DII and the LVEF value. Finally, the set of variables including DII, HDL, TG, LDL, and saturated fatty acid significantly explained 9% of variance in EF status [$F_{(9, 215)} = 3.54, p \leq 0.001$].

TABLE 4 | Distribution of some important clinical markers across categories of DII.

Variables	Tertile 1	Tertile 2	Tertile 3	p_{trend}
EF	43.12 ± 24.94	37.08 ± 14.23	33.11 ± 12.76	**0.044**
LDL (mg/dl)	123.05 ± 31.68	128.03 ± 33.62	126.96 ± 34.36	0.627
HDL (mg/dl)	42.07 ± 9.22	43.00 ± 8.50	41.37 ± 8.35	0.515
Cholesterol (mg/dl)	174.64 ± 41.75	169.46 ± 46.93	187.80 ± 50.11	0.371
TG (mg/dl)	145.81 ± 52.24	149.43 ± 44.22	141.17 ± 49.83	0.582
NT-proBNP	109.81 ± 47.24	101.53 ± 43.12	155.17 ± 59.21	**0.036**

*For abbreviations, see **Table 1**. Values are presented as mean ± SD for variables with normal distribution or median (interquartile) for variables without normal distribution.*
Tertile 1 ≤ −1.132; Tertile 2 = −1.132 to 0.467; Tertile 3 ≥ 0.467.
Bold values are statistically significant.

DISCUSSION

The current case–control study applied the DII score to the dietary intake of patients with HF for the first time. We detected that the DII score was related to increased risk of HF, thus implicating a pro-inflammatory diet in its etiology. However, EF was not associated with DII score.

It has been claimed that inflammation has a significant impact on the pathogenesis of CVDs and that higher high-sensitivity C-reactive protein (CRP) concentration accelerates

TABLE 5 | Conditional logistic regression analysis with HF status as outcome.

Variables	Odds ratio	95% CI	*p*-value
DII	1.303	1.003, 1.693	0.047
HDL	1.127	1.060, 1.198	< 0.001
TG	0.988	0.979, 0.997	0.008
LDL	0.985	0.972, 0.998	0.034
Saturated fatty acids	0.905	0.861, 0.951	< 0.001

For abbreviations, see ***Table 1****.*
Adjusted for BMI and smoking.

TABLE 6 | Summary of linear regression analysis based on EF as outcome.

Variables	B	SE	95% CI	*p*-value
DII	0.73	0.85	−1.12, −0.03	0.389
HDL	0.28	0.13	0.01, 0.55	0.038
TG	−0.08	0.02	−0.12, −0.03	0.001
LDL	−0.06	0.03	−0.13, 0.01	0.090
Saturated fatty asides	−0.34	0.13	−0.61, −0.07	0.012
Adjusted R^2	0.09			

For abbreviations, see ***Table 1****. Adjusted for age, sex, BMI, and smoking.*

the development of HF (28). Similarly, plasma levels of tumor necrosis factor-α (TNF-α) and IL-6 also predict HF outcomes (29). In addition, as beginning and development of HF accompany the chronic pro-inflammatory state, extra pro-inflammatory dietary patterns are associated with increased HF incidence and worse clinical outcome (30). One potential mechanism for the apparent relationship between the DII score and high risk of inflammatory diseases like CVD is the impact of diet on the cytokines levels, which regulate inflammatory response. Inflammatory cytokines also play a vital role in the underlying pathophysiological processes of HF (31).

While there are many studies supporting the concept of the protective effect of diets, including approaches to stop hypertension [Paleolithic, Dietary Approaches to Stop Hypertension (DASH) diet, low carb diet, vegetarian diet, and low-fat diet] on the prevention of HF, their effectiveness is not clear yet. DASH and Mediterranean diets revealed a protective impact on the HF incidence and/or deteriorating on EF (13, 32), but these results need to be able to replicate and investigate other diets (such as low DII) and to test the generalizability in post-MI patients. In other words, the consumption of vegetables and fruits has been proven to decrease inflammation, whereas the consumption of foods like meat and butter increases inflammation through increasing levels of CRP (33, 34). Indeed, focusing on the entire diet by computing DII score, which takes many categories of dietary components into account, more precisely indicates the relationship between diet and the risk of HF.

Previous findings have shown the relationship between the DII score and incidence of CVD (MI, stroke, and CVD death) (19). Numerous studies have indicated the significant role of chronic inflammation as an important factor that interferes in the development of CVD. In this context, dietary patterns are adjustable factors that have a huge potential to exert a powerful anti-inflammatory or pro-inflammatory effect (35). We observed a higher DII score in HF subjects compared with controls. This result is consistent with a previous systematic review of studies, which found that the DII scores were inversely associated with cardio-metabolic risk factors and CVDs (36). Therefore, a diet including pro-inflammatory components such as saturated and trans fat can cause proliferation of MI, oxidative stress (37, 38), and inflammation, which can cause ventricular remodeling and possibly HF development.

Our finding is consistent with previous result for DII and chronic disease in many clinical settings. Previously, we observed a negative association between DII and EF, which agrees with a previous SUN ("Seguimiento University of Navarra") cohort study that was conducted in 18,794 individuals with 8.9 years' follow-up, where the number of new CVD events cases in the highest DII score was 2.03 times more than the lowest quartile (39). In another cohort study, carried out on 7,216 subject (55–80 years) at high risk of cardiovascular events, the highest quartile (most pro-inflammatory diet) was reversely associated with the number of CVD incidences (OR = 1.73; 95% CI: 1.15, 2.60) (40). A comparable negative relationship was reported between HF risk and DII score in patients with previously diagnosed CVDs (OR = 0.31; 95% CI: 0.12, 0.82; $p = 0.018$) (41). In contrast, the SU.VI.MAX study included 7,743 participants (aged 35–60 years) after 11.4 years' follow-up; no associations were observed for DII scores and the composite CVD outcomes (32). Effect sizes for HF risk have mostly been in the range of nearly OR 1.5–3, which is similar to our results. By comparing the results from this study, we hope to determine the association between DII and HF. The DII scores also in current population were comparable with those of earlier studies. The DII based on FFQ in our study population seems to be acceptable for this type of examination and for interpretation of the results in relation to earlier results. The DII score was highly positively associated with the intakes of saturated fatty acid. The higher intakes of saturated fatty acid are associated with inflammatory properties (5, 31); so it is not unexpected that there was a correlation with HF as reported by DII.

Numerous investigations have revealed a positive correlation between lipid profile (including total cholesterol, LDL, and HDL) and risk of HF and clinical outcomes (42, 43). The lack of a significant association in our study may be partially a result of the low levels of these outcomes among participants at baseline; also 60% of patients were under statin therapy. Low serum total cholesterol is related with increased mortality in patients with HF (43). In particular, HDL cholesterol was proposed to exert anti-inflammatory and antioxidant activities, which would lessen the pro-inflammatory state in patients with HF (44). Indeed, an association among HDL cholesterol, HF, and DII may be explained on the basis of the inflammation hypothesis (24), which suggests that low DII score modulates inflammatory immune function and also that HDL cholesterol has antioxidant and anti-inflammatory properties, both of which can further reduce risk of HF.

The potential cardiovascular effects of several foods and dietary patterns are still incompletely understood. Some research has suggested that "Western" dietary patterns, which contain high intakes of saturated and trans fatty acids, and low-fruit/low-vegetable intake, result in higher CRP levels and increased risk of CVD event (5, 10, 31, 40). In this regard, it seems that the dietary patterns with low DII scores prevent the development of HF.

Previously, the DII has been revealed to be related with different inflammatory markers including homocysteine and CRP (9). Diets having high amounts of vegetables and fruits are related with low levels of hs-CRP (34). Certain nutrients such as magnesium, fiber, and omega-3 fatty acids are associated with low levels of inflammation (14). A further novel finding is that those higher in DII had higher NT-proBNP and had lower EF, which mean low intensity of HF. The NT-proBNP levels were measured in all patients, and they were followed up and had a well-accepted biomarker of cardiac function (45). The present work led us to conclude that low DII score is associated with better cardiac function in HF patients.

This is the first study in the world to explore the relationship between the DII score and HF. Despite its strengths, our study had several limitations. First, we did not quantity inflammatory biomarkers, and as a result, we were incapable of evaluating this association. The second limitations relate to the generalizability of our results because of its design, which does not permit the distinction between cause and effect based on temporality. Therefore, we were unable to determine if a pro-inflammatory dietary pattern and higher DII score cause HF development or whether the existence of HF resulted in a more pro-inflammatory diet, which in turn resulted in higher DII. Thus, perspective studies, including intervention trials, are required to determine the role of dietary intakes as a cause of HF more firmly.

CONCLUSION

In summary, the DII has presented a valuable means for evaluating the potential inflammatory of diets in HF patients. This study on HF patients conducted in Iranian subjects indicated a possible role of diet through the development of inflammation. Our results proposed evidence suggesting that an upper DII score (representative an extra pro-inflammatory diet) is strictly connected with the occurrence of HF. These results propose the significance of promoting dietary intake with low DII score for the subjects at risk for HF. Future studies, including intervention trials, are required to find this association precisely. The significance of this work is of major importance for public health-care planners, since it would test the low inflammatory diet hypothesis at population basis and may provide an additional, non-pharmacologic means for the prevention of HF.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the research council of the Tabriz University of Medical Sciences (No: IR.TBZMED.REC.1397.184). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JM and MA: conceived and designed the experiments. JM performed the experiments. SA, JM, and NS: analyzed the data. All authors: wrote the paper.

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REFERENCES

1. Khatibzadeh S, Farzadfar F, Oliver J, Ezzati M, Moran A. Moran worldwide risk factors for heart failure: a systematic review and pooled analysis. *Int J Cardiol.* (2013) 168:1186–94. doi: 10.1016/j.ijcard.2012.11.065
2. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am College Cardiol.* (2014) 63:1123–33. doi: 10.1016/j.jacc.2013.11.053
3. Ingelsson E, Arnlöv J, Sundström J, Lind L. Inflammation, as measured by the erythrocyte sedimentation rate, is an independent predictor for the development of heart failure. *J Am College Cardiol.* (2005) 45:1802–6. doi: 10.1016/j.jacc.2005.02.066
4. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, et al. Inflammatory markers and incident heart failure risk in older adults: the health ABC (health, aging, and body composition) study. *J Am College Cardiol.* (2010) 55:2129–37. doi: 10.1016/j.jacc.2009.12.045
5. Aukrust P, Gullestad L, Ueland T, Damås JK, Yndestad A. Inflammatory and anti-inflammatory cytokines in chronic heart failure: potential therapeutic implications. *Ann Med.* (2005) 37:74–85. doi: 10.1080/07853890510007232
6. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol.* (2011) 106:563. doi: 10.1038/ajg.2011.44
7. Gholizadeh F, Moludi J, Lotfi Yagin N, Alizadeh M, Mostafa Nachvak S, Abdollahzad H, et al. The relation of dietary diversity score and food insecurity to metabolic syndrome features and glucose level among pre-diabetes subjects. *Primary Care Diabetes.* (2018) 12:338–44. doi: 10.1016/j.pcd.2018.03.003
8. McCullough ML, Patel AV, Kushi LH, Patel R, Willett WC, Doyle C, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular

disease and all-cause mortality. *Cancer Epidemiol Prevent Biomark.* (2011) 20:1089–97. doi: 10.1158/1055-9965.EPI-10-1173

9. Catapano G, Pedone C, Nunziata E, Zizzo A, Passantino A, Incalzi RA. Nutrient intake and serum cytokine pattern in elderly people with heart failure. *Eur J Heart Failure.* (2008) 10:428–34. doi: 10.1016/j.ejheart.2008.02.016
10. Ciccone MM, Cortese F, Gesualdo M, Carbonara S, Zito A, Ricci G, et al. Dietary intake of carotenoids and their antioxidant and anti-inflammatory effects in cardiovascular care. *Med Inflamm.* (2013) 2013:782137. doi: 10.1155/2013/782137
11. Sinatra ST. Coenzyme Q10: a vital therapeutic nutrient for the heart with special application in congestive heart failure. *Connecticut Med.* (1997) 61:707–12.
12. Schroten NF, Ruifrok WP, Kleijn L, Dokter MM, Silljé HH, Lambers Heerspink HJ, et al. Short-term vitamin D3 supplementation lowers plasma renin activity in patients with stable chronic heart failure: an open-label, blinded end point, randomized prospective trial (VitD-CHF trial). *Am Heart J.* (2013) 166:357–64.e2. doi: 10.1016/j.ahj.2013.05.009
13. Nettleton JA, Steffen LM, Mayer-Davis EJ, Jenny NS, Jiang R, Herrington DM, et al. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA)–. *Am J Clin Nutr.* (2006) 83:1369–79. doi: 10.1093/ajcn/83.6.1369
14. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Dietary sodium intake and incidence of congestive heart failure in overweight US men and women: first national health and nutrition examination survey epidemiologic follow-up study. *Arch Internal Med.* (2002) 162:1619–24. doi: 10.1001/archinte.162.14.1619
15. Levitan EB, Wolk A, Mittleman MA. Consistency with the DASH diet and incidence of heart failure. *Arch Internal Med.* (2009) 169:851–7. doi: 10.1001/archinternmed.2009.56
16. Gambardella J, Santulli G. Integrating diet and inflammation to calculate cardiovascular risk. *Atherosclerosis.* (2016) 253:258. doi: 10.1016/j.atherosclerosis.2016.08.041
17. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr.* (2014) 17:1825–33. doi: 10.1017/S1368980013002565
18. Shivappa N, Hébert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios study. *Brit J Nutr.* (2015) 113:665–71. doi: 10.1017/S000711451400395X
19. Garcia-Arellano A, Ramallal R, Ruiz-Canela M, Salas-Salvadó J, Corella D, Shivappa N, et al. Dietary inflammatory index and incidence of cardiovascular disease in the PREDIMED study. *Nutrients.* (2015) 7:4124–38. doi: 10.3390/nu7064124
20. Phillips CM, Shivappa N, Hébert JR, Perry IJ. Dietary inflammatory index and biomarkers of lipoprotein metabolism, inflammation and glucose homeostasis in adults. *Nutrients.* (2018) 10:1033. doi: 10.3390/nu10081033
21. Shivappa N, Bosetti C, Zucchetto A, Montella M, Serraino D, La Vecchia C, et al. Association between dietary inflammatory index and prostate cancer among Italian men. *Brit J Nutr.* (2015) 113:278–83. doi: 10.1017/S0007114514003572
22. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public health Nutr.* (2014) 17:1689–96. doi: 10.1017/S1368980013002115
23. Ahluwalia N, Andreeva VA, Kesse-Guyot E, Hercberg S. Dietary patterns, inflammation and the metabolic syndrome. *Diabetes Metabo.* (2013) 39:99–110. doi: 10.1016/j.diabet.2012.08.007
24. Dick SA, Epelman S. Chronic heart failure and inflammation: what do we really know? *Circulat Res.* (2016) 119:159–76. doi: 10.1161/CIRCRESAHA.116.308030
25. Farhangi MA, Najafi M, Asghari Jafarabadi M, Jahangiry L. Mediterranean dietary quality index and dietary phytochemical index among patients candidate for coronary artery bypass grafting (CABG) surgery. *BMC Cardiovasc Disord.* (2017) 17:114. doi: 10.1186/s12872-017-0544-z
26. Mirmiran P, Esfahani FH, Mehrabi Y, Hedayati M, Azizi F. Reliability and relative validity of an FFQ for nutrients in the Tehran lipid and glucose study. *Public Health Nutr.* (2010) 13:654–62. doi: 10.1017/S1368980009991698
27. Moludi J, Alizadeh M, Davari M, Golmohammadi A, Maleki V. The efficacy and safety of probiotics intervention in attenuating cardiac remodeling following myocardial infraction: Literature review and study protocol for a randomized, double-blinded, placebo controlled trial. *Contemp Clin Trials Commun.* (2019) 15:100364. doi: 10.1016/j.conctc.2019.100364
28. Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. *Circulation.* (2005) 112:1428–34. doi: 10.1161/CIRCULATIONAHA.104.508465
29. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation.* (2000) 102:3060–7. doi: 10.1161/01.CIR.102.25.3060
30. Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart.* (2004) 90:464–70. doi: 10.1136/hrt.2002.007005
31. Basu A, Devaraj S, Jialal I. Dietary factors that promote or retard inflammation. *Arterioscler Thrombo Vasc Biol.* (2006) 26:995–1001. doi: 10.1161/01.ATV.0000214295.86079.d1
32. Neufcourt L, Assmann KE, Fezeu LK, Touvier M, Graffouillère L, Shivappa N, et al. Prospective association between the dietary inflammatory index and cardiovascular diseases in the supplémentation en vitamines et minéraux antioxydants (SU. VI. MAX) cohort. *J Am Heart Assoc.* (2016) 5:e002735. doi: 10.1161/JAHA.115.002735
33. Holt EM, Steffen LM, Moran A, Basu S, Steinberger J, Ross JA, et al. Fruit and vegetable consumption and its relation to markers of inflammation and oxidative stress in adolescents. *J Am Dietetic Assoc.* (2009) 109:414–21. doi: 10.1016/j.jada.2008.11.036
34. Raff M, Tholstrup T, Basu S, Nonboe P, Sørensen MT, Straarup EM. A diet rich in conjugated linoleic acid and butter increases lipid peroxidation but does not affect atherosclerotic, inflammatory, or diabetic risk markers in healthy young men. *J Nutr.* (2008) 138:509–14. doi: 10.1093/jn/138.3.509
35. Galland L. Diet and inflammation. *Nutr Clin Pract.* (2010) 25:634–40. doi: 10.1177/0884533610385703
36. Ruiz-Canela M, Bes-Rastrollo M, Martínez-González MA. The role of dietary inflammatory index in cardiovascular disease, metabolic syndrome and mortality. *Int J Mol Sci.* (2016) 17:1265. doi: 10.3390/ijms17081265
37. de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ.* (2015) 351:h3978. doi: 10.1136/bmj.h3978
38. Dhibi M, Brahmi F, Mnari A, Houas Z, Chargui I, Bchir L, et al. The intake of high fat diet with different trans fatty acid levels differentially induces oxidative stress and non alcoholic fatty liver disease (NAFLD) in rats. *Nutr Metabo.* (2011) 8:65. doi: 10.1186/1743-7075-8-65
39. Garcia-Arellano A, Martínez-González MA, Ramallal R, Salas-Salvadó J, Hébert JR, Corella D, et al. Dietary inflammatory index and allcause mortality in large cohorts: the SUN and PREDIMED studies. *Clin Nutr.* (2019) 38:1221–31. doi: 10.1016/j.clnu.2018.05.003
40. Corella D, Shivappa N, Schröder H, Hébert JR, Ros E, Fitó M, et al. *Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the PREDIMED Study.*
41. Wirth MD, Shivappa N, Hurley TG, Hébert JR. Association between previously diagnosed circulatory conditions and a dietary inflammatory index. *Nutr Res.* (2016) 36:227–33. doi: 10.1016/j.nutres.2015.11.016
42. Freitas H, Barbosa EA, Rosa FH, Lima AC, Mansur AJ. Association of HDL cholesterol and triglycerides with mortality in patients with heart failure. *Brazil J Med Biol Res.* (2009) 42:420–5. doi: 10.1590/S0100-879X2009000500004
43. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am College Cardiol.* (2003) 42:1933–40. doi: 10.1016/j.jacc.2003.07.016
44. Säemann MD, Poglitsch M, Kopecky C, Haidinger M, Hörl WH, Weichhart T. The versatility of HDL: a crucial anti-inflammatory regulator. *Eur J Clin Investig.* (2010) 40:1131–43. doi: 10.1111/j.1365-2362.2010.02361.x

45. Michaud K, Augsburger M, Donzé N, Sabatasso S, Faouzi M, Bollmann M, et al. Evaluation of postmortem measurement of NT-proBNP as a marker for cardiac function. *Int. J Legal Med*. (2008) 122:415–20. doi: 10.1007/s00414-008-0257-z

Conflict of Interest: JH owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. NS was an employee of CHI. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association Between Dietary Inflammatory Index and Mental Health: A Systematic Review and Dose–Response Meta-Analysis

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Objective: We aimed to systematically evaluate the association between Dietary Inflammatory Index (DII) and mental health.

Methods: We searched PubMed, Embase, and Web of Science from their inception to December 31, 2020. Categorical meta-analysis and dose–response meta-analysis were performed to evaluate the association between DII and mental health.

Results: A total of 16 studies were included in this meta-analysis. Compared with the lowest DII category, the highest category was significantly associated with a variety of mental health outcomes, with the following pooled odds ratios (ORs) and 95% confidence intervals (95% CIs): 1.28 (1.17–1.39) for symptoms of depression, 1.27 (1.08–1.49) for symptoms of anxiety, 1.85 (1.43–2.40) for distress, and 4.27 (1.27–14.35) for schizophrenia. Furthermore, there was a linear dose–response relationship between DII and symptoms of depression in that a 1-unit increment in DII was associated with an increased risk of 6% for symptoms of depression (OR: 1.06, 95% CI: 1.03–1.19).

Conclusion: The present study indicates that more pro-inflammatory diet, as estimated by the higher DII score, is associated with symptoms of mental disorder. It may be of clinical and public health significance regarding the development of novel nutritional psychiatry approaches to promote good mental health.

Keywords: mental health, dietary inflammatory index, depression, anxiety, dose-response meta-analysis

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INTRODUCTION

Mental health disorders, as the leading cause of disability, represent a major public health concern (1, 2). It is estimated by WHO that one in four people worldwide is affected by mental health disorders in his or her lifetime, with around 450 million people currently suffering from such conditions (3). Considering the significant prevalence and associated socioeconomic burden, early identification of the modifiable factors consists crucial preventive strategies against the development of mental disorders and their progression to serious complications.

Among the modifiable factors, diet is one of the main lifestyle-related factors for mental disorders that individuals are exposed to daily. Of note, the experts from the International Society for Nutritional Psychiatry Research state that "diet and nutrition are central determinants of mental health" (4). It has been increasingly recognized that diet could serve as a key source of inflammation due to the ability of specific food parameters to regulate inflammatory biomarkers (5–7). Some specific nutrients with presumed pro-inflammatory properties, such as red meat, fried food, and high-fat dairy products, are associated with a higher likelihood of developing mental disorders (8–10). Meanwhile, existing systematic reviews have shown that healthy dietary patterns with presumed anti-inflammatory features, such as the Mediterranean diet characterized by high intakes of vegetables, fruit, fish, and healthy oils, are associated with a lower risk of mental disorders (11). Therefore, it is proposed that diet-induced inflammation may serve to be one of potential pathways through which diet links to mental health outcomes.

To better understand the inflammatory potential of diet, the Dietary Inflammatory Index (DII) was developed to assess the inflammatory capacity of the overall diet according to the pro- and anti-inflammatory efficacy of different dietary components (12), which has been validated successfully with various inflammatory markers (13, 14). Existing epidemiological studies have explored the association between DII and mental health disorders, with some reporting an increased risk associated with a higher DII, and others, no association (15, 16). Recent systematic reviews indicate that a higher DII is associated with an increased risk of depression; however, the strength and shape of the dose–response relationship have not been determined (17). Furthermore, although there is evidence to suggest that the biological mechanism underlying the association between DII and mental health is not just limited to depression, previous systematic reviews have only focused on the very particular aspect of mental health outcomes (18, 19), and no review has investigated the effect of DII on the other kinds of mental health symptoms or disorders, such as anxiety, distress, and schizophrenia.

The inconsistent findings of previous research and the lack of exhaustive overview on different mental health outcomes make it difficult to draw a reliable and universal conclusion. Therefore, the present meta-analysis was undertaken to provide an updated, comprehensive, and dose–response review about the association between DII and a broader range of mental health symptoms or disorders.

METHODS

We formulated research questions following the Population, Intervention, Comparator, Outcomes and Study Design (PICOS) strategy. In the form of PICOS, the study was described as follows: P, patients with mental health symptoms or disorders; I, patients with higher DII level; C, patients with lower DII level; O, mental health symptoms or disorders; S, cohort, case-control, or cross-sectional study. This systematic review was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (20). The PRISMA checklist was shown in **Supplementary Table 1.**

Search Strategy

A comprehensive search was conducted to identify relevant articles in PubMed, Web of Science, and Embase from their inception to December 31, 2020. Search terms were as follows: (diet*) AND (inflammat*) AND (depress* OR anxi* OR emotion* OR affect* OR *stress OR schizophrenia OR mental OR psychological OR psychiatric). In addition, the reference lists of all relative reviews and articles were also manually searched.

Eligibility Criteria

Studies were included if they met the following inclusion criteria: (1) the study design was case-control, cohort, or cross-sectional study; (2) the DII was the exposure of interest; (3) the outcome of interest should be at least one kind of mental health symptom or disorder, as determined by a clinical diagnosis, or a validated self-report scale with a standardized cutoff point, including depression, anxiety, distress, and schizophrenia; (4) the study reported adjusted risk estimate with their corresponding 95% confidence interval (CI). If data were duplicated or shared in more than one study, the study with the largest dataset was included.

Data Extraction and Quality Assessment

The following information was extracted from each included study: the first author's name, journal, year of publication, country where the study was performed, study design, sex, age range or mean age (years), sample size, number of cases, follow-up period (if applicable), diet assessment, comparison of DII score, mental health assessment, covariates adjusted for in the statistical analysis, as well as multivariable-adjusted risk estimate with 95% CI for each category of DII. Two authors (GQC and CLP) independently extracted variables from all eligible studies into a predesigned form. Any discrepancy was discussed and resolved by consensus with another author (GPW). Quality of cohort and case-control studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) with the score ranging from 0 to 9 (21). Quality of cross-sectional studies was assessed using Agency for Healthcare Research and Quality (AHRQ) scale, which includes 11 items. An item was scored 0 for "No" or "Unclear" and 1 for "Yes" (22).

Statistical Analyses

For categorical meta-analysis, odds ratios (ORs) and the corresponding 95% CIs were initially pooled for the highest vs. lowest category as well as the second highest vs. lowest category of DII. Cochran's Q-test and I^2 were used to examine the heterogeneity among studies. I^2 equaling 0–25% indicates that the heterogeneity might not be important; 25–50% represents moderate heterogeneity; 50–75% represents substantial heterogeneity; and 75–100% represents considerable heterogeneity. A fixed-effects model was used if no or low heterogeneity was detected; otherwise, the random-effects model was adopted. Subgroup analyses were conducted based on study design, gender, geographic location, and

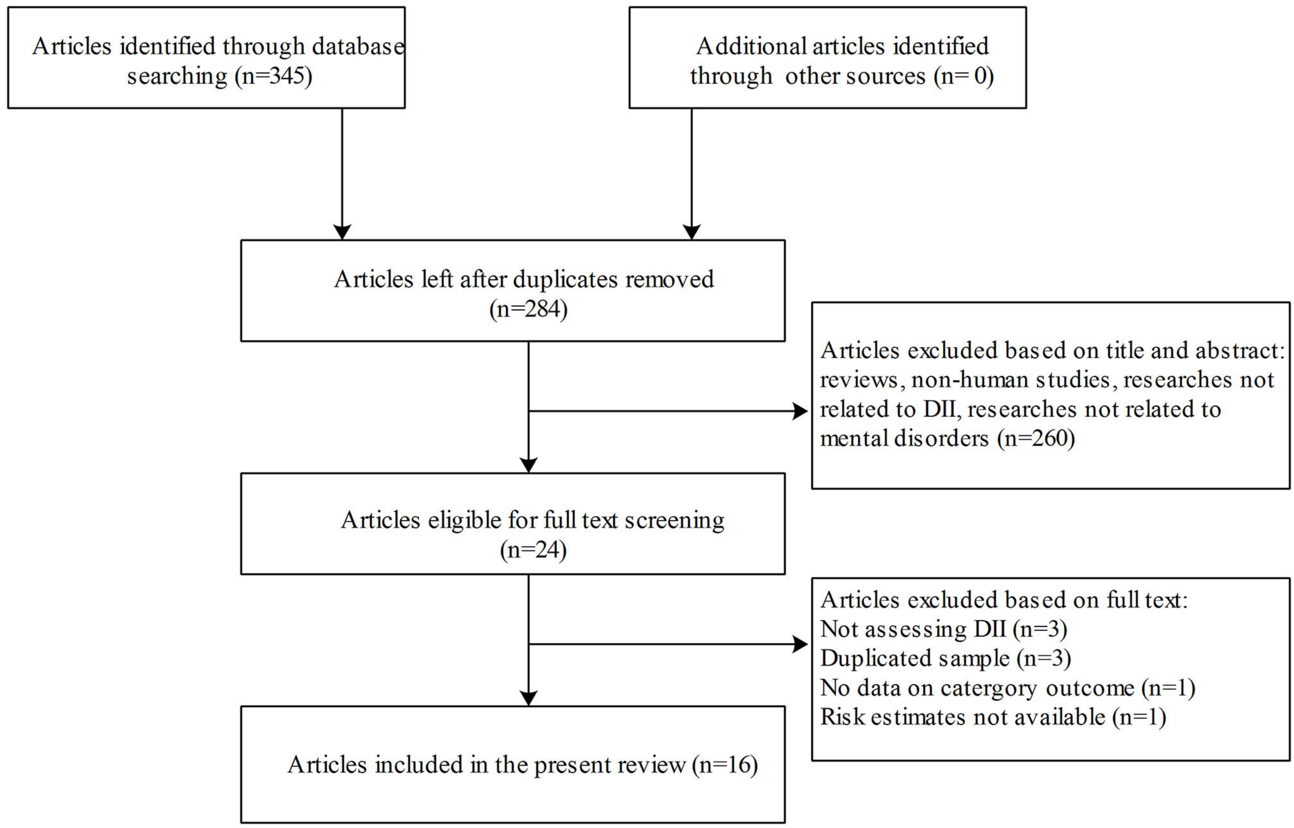

FIGURE 1 | Flowchart for study selection process.

number of DII components according to an *a priori* protocol. Sensitivity analyses were conducted by excluding one study at one time from each analysis to confirm the robustness of our analyses. Publication bias was assessed by Egger's and Begg's tests. The trim-and-fill approach was performed to explore the adjusted effect size, taking publication bias into account.

Dose–response meta-analysis was conducted using the method developed by Greenland and Longnecker (23) and Orsini et al. (24). Studies with at least three quantitative categories of exposures were adopted. The median or mean of DII, cases, person-years or person, and risk estimate with 95% CI for each DII category of included studies were extracted for trend estimations. If the medians were not reported, we approximated it using the midpoint of upper and lower boundaries. If the upper boundary for the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. Potential non-linear relationships between DII and risk of mental disorders were examined by using restricted cubic splines, with 3 knots fixed at the 10th, 50th, and 90th percentiles of the distribution of DII. A *P*-value for non-linearity was calculated by testing the coefficient of the second spline equal to zero, as described previously (25). In addition, the two-stage generalized least squares regression was used to estimate the linear dose–response relationship for 1-unit increment in DII score with the risk of mental health disorders. All statistical analyses were performed using STATA version 14 (Stata Corporation, College Station, Texas, USA). *P*-values were considered significant at a level of <0.05.

RESULTS

Study Characteristics

The process of literature selection is shown in **Figure 1**. A total of 16 articles with 92,242 participants were included in this meta-analysis, including five cohort studies, one case-control study, and 10 cross-sectional studies (16, 26–41). All studies assessed the DII score based on interviewed food-frequency questionnaires or 24-h diet recalls. Eight studies were conducted in Asia, four in American countries, three in Europe, and one in Australia. Of all the included studies, symptoms of depression were measured in 13 studies, symptoms of anxiety in four studies, distress in three studies, and schizophrenia in one study. The characteristics of all included studies are presented in **Table 1**. The mean quality score was 7.3 assessed by the NOS for cohort and case-control studies and 7.2 by the AHRQ for cross-sectional studies (**Supplementary Tables S2a,b**).

TABLE 1 | The characteristics of studies included in the meta-analysis.

References	Location	Case/Total No.	Sex: female	Age (mean /range)	Study design follow-up (years)	Measures of Outcome	Mental health assessment	Dietary assessment tool	DII score comparison	OR (95%CI)	Adjustment for covariates
Sánchez-Villegas et al. (26)	Spain	1,051/15,093	58.70%	38.3	Cohort (8.5)	Depression	Self-reported physician provided diagnosis	FFQ	Quintile 5 vs. 1 Quintile 4 vs. 1 Quintile 3 vs. 1 Quintile 2 vs. 1	1.37 (1.09–1.73) 1.24 (1.00–1.53) 1.17 (0.95–1.43) 1.21 (0.99–1.47)	Age, sex, BMI, smoking, PA, vitamin supplements, TEI, presence of CVD, DM, hypertension or dyslipidemia
Shivappa et al. (27)	Australia	1,573/6,438	100%	52.0	Cohort (12)	Depressive symptoms	CES-D-10≥10	FFQ	Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1	1.23 (1.05–1.45) 1.14 (0.97–1.32) 1.08 (0.93–1.25)	Total energy intake, highest qualification completed, marital status, menopause, night sweats, major personal illness or injury, lifestyle factors, smoking, PA, BMI, depression
Shivappa et al. (27)	USA	837/3,608	56.50%	61.4	Cohort (10)	Depressive symptoms	CES-D-20>20	FFQ	Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1	1.24 (1.01–1.53) 1.06 (0.86–1.30) 1.21 (0.99–1.48)	Age; sex; race; body mass index; education; smoking habits; yearly income; Physical Activity Scale for Elderly score; Charlson Comorbidity Index; CES-D: Center for Epidemiologic Studies Depression Scale at baseline; statins use; NSAIDS or cortisone use

(Continued)

TABLE 1 | Continued

References	Location	Case/Total No.	Sex: female	Age (mean /range)	Study design follow-up (years)	Measures of Outcome	Mental health assessment	Dietary assessment tool	DII score comparison	OR (95%CI)	Adjustment for covariates
Adjibade et al. (28)	France	172/3,523	57.60%	52.1	Cohort (12.6)	Depressive symptoms	CES-D-10 scale≥17 for men and ≥23 for women	24-h diet recalls	Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1	1.06 (0.66–1.71) 0.87 (0.55–1.39) 0.74 (0.47–1.18)	Age, sex, intervention group during the trial phase, education, energy intake, marital status, socio professional status, number of 24 h dietary records, interval between two CES-D measures.
Phillips et al., (16)	USA	NA/2,047	50.80%	50–69	Cross-sectional	Depressive symptoms Anxiety	CES-D-20 > 16 HADS>13	FFQ	Tertile 3 vs. 1 Tertile 2 vs. 1 Tertile 3 vs. 1 Tertile 2 vs. 1	1.36 (0.83–2.24) 1.69 (1.06–2.69) 1.38 (0.95–2.24) 1.33 (0.83–2.11)	Age and gender, BMI, physical activity, smoking and alcohol consumption, antidepressant use and history of depression.
Wirth et al. (38)	USA	1,648/18,875	50.70%	46.9	Cross-sectional	Depressive symptoms	PHQ-9≥10	24-h diet recalls	Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1	1.13 (0.92–1.39) 1.14 (0.87–1.49) 1.08 (0.87–1.33)	Race, education, marital status, perceived health, current infection status, family history of smoking, smoking status, past cancer diagnosis, arthritis, age, and average nightly sleep duration.

(Continued)

TABLE 1 | Continued

References	Location	Case/Total No.	Sex: female	Age (mean /range)	Study design follow-up (years)	Measures of Outcome	Mental health assessment	Dietary assessment tool	DII score comparison	OR (95%CI)	Adjustment for covariates
Shivappa et al. (31)	Iran	43/300	100%	15–18	Cross-sectional	Depressive symptoms	DASS-21 > 9	FFQ	Tertile 3 vs. 1 Tertile 2 vs. 1	3.96 (1.12–13.97) 3.03 (1.11–8.26)	Age and energy, physical activity, BMI, smoking, presence of chronic disease, diet supplement use, salary and marital status
Açik et al. (33)	Turkey	79/134	100%	19–24	Cross-sectional	Depressive symptoms	Zung self-rating depression scale	24-h diet recalls	Tertile 3 vs. 1 Tertile 2 vs. 1	2.90 (1.51–5.98) 1.07 (0.48–2.48)	Age, smoking and alcohol consumption, physical activity, BMI, and energy intake
Shivappa et al. (34)	Iran	84/299	100%	15–18	Cross-sectional	Distress	DASS-21 >9	FFQ	Tertile 3 vs. 1 Tertile 2 vs. 1	3.48 (1.33–9.09) 3.16 (1.43–7.00)	Age, energy, physical activity, BMI, smoking, presence of chronic disease, diet supplement use, salary and marital status.
Bergmans et al. (30)	USA	1,486/11,592 2,089/11,592	52%	20–80	Cross-sectional	Distress Symptoms of anxiety	HRQOL HRQOL	24-h diet recalls	Quintile 5 vs. 1 Quintile 4 vs. 1 Quintile 3 vs. 1 Quintile 2 vs. 1 Quintile 5 vs. 1 Quintile 4 vs. 1 Quintile 3 vs. 1 Quintile 2 vs. 1	1.81 (1.2–2.71) 1.42 (0.95–2.11) 1.27 (0.90–1.80) 1.02 (0.72–1.46) 1.64 (1.14–2.35) 1.38 (1.02–1.88) 1.24 (0.95–1.62) 1.29 (0.99–1.68)	Age and gender, race/ethnicity, poverty income ratio category, employment status, health insurance status, educational status, and marital status, BMI, smoking, physical activity, sedentary time, use of vitamin supplements, total energy intake, menopause (among women), and any comorbidity.

(Continued)

TABLE 1 | Continued

References	Location	Case/Total No.	Sex: female	Age (mean /range)	Study design follow-up (years)	Measures of Outcome	Mental health assessment	Dietary assessment tool	DII score comparison	OR (95%CI)	Adjustment for covariates
Salari-Moghaddam et al., 2018	Iran	963/3,363 779/3,363 456/3,363	58.25%	36.3	Cross-sectional	Depressive symptoms Distress Symptoms of anxiety	HADS GHQ HADS	FFQ	Quintile 5 vs. 1 Quintile 4 vs. 1 Quintile 3 vs. 1 Quintile 2 vs. 1 Quintile 5 vs. 1 Quintile 4 vs. 1 Quintile 3 vs. 1 Quintile 2 vs. 1 Quintile 5 vs. 1 Quintile 4 vs. 1 Quintile 3 vs. 1 Quintile 2 vs. 1	1.84 (1.30–2.60) 1.70 (1.21–2.40) 1.49 (1.06–2.10) 1.17 (0.83–1.66) 1.72 (1.20–2.46) 1.44 (1.01–2.05) 1.18 (0.82–1.69) 1.04 (0.72–1.50) 1.69 (1.07–2.67) 1.34 (0.85–2.10) 1.26 (0.80–2.00) 0.96 (0.60–1.55)	Age, sex, energy intake, marital status, education, family size, home ownership, antidepressant use, vitamin supplements use, smoking status, physical activity, chronic conditions and BMI
Jahrami et al. (36)	Bahrain	120/240	54.17%	20–60	Case–Control	Schizophrenia	ICD-10	FFQ	Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1	5.96 (1.74–20.38) 2.78 (0.77–10.0) 4.27 (1.27–14.35)	Age, sex, body mass index, education, employment, diabetes, hypertension, and cardiovascular disease

(Continued)

TABLE 1 | Continued

References	Location	Case/Total No.	Sex: female	Age (mean /range)	Study design follow-up (years)	Measures of Outcome	Mental health assessment	Dietary assessment tool	DII score comparison	OR (95%CI)	Adjustment for covariates
Adjibade et al. (35)	France	2,221/26,730	76.24%	18–86	Cohort (5.4)	Depressive symptoms	CES-D ≥17 for men ≥23 for women	24-h diet recalls	Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1	1.16 (1.02–1.32) (0.89–1.15) 0.97 (0.86–1.10)	Age, sex, marital status, educational level, occupational categories, household income per consumption unit, residential area, energy intake without alcohol, number of 24 h-dietary records, and inclusion month, alcohol intake, smoking status, physical activity, and BMI, health events during follow-up (cancer, type 2 diabetes, and cardiovascular events).
Shin et al. (39)	Korea	752/15,929	54.79%	≥19	Cross-sectional	Depressive symptoms	PHQ score of ≥10		Tertile 3 vs. 1 Tertile 2 vs. 1	1.65 (1.14–2.39) 1.39 (0.98–1.96)	Age, gender, education, occupation, alcohol consumption, smoking status, physical activity, and BMI.

(Continued)

TABLE 1 | Continued

References	Location	Case/Total No.	Sex: female	Age (mean /range)	Study design follow-up (years)	Measures of Outcome	Mental health assessment	Dietary assessment tool	DII score comparison	OR (95%CI)	Adjustment for covariates
Ghazizadeh et al. (40)	Iran	2,631/7,083 3,580/7,083	57.5%	35–65	Cross-sectional	Depressive symptoms Symptoms of anxiety	BDI-II ≥14 BAI ≥ 7		Female Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1 Male Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1 Female Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1 Male Quartile 4 vs. 1 Quartile 3 vs. 1 Quartile 2 vs. 1	1.18 (1.05–1.33) 1.10 (0.97–1.24) 0.97 (0.85–1.09) 1.17 (0.95–1.43) 0.98 (0.80–1.19) 0.85 (0.65–1.12) 1.09 (0.95–1.25) 1.03 (0.89–1.19) 1.08 (0.94–1.25) 1.18 (0.98–1.43) 1.03 (0.76–1.39) 1.08 (0.90–1.29)	Age, BMI, smoking status, education level, marital status, physical activity level, high sensitivity C-reactive protein, and dyslipidemia.
Moludi et al. (41)	Iran	275/4,630	100%	35–65	Cross-sectional	Depressive symptoms	Screening questionnaire	FFQ	Tertile 3 vs. 1 Tertile 2 vs. 1	1.47 (1.07–2.03) 1.27 (0.92–1.75)	Age, BMI, smoking, alcohol abuse, physical activity, and place of living.

FFQ, Food frequency questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale; HRQOL, Health-Related Quality of Life; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; PHQ-9, Patient Health Questionnaire-9; DASS, Depression Anxiety and Stress Scale; ICD-10, International Statistical Classification of Diseases-10; BDI-II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory.

Association Between Dietary Inflammatory Index and Symptoms of Depression

Here, 13 studies (five cohort studies with 55,392 participants and eight cross-sectional studies with 52,361 participants) investigated the association between DII and symptoms of depression. A significant association was found between the highest DII category and symptoms of depression (pooled OR: 1.28, 95% CI: 1.17–1.39) compared with the lowest category, with moderate heterogeneity ($I^2 = 39.6\%$, $P = 0.06$). Sensitivity analyses showed that the pooled ORs and 95% CIs did not alter substantially by removing any one study, confirming the stability of the present results. Both Egger's and Begg's tests revealed significant publication bias, and the *P*-values were 0.01 and 0.01, respectively. After imputing four missing studies using the trim-and-fill method, the recalculated pooled OR did not substantially change from the initial estimate (imputed OR: 1.21, 95% CI: 1.14–1.27). The pooled OR of symptoms of depression was 1.15 (95% CI: 1. 05–1.25) for the second highest vs. lowest DII category, with moderate heterogeneity ($I^2 = 38.8\%$, $P = 0.07$). There was evidence of publication bias ($P = 0.04$ for Begg's test, $P = 0.03$ for Egger's test). After imputing four missing studies using the trim-and-fill method, the recalculated pooled OR did not substantially change from the initial estimate (imputed OR: 1.08, 95% CI: 1.02–1.15).

For dose–response meta-analysis, it was shown that there was no significant non-linear relationship between DII and symptoms of depression ($P_{\text{nonlinearity}} = 0.92$). The pooled OR for 1-unit increment in DII was 1.06 (95% CI: 1.03–1.09) in linear dose–response analysis. More details can be seen in **Table 2** and **Figure 2**.

Association Between Dietary Inflammatory Index and Symptoms of Anxiety

The association between DII and symptoms of anxiety was investigated in four cross-sectional studies, with a total of 21,632 participants. The pooled OR for the highest vs. lowest DII category was 1.27 (95% CI: 1.08–1.49), with moderate heterogeneity ($I^2 = 45.4\%$, $P = 0.12$). The pooled OR for the second highest vs. lowest DII category was 1.11 (95% CI: 0.99–1.24), with no significant heterogeneity ($I^2 = 10.0\%$, $P = 0.35$). More details can be seen in **Table 2** and **Figure 3**.

Association Between Dietary Inflammatory Index and Distress

There were three cross-sectional studies with a total of 15,254 participants investigating the association between DII and distress. The pooled OR for the highest vs. lowest DII category was 1.85 (95% CI: 1.43–2.40), with no significant heterogeneity ($I^2 = 0\%$, $P = 0.40$). The pooled OR for the second highest vs. lowest DII category was 1.62 (95% CI: 1.14–2.31), with moderate heterogeneity ($I^2 = 41.9\%$, $P = 0.18$). More details can be seen in **Table 2** and **Figure 4**.

Association Between Dietary Inflammatory Index and Schizophrenia

Only one study reported the association between DII and schizophrenia. The OR (95% CIs) of schizophrenia were 4.27 (1.27–14.35) and 2.78 (0.77–10.00) for the highest and second highest categories compared with the lowest DII category.

DISCUSSION

This systematic review and meta-analysis provided a comprehensive evaluation of current evidence on the association between DII and a great variety of mental health outcomes. The findings indicated that higher DII was associated with an increased risk of common mental health outcomes, including symptoms of depression, symptoms of anxiety, distress, as well as schizophrenia. Particularly important, there is a novel conclusion from dose–response analysis that 1-unit increment of DII was associated with a 6% higher risk of depressive symptoms.

Our findings indicated a significant association between pro-inflammatory diet and depression, which is in line with evidence from a recent meta-analysis. However, a previous meta-analysis on this topic did not perform subgroup analyses, sensitivity analyses, and publication bias test (17). A meta-analysis did not distinguish pro-inflammatory diet from unhealth dietary pattern (11), and another assessed the dietary inflammatory potential combining dietary and biomarker together (18). All above may potentially affect, to a certain degree, the precision and stability of pooled results. Specifically, our study presented a more comprehensive and clear understanding of the association between DII and depressive symptoms by performing a dose–response analysis and assessing dietary inflammatory potential through a simple and intuitive method. Importantly, we expanded on the previously described diet–depression association and suggested the potential implications of pro-inflammatory diet in a broad range of mental health outcomes, further reinforcing the role of diet in the pathophysiology of mental health symptoms or disorders.

The DII is a literature-derived, population-based diet quality index designed to standardize the inflammatory potential of an individual's diet (12). Up until the development of DII, there are two other categories of dietary indices used to clarify the association between diet and mental health outcomes. One category of these indices is derived using statistical methods (42), which closely matches the dietary habits of the studied population but does not necessarily reflect an optimal diet and is hardly replicable to other populations. Another category is developed based on healthy dietary guidelines, such as the Healthy Eating Index (HEI) (43), all of which do not target specific mechanisms. DII represents a unique biological mechanism underlying the diet–mental health link over other diet indices by capturing the inflammatory effect of diet. In addition, previous studies have demonstrated the predictive value of DII in chronic inflammatory disease, including obesity (44), cardiovascular disease (45), metabolic syndrome (46), and various types of cancers (47). All findings mentioned above indicate that the

TABLE 2 | Results of subgroup analyses for DII and mental disorders.

	The highest category				The second highest category			
Type of mental disorders	**Studies, *n***	**OR (95% CI)**	**I^2 (%)**	***P***	**Studies, *n***	**OR (95% CI)**	**I^2 (%)**	***P***
Symptoms of depression								
All study	13	1.28 (1.17–1.39)	39.6	0.06	13	1.15 (1.05–1.25)	38.7	0.07
Study design								
Cohort study	5	1.21 (1.12–1.32)	0	0.75	5	1.08 (0.99–1.17)	0.3	0.40
Cross-sectional study	8	1.39 (1.19–1.63)	58.2	0.01	8	1.24 (1.08–1.44)	49.0	0.05
Gender								
Male	6	1.14 (0.99–1.31)	16.4	0.31	6	1.06 (0.93–1.22)	0	0.46
Female	10	1.34 (1.17–1.54)	56.9	0.01	10	1.31 (1.05–1.21)	30.6	0.16
Location								
America	3	1.20 (1.04–1.38)	0	0.72	3	1.18 (0.95–1.45)	37.9	0.20
Asia	6	1.50 (1.22–1.83)	66.3	<0.01	6	1.24 (1.04–1.47)	54.2	0.04
Europe	3	1.20 (1.07–1.34)	0	0.41	3	1.07 (0.90–1.26)	39.9	0.19
Australia	1	1.23 (1.05–1.45)	–	–	1	1.14 (0.97–1.32)	–	–
DII components								
<30	8	1.32 (1.19–1.46)	19.2	0.28	8	1.23 (1.11–1.36)	20.9	0.26
≥30	5	1.22 (1.06–1.42)	51.7	0.06	5	1.04 (0.94–1.15)	20.3	0.28
Symptoms of anxiety								
All study	4	1.27 (1.08–1.49)	45.4	0.12	4	1.11 (0.99–1.24)	10.0	0.35
Study design								
Cross-sectional study	4	1.27 (1.08–1.49)	45.4	0.12	4	1.11 (0.99–1.24)	10.0	0.35
Gender								
Male	3	1.23 (0.85–1.77)	29.4	0.24	3	1.26 (0.74–2.14)	50.7	0.13
Female	3	1.32 (0.94–1.86)	50.7	0.13	3	1.05 (0.92–1.20)	0	0.68
Location								
America	2	1.53 (1.16–2.01)	0	0.55	2	1.36 (1.06–1.76)	0	0.90
Asia	2	1.18 (1.00–1.38)	40.8	0.19	2	1.05 (0.93–1.19)	0	0.55
DII components								
<30	3	1.57 (1.24–1.99)	0	0.78	3	1.36 (1.09–1.70)	0	0.99
≥30	1	1.12 (1.00–1.25)	–	–	1	1.03 (0.90–1.17)	–	–
Distress								
All study	3	1.85 (1.43–2.40)	0	0.40	3	1.62 (1.14–2.31)	41.9	0.18
Study design								
Cross-sectional study	3	1.85 (1.43–2.40)	0	0.40	3	1.62 (1.14–2.31)	41.9	0.18
Gender								
Male	1	2.09 (1.09–4.02)	–	–	1	1.84 (0.92–3.66)	–	–
Female	1	1.61 (1.03–2.50)	–	–	1	1.34 (0.88–2.04)	–	–
Location								
America	1	1.81 (1.20–2.72)	–	–	1	1.42 (0.95–2.12)	–	–
Asia	2	2.11 (1.13–3.96)	44.8	0.18	2	1.96 (0.92–4.16)	68.1	0.08
DII components								
<30	2	1.76 (1.34–2.30)	0	0.85	2	1.43 (1.10–1.86)	0	0.96
≥30	1	3.48 (1.33–9.09)	–	–	1	3.16 (1.43–7.00)	–	–
Schizophrenia								
Case-control study	1	4.27 (1.27–14.35)	–	–		2.78 (0.77–10.00)	–	–

FFQ: Food frequency questionnaire, CES-D: Centre for Epidemiologic Studies Depression Scale, HRQOL: Health-Related Quality of Life, GHQ: General Health Questionnaire, HADS: Hospital Anxiety and Depression Scale, PHQ-9: Patient Health Questionnaire-9, DASS: Depression Anxiety and Stress Scale, ICD-10: International Statistical Classification of Diseases-10, BDI-II: Beck Depression Inventory II, BAI: Beck Anxiety Inventory. DII, Dietary Inflammatory Index.

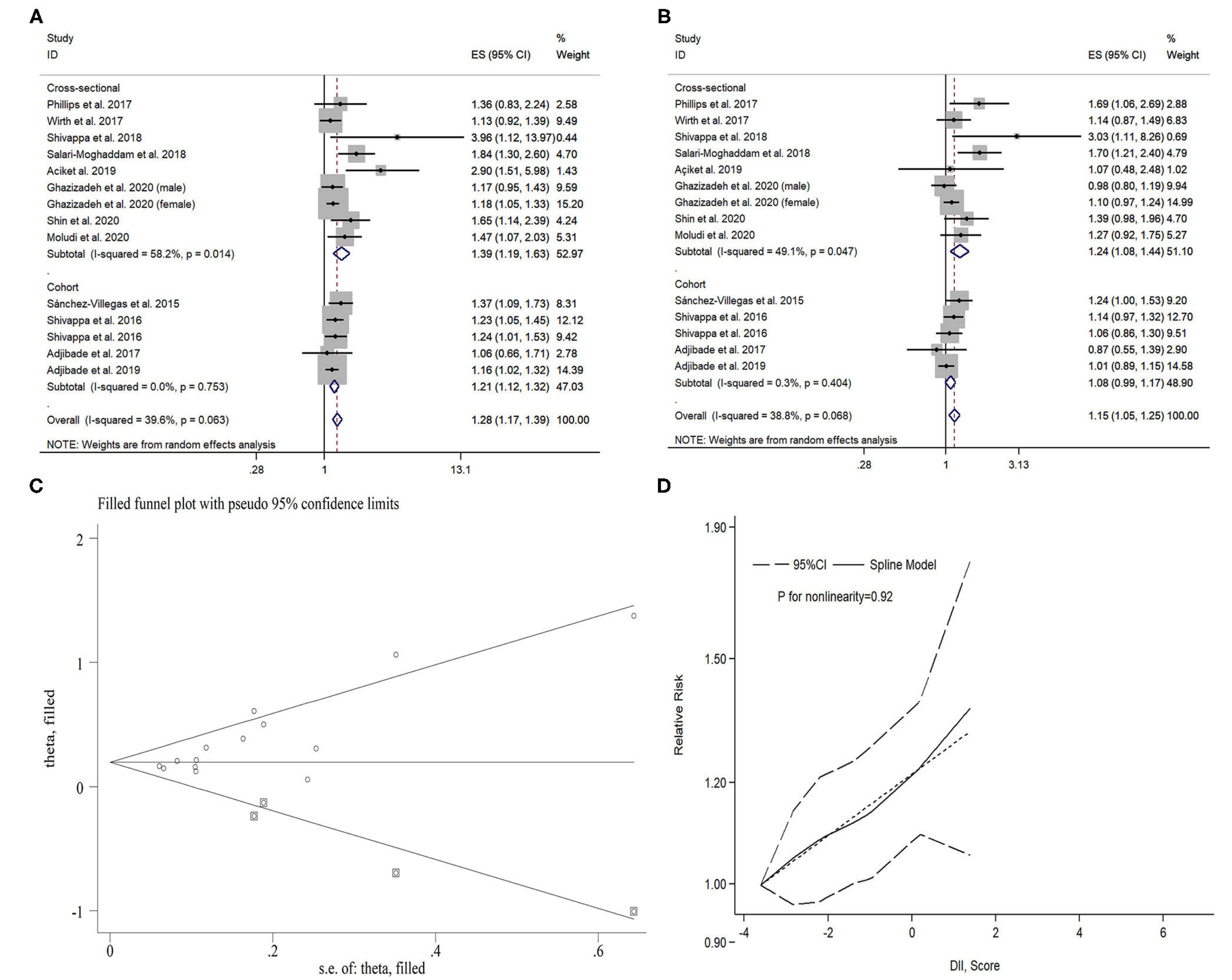

FIGURE 2 | Forest plot of the pooled effect estimates of symptoms of depression. **(A)** The highest Dietary Inflammatory Index (DII) category compared with the lowest category. **(B)** The second highest DII category compared with the lowest category. **(C)** Filled funnel plot with 95% CI using the trim-and-fill method. **(D)** Dose–response relationship between DII and symptoms of depression.

DII may potentially serve to be prevention targets of mental health disorders.

Depression, anxiety, and other common mental health symptoms or disorders have a high comorbidity, and it is well-documented that these disorders share genetic determinants as well as underlying neurobiological mechanisms (48, 49). Several potential mechanisms have been proposed to explain the observed association. First, the pro-inflammatory diet is associated with high levels of circulating inflammatory markers (50, 51). It has been shown that inflammatory markers, such as cytokines, could regulate neurotransmitter metabolism and neural plasticity, which in turn induce the development of neuropsychiatric diseases (52). Second, oxidative stress is implicated as an important determinant relevant to mental health disorders (53). It has been indicated that pro-inflammatory diet can modulate oxidative processes, and oxidant–antioxidant imbalance is associated with elevated levels of reactive oxygen and nitrogen species, which increase DNA damage (54). Such damage may underlie the demonstrated association between DII and mental health (54). In addition, the microbiome–gut–brain axis may represent a critical pathway through which a pro-inflammatory diet contributes to the etiology of mental disorders (55). It is demonstrated that pro-inflammatory diet can modify the gut microbiota composition and activity (56), and gut microbiota can potentially influence immune system activation, production of neurotransmitters, and regulation of neuroendocrine pathways, which in turn influence mental health (57, 58). Although the common mental health symptoms or disorders share mechanisms, the distinct pathophysiologic mechanisms for different disorders should be further elucidated in order to determine whether nutritional factors affect the development of these disorders differently.

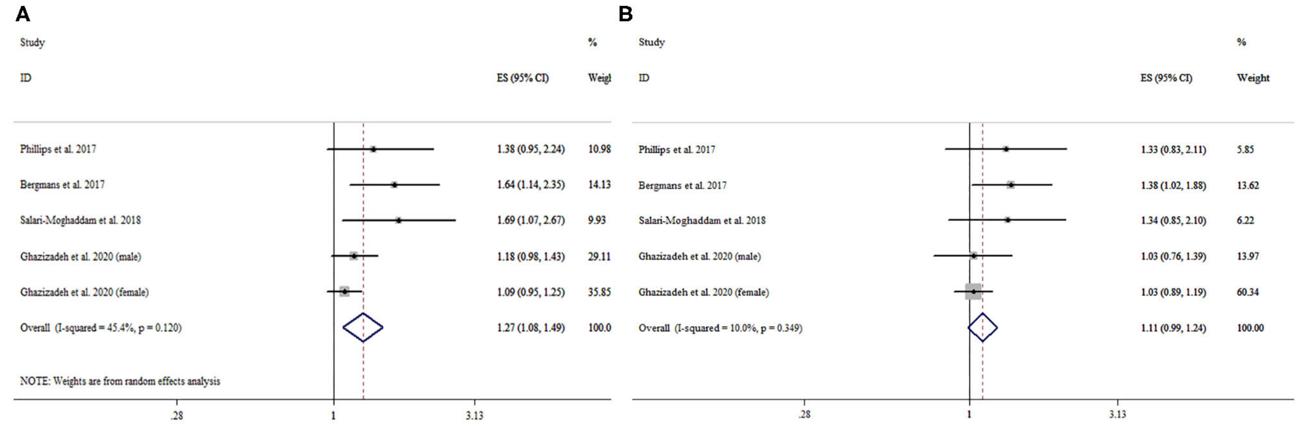

FIGURE 3 | Forest plot of the pooled effect estimates of symptoms of anxiety. **(A)** The highest Dietary Inflammatory Index (DII) category compared with the lowest category. **(B)** The second highest DII category compared with the lowest category.

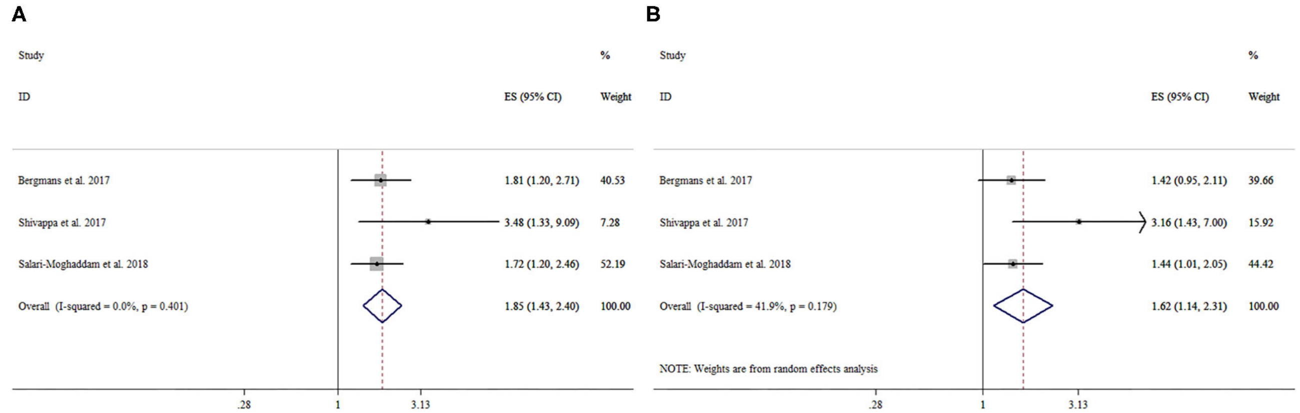

FIGURE 4 | Forest plot of the pooled effect estimates of distress. **(A)** The highest Dietary Inflammatory Index (DII) category compared with the lowest category. **(B)** The second highest DII category compared with the lowest category.

A major strength of this study is that the meta-analysis provided a comprehensive overview on a wide range of mental health outcomes rather than a specific type related to DII, which provides convincing support of the diet–mental health link. Second, compared with previous studies on this topic, the current linear dose–response analysis can help clarify how the risk of depression changes along with the increase of the dietary inflammatory potential. Third, sensitivity analyses and detailed subgroup analyses further support the stability of our conclusions. Despite the strengths of the current systematic review, there are certain limitations that need to be addressed. First, cross-sectional design was used in most of the included studies, which did not give a causal relationship. Previous studies indicated that mental stress can lead to increased intake of high-energy and high-fat foods and result in a higher DII score, and it is probable that the bidirectional relationship exists between DII and mental health symptoms or disorders. Thus, well-designed cohort studies and randomized controlled trials are needed to further demonstrate the causal relationships. Second, although all original studies adjusted for different covariates, due to confounding biases inherent in each study, the possibility of remaining residual confounding is to be expected. Third, the results of this study might be affected by the moderate level of heterogeneity. Meta-regression analyses were used to explore the source of heterogeneity. The following independent variables including location and number of DII components were introduced into the meta-regression model. Finally, publication bias was observed in Begg's or Egger's tests, but using the trim-and-fill method to include supposedly missing negative studies, a significant association still persists. These limitations may impose a modest constraint on the interpretation of these findings, but they should not substantively undermine the internal validity of the study.

Our findings have significant implications for both public health and clinical practice. From the public health perspective, avoiding a pre-inflammatory diet could be a feasible approach in the primary prevention of adverse mental health. From the clinical perspective, the demonstrated associations may have potential benefits in formulating appropriate targeted therapeutic and intervention strategies for mental health symptoms or disorders. Therefore, future nutritional psychiatry research should aim to develop targeted nutritional protocols and then incorporate them into prevention and treatment guidelines of mental health symptoms or disorders.

In conclusion, more pro-inflammatory diet, as estimated by the higher DII score, could increase the risk of a variety of mental health disorders. It may be of public health and clinical significance regarding the development of novel nutritional psychiatry approaches to promote good mental health. Further well-designed prospective trials are needed to strengthen the evidence of the associations between the DII and mental health symptoms or disorders.

DATA AVAILABILITY STATEMENT

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

G-QC and YL searched the databases, performed screening of titles and abstracts, performed screening of full texts, extracted data, performed all analyses, and wrote the manuscript. P-YC, B-WW, and C-LP were involved in revising the paper. G-PW supervised the study and contributed to the critical revision. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.662357/full#supplementary-material

Supplementary Table 1 | PRISMA Checklist.

Supplementary Table 2 | Methodological quality of the included studies.

REFERENCES

1. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. *Lancet Psychiatry*. (2016) 3:171–8. doi: 10.1016/S2215-0366(15)00505-2
2. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. (2018) 392:1859–922. doi: 10.1016/S0140-6736(18)32335-3
3. WHO. *Depression and Other Common Mental Disorders Global Health Estimates*. Geneva: World Health Organization. (2017).
4. Sarris J, Logan AC, Akbaraly TN, Paul A.mminger G, Balanza-Martinez V, Freeman MP, et al. International Society for Nutritional Psychiatry Research consensus position statement: nutritional medicine in modern psychiatry. *World Psychiatry*. (2015) 14:370–1. doi: 10.1002/wps20223
5. Sureda A, Bibiloni MDM, Julibert A, Bouzas C, Argelich E, Llompart I, et al. Adherence to the mediterranean diet and inflammatory markers. *Nutrients*. (2018) 10:62. doi: 10.3390/nu10010062
6. Su H, Liu R, Chang M, Huang J, Wang X. Dietary linoleic acid intake and blood inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Food Funct*. (2017) 8:3091–103. doi: 10.1039/C7FO00433H
7. O'Connor L, Imamura F, Brage S, Griffin SJ, Wareham NJ, Forouhi NG. Intakes and sources of dietary sugars and their association with metabolic and inflammatory markers. *Clin Nutr*. (2018) 37:1313–22. doi: 10.1016/j.clnu.2017.05030
8. Zheng L, Sun J, Yu X, Zhang D. Ultra-processed food is positively associated with depressive symptoms among United States adults. *Front Nutr*. (2020) 7:600449. doi: 10.3389/fnut.2020600449
9. Gregório MJ, Rodrigues AM, Eusébio M, Sousa RD, Dias S, André B, et al. Dietary patterns characterized by high meat consumption are associated with other unhealthy life styles and depression symptoms. *Front Nutr*. (2017) 4:25. doi: 10.3389/fnut.201700025
10. Smith AP, Rogers R. Positive effects of a healthy snack (fruit) versus an unhealthy snack (chocolate/crisps) on subjective reports of mental and physical health: a preliminary intervention study. *Front Nutr*. (2014) 1:10. doi: 10.3389/fnut.201400010
11. Molendijk M, Molero P, Ortuno Sanchez-Pedreno F, Van der Does W, Angel Martinez-Gonzalez M. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. *J Affect Disord*. (2018) 226:346–54. doi: 10.1016/j.jad.2017.09022
12. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public health Nutr*. (2014) 17:1689–96. doi: 10.1017/S1368980013002115
13. Kotemori A, Sawada N, Iwasaki M, Yamaji T, Shivappa N, Hebert JR, et al. Validating the dietary inflammatory index using inflammatory biomarkers in a Japanese population: a cross-sectional study of the JPHC-FFQ validation study. *Nutrition*. (2020) 69:110569. doi: 10.1016/j.nut.2019110569
14. Shin D, Lee KW, Brann L, Shivappa N, Hebert JR. Dietary inflammatory index is positively associated with serum high-sensitivity C-reactive protein in a Korean adult population. *Nutrition*. (2019) 63–64:155–61. doi: 10.1016/j.nut.2018.11016
15. Haghighatdoost F, Feizi A, Esmaillzadeh, Feinle-Bisset C, Keshteli AH, Afshar H, et al. Association between the dietary inflammatory index and common mental health disorders profile scores. *Clin Nutr*. (2019) 38:1643–50. doi: 10.1016/j.clnu.2018.08016
16. Phillips CM, Shivappa N, Hebert JR, Perry IJ. Dietary inflammatory index and mental health: A cross-sectional analysis of the relationship with depressive symptoms, anxiety and well-being in adults. *Clin Nutr*. (2018) 37:1485–91. doi: 10.1016/j.clnu.2017.08029
17. Wang J, Zhou Y, Chen K, Jing Y, He J, Sun H, et al. Dietary inflammatory index and depression: a meta-analysis. *Public Health Nutr*. (2018) 1–7. doi: 10.1017/S1368980018002628

18. Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: a systematic review and meta-analysis. *Clinical Nutr*. (2019) 38:2045–52. doi: 10.1016/j.clnu.2018.11007
19. Kheirouri S, Alizadeh M. Dietary inflammatory potential and the risk of incident depression in adults: a systematic review. *Adv Nutr*. (2019) 10:9–18. doi: 10.1093/advances/nmy100
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6:e1000097. doi: 10.1371/journal.pmed1000097
21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z
22. Rostom A, Dube C, Cranney A, Saloojee N, Sy R, Garritty C, et al. Celiac disease. *Evid Rep Technol Assess (Summ)*. (2004)(104):1-6.
23. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol*. (1992) 135:1301–9. doi: 10.1093/oxfordjournals.ajea116237
24. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol*. (2012) 175:66–73. doi: 10.1093/aje/kwr265
25. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med*. (2010) 29:1037–57. doi: 10.1002/sim3841
26. Sanchez-Villegas A, Ruiz-Canela M, de la Fuente-Arrillaga C, Gea A, Shivappa N, Hebert JR, et al. Dietary inflammatory index, cardiometabolic conditions and depression in the Seguimiento Universidad de Navarra cohort study. *Br J Nutr*. (2015) 114:1471–9. doi: 10.1017/S0007114515003074
27. Shivappa N, Schoenaker DA, Hebert JR, Mishra GD. Association between inflammatory potential of diet and risk of depression in middle-aged women: the Australian Longitudinal Study on Women's Health. *Br J Nutr*. (2016) 116:1077–86. doi: 10.1017/S0007114516002853
28. Adjibade M, Andreeva VA, Lemogne C, Touvier M, Shivappa N, Hebert JR, et al. The inflammatory potential of the diet is associated with depressive symptoms in different subgroups of the general population. *J Nutr*. (2017) 147:879–87. doi: 10.3945/jn.116245167
29. Shivappa N, Hebert JR, Veronese N, Caruso MG, Notarnicola M, Maggi S, et al. The relationship between the dietary inflammatory index (DII((R))) and incident depressive symptoms: a longitudinal cohort study. *J Affect Disord*. (2018) 235:39–44. doi: 10.1016/j.jad.2018.04014
30. Bergmans RS, Malecki KM. The association of dietary inflammatory potential with depression and mental well-being among U.S. adults. *Prev Med*. (2017) 99:313–9. doi: 10.1016/j.ypmed.2017.03016
31. Shivappa N, Hebert JR, Neshatbini T.ehrani A, Bayzai B, Naja F, Rashidkhani B. A pro-inflammatory diet is associated with an increased odds of depression symptoms among iranian female adolescents: a cross-sectional study. *Front Psychiatry*. (2018) 9:400. doi: 10.3389/fpsyt.201800400
32. Salari-Moghaddam A, Keshteli AH, Afshar H, Esmaillzadeh A, Adibi P. Association between dietary inflammatory index and psychological profile in adults. *Clinical Nutr*. (2019) 38:2360–8. doi: 10.1016/j.clnu.2018.10015
33. Acik M, Cakiroglu FP. Evaluating the relationship between inflammatory load of a diet and depression in young adults. *Ecol Foo Nutr*. (2019) 58:366–78. doi: 10.1080/03670244.20191602043
34. Shivappa N, Hebert JR, Rashidkhani B. Association between inflammatory potential of diet and stress levels in adolescent women in Iran. *Arch Iranian Med*. (2017) 20:108–12.
35. Adjibade M, Lemogne C, Touvier M, Hercberg S, Galan P, Assmann KE, et al. The inflammatory potential of the diet is directly associated with incident depressive symptoms among French adults. *J Nutr*. (2019) 149:1198–207. doi: 10.1093/jn/nxz045
36. Jahrami H, Faris MA, Ghazzawi HA, Saif Z, Habib L, Shivappa N, et al. Increased dietary inflammatory index is associated with schizophrenia: results of a case-control study from Bahrain. *Nutrients*. (2019) 11:1867. doi: 10.3390/nu11081867
37. Akbaraly T, Kerlau C, Wyart M, Chevallier N, Ndiaye L, Shivappa N, et al. Dietary inflammatory index and recurrence of depressive symptoms: results from the Whitehall II Study. *Clin Psychol Sci*. (2016) 4:1125–34. doi: 10.1177/2167702616645777
38. Wirth MD, Shivappa N, Burch JB, Hurley TG, Hebert JR. The dietary inflammatory index, shift work, and depression: results from NHANES. *Health Psychol*. (2017) 36:760–9. doi: 10.1037/hea0000514
39. Shin D, Shivappa N., Hébert JR, Lee KW. Examining regional differences of dietary inflammatory index and its association with depression and depressive symptoms in Korean Adults. *Int J Environ Res Public Health*. (2020) 17:3205. doi: 10.3390/ijerph17093205
40. Ghazizadeh H., Yaghooti-Khorasani M, Asadi Z, Zare-Feyzabadi R, Saeidi F, Shabani N, et al. Association between Dietary Inflammatory Index (DII®) and depression and anxiety in the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study population. *BMC Psychiatry*. (2020) 20:282. doi: 10.1186/s12888-020-02663-4
41. Moludi J, Moradinazar M, Hamzeh B, Najafi F, Soleimani D, Pasdar Y. Depression relationship with dietary patterns and dietary inflammatory index in women: result from ravansar cohort study. *Neuropsychiatr Dis Treat*. (2020) 16:1595–603. doi: 10.2147/NDTS255912
42. Miki T, Eguchi M, Akter S, Kochi T, Kuwahara K, Kashino I, et al. Longitudinal adherence to a dietary pattern and risk of depressive symptoms: the Furukawa Nutrition and Health Study. *Nutrition*. (2018) 48:48–54. doi: 10.1016/j.nut.2017.10023
43. Kennedy ET, Ohls J, Carlson S, Fleming K. The healthy eating index: design and applications. *J Am Diet Assoc*. (1995) 95:1103–8. doi: 10.1016/S0002-8223(95)00300-2
44. Oliveira TMS, Bressan J, Pimenta AM., Martinez-Gonzalez MA, Shivappa N, Hebert JR, et al. Dietary inflammatory index and prevalence of overweight and obesity in Brazilian graduates from the Cohort of Universities of Minas Gerais (CUME project). *Nutrition*. (2020) 71:110635. doi: 10.1016/j.nut.2019110635
45. Shivappa N, Godos J, Hebert JR, Wirth MD, Piuri G, Speciani AF, et al. Dietary inflammatory index and cardiovascular risk and mortality-a meta-analysis. *Nutrients*. (2018) 10:200. doi: 10.3390/nu10020200
46. Carvalho CA, Silva AAM, Assuncao MCF, Fonseca PCA, Barbieri MA, Bettiol H, et al. The dietary inflammatory index and insulin resistance or metabolic syndrome in young adults. *Nutrition*. (2019) 58:187–93. doi: 10.1016/j.nut.2018.07014
47. Li D, Hao X, Li J, Wu Z, Chen S, Lin J, et al. Dose-response relation between dietary inflammatory index and human cancer risk: evidence from 44 epidemiologic studies involving 1,082,092 participants. *Am J Clin Nutr*. (2018) 107:371–88. doi: 10.1093/ajcn/nqx064
48. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. *Neuropsychopharmacology*. (2017) 42:254–70. doi: 10.1038/npp.2016146
49. Goodwin GM. The overlap between anxiety, depression, and obsessive-compulsive disorder. *Dialogues Clin Neurosci*. (2015) 17:249–60. doi: 10.31887/DCNS.2015.173/ggoodwin
50. Phillips CM, Shivappa N, Hebert JR, Perry IJ. Dietary inflammatory index and biomarkers of lipoprotein metabolism, inflammation and glucose homeostasis in adults. *Nutrients*. (2018) 10:1033. doi: 10.3390/nu10081033
51. Almeida-de-Souza J, Santos R, Barros R, Abreu S, Moreira C, Lopes L, et al. Dietary inflammatory index and inflammatory biomarkers in adolescents from LabMed physical activity study. *Eur J Clin Nutr*. (2018) 72:710–9. doi: 10.1038/s41430-017-0013-x
52. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. (2009) 65:732–41. doi: 10.1016/j.biopsych.2008.11029
53. Abshirini M, Siassi F, Koohdani F, Qorbani M, Mozaffari H, Aslani Z, et al. Dietary total antioxidant capacity is inversely associated with depression, anxiety and some oxidative stress biomarkers in postmenopausal women: a cross-sectional study. *Ann Gen Psychiatry*. (2019) 18:3. doi: 10.1186/s12991-019-0225-7
54. Czarny P, Wigner P, Galecki P, Sliwinski T. The interplay between inflammation, oxidative stress, DNA damage, DNA repair and mitochondrial dysfunction in depression. *Prog Neuropsychopharmacol Biol Psychiatry*. (2018) 80(Pt C):309–21. doi: 10.1016/j.pnpbp.2017.06036
55. Sanada K, Nakajima S, Kurokawa S., Barcelo-Soler A, Ikuse D, Hirata A, et al. Gut microbiota and major depressive disorder: a systematic review and meta-analysis. *J Affect Disord*. (2020) 266:1–13. doi: 10.1016/j.jad.2020.01102

56. Dash S, Clarke G, Berk M, Jacka FN. The gut microbiome and diet in psychiatry: focus on depression. *Curr Opin Psychiatry*. (2015) 28:1–6. doi: 10.1097/YCO0000000000000117
57. Rieder R, Wisniewski PJ, Alderman BL, Campbell SC. Microbes and mental health: a review. *Brain Behavr Immun*. (2017) 66:9–17. doi: 10.1016/j.bbi.2017.01016
58. Iannone LF, Preda A., Blottière HM, Clarke G, Albani D, Belcastro V, et al. Microbiota-gut brain axis involvement in neuropsychiatric disorders. *Expert Rev Neurother*. (2019) 19:1037–50. doi: 10.1080/14737175.20191638763

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Dietary Inflammatory Index and Health Outcomes: An Umbrella Review of Systematic Review and Meta-Analyses of Observational Studies

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Background and Aims: The dietary inflammatory index (DII) is associated with non-communicable disease. We conducted an umbrella review to systematically evaluate meta-analyses of observational studies on DII and diverse health outcomes.

Methods: We comprehensively searched the PubMed, Web of Science, and Embase databases to identify related systematic reviews and meta-analyses of observational studies. Those investigating the association between DII and a wide range of health outcomes in humans were eligible for inclusion. For each meta-analysis, we estimated the summary effect size by using fixed and random effects models, the 95% confidence interval, and the 95% prediction interval. We assessed heterogeneity, evidence of small-study effects, and excess significance bias.

Results: The umbrella review identified 35 meta-analyses assessing associations between DII and various health outcomes: cancer ($n = 24$), mortality ($n = 4$), metabolic ($n = 4$), and other ($n = 3$). The methodological quality was high or moderate. Of the 35 meta-analyses, we observed highly suggestive evidence for harmful associations between digestive tract cancer, colorectal cancer, overall cancer, pharyngeal cancer, UADT cancer, and CVD mortality. Moreover, 11 harmful associations showed suggestive evidence: hormone-dependent cancer, rectal cancer, colon cancer, breast and prostate cancer, gynecological cancer, breast cancer, ovarian cancer, colorectal cancer, prostate cancer, all-cause mortality, and depression.

Conclusion: DII is likely to be associated with harmful effects in multiple health outcomes. Robust randomized controlled trials are warranted to understand whether the observed results are causal.

Systematic Review Registration: CRD42021218361

Keywords: dietary inflammatory index, health outcomes, meta-analysis, umbrella review, observational studies

INTRODUCTION

The dietary inflammatory index (DII) is a new dietary index developed to reflect the inflammatory potential of diet. It scores an individual's diet on a continuum from anti- to pro-inflammatory. This scoring system is based on the results of scientific publications rather than population means or recommended intakes. The literature includes studies on the relationships among dietary factors—including foods, nutrients, and other bioactive compounds—and six inflammatory biomarkers: C-reactive protein, interleukin (IL)-1b, IL-4, IL-6, IL-10, and tumor necrosis factor-α (1–7). The index distinguishes individuals' diets on the basis of their inflammatory potential on a spectrum from maximally pro-inflammatory components to maximally anti-inflammatory components (1). A higher DII score indicates a more pro-inflammatory diet, whereas a lower DII score indicates a more anti-inflammatory diet. Therefore, the DII offers a valid and readily comparable method for evaluating individuals' dietary inflammatory potential according to the pro- and anti-inflammatory aspects of the overall diet (7). In recent years, the role of DII in relation to non-communicable diseases, including cardiovascular disease (CVD) (8, 9), metabolic syndrome (10), and various types of cancer (11), has been examined in the epidemiological literature. According to the consensus, higher DII scores are deleterious to health. In 2019, a narrative review on the association between DII and non-communicable disease risk was published, describing evidence of relationships between DII and a wide array of cancers, CVD risk and mortality, on the basis of a descriptive presentation of the results of individual studies without quantitative synthesis (12). Although previous studies have examined this topic, a quantitative appraisal of epidemiological credibility is lacking, as are examinations of the potential bias between DII and health-related outcomes and assessments of the most influential outcomes.

In this context, we performed an umbrella review of the evidence through current systematic reviews and meta-analyses of observational studies, to provide an overview of the range and validity of the published relationships between DII and health-related outcomes. We summarized the multiple health outcomes that have been associated with DII in meta-analyses, assessed the diverse bias in these meta-analyses, and identified which of the previously studied associations are supported by the strongest epidemiological evidence.

MATERIALS AND METHODS

Umbrella Review Methods

Umbrella reviews perform in-depth evaluations of the quantitative results of meta-analyses of observational associations and the potential bias in these meta-analyses. Umbrella reviews comprehensively and systematically search and evaluate existing systematic reviews and meta-analyses and can readily be used by decision-makers in healthcare to understand a broad topic field (13).

Literature Search

We systematically searched PubMed, Embase, and the Web of Science from inception until August 8, 2020, to identify systematic reviews and meta-analyses examining the association between DII and any health outcome. The search terms included DII, dietary inflammatory score, dietary score, inflammatory diet, inflammatory potential of diet, dietary inflammation potential, inflammatory potential intake, anti-inflammatory diet, pro-inflammatory diet, dietary pattern, diet-related inflammation, index-based dietary patterns, or DII, combined with systematic review or meta-analysis (**Supplementary Table 1**). We also hand-checked the reference lists of eligible systematic reviews and meta-analyses. Potentially eligible articles were retrieved independently by two researchers (F-HL and MZ), and any discrepancies were resolved by a third author (Q-JW).

Eligibility Criteria

Studies were included if they met the following criteria, established by using the PICOS strategy:

Population: adults.
Intervention/comparison: the DII (including categorical and continuous variables).
Outcomes: health outcomes (e.g., cancer, CVD, mortality, etc.).
Study design: meta-analyses of observational studies (cohort, case–control, or cross-sectional studies).
In addition, if an article performed different meta-analyses on more than one health outcome, each analysis was assessed separately. When two or more meta-analyses were available on the same scientific question, the one including the largest number of studies was selected.

Studies were excluded if they met the following criteria, established by using the PICOS strategy:

Population: non-adults.
Intervention/comparison: not DII.
Outcomes: any other outcome outside of the inclusion criteria.
Study design: systematic reviews of observational studies without quantitative analysis, meta-analyses not reporting comprehensive data (e.g., effect sizes, 95% CIs, and the numbers of cases, controls and total participants), or meta-analyses including primary studies are <3.

Data Extraction

Two independent authors (F-HL and MZ) extracted data from each eligible meta-analysis, and disagreements were resolved by the third author (Q-JW). First-author name, publication year, journal, number of total studies, study design, method of exposure ascertainment (e.g., food-frequency questionnaire, 24-h recall, etc.), and outcomes were abstracted from each included meta-analysis. From each observational study included in the meta-analysis, we further recorded the name of the first author, publication year, number of cases and controls (case–control study), sample size, measure of exposure (highest vs. lowest category, or dose–response), specific risk estimates, and 95% CIs.

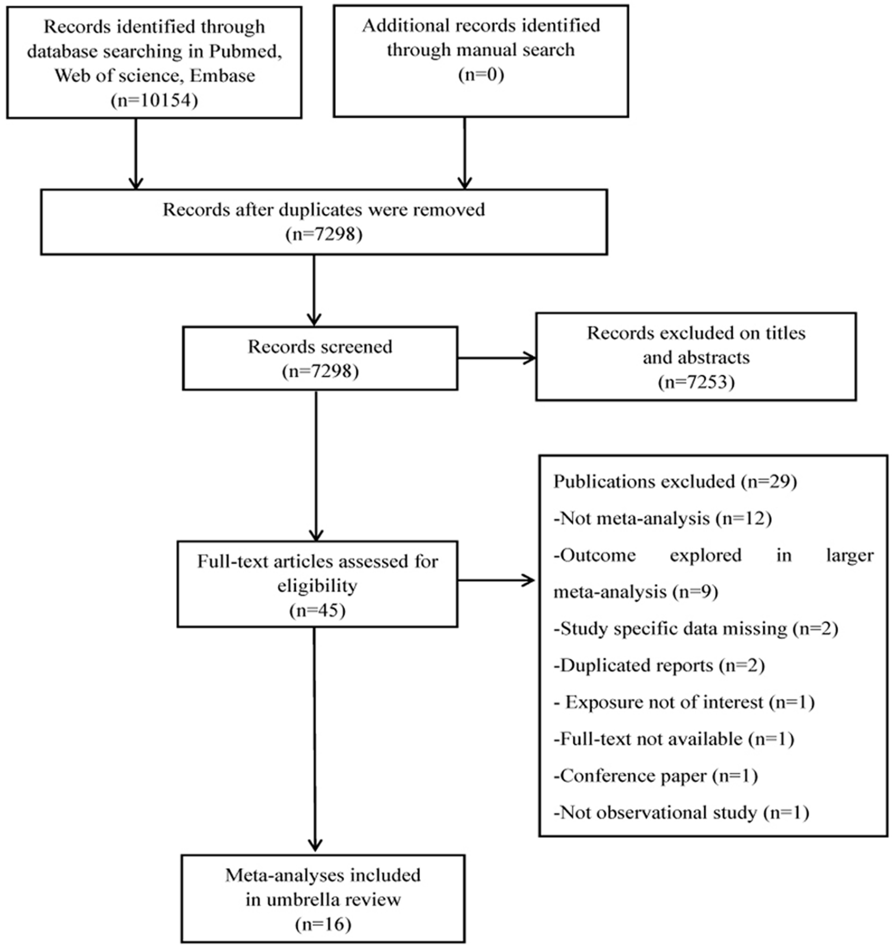

FIGURE 1 | Flowchart of selection of studies for inclusion in umbrella review on DII and health outcomes.

Data Analysis

For each chosen meta-analysis, we re-calculated the summary effect size estimate, its 95% CIs, and *P*-values by using both fixed- and random-effects models (14, 15). For the summary random effects, we estimated the 95% prediction interval (PI), which accounts for the degree of between-study heterogeneity and indicates the uncertainty for the effect that would be expected in another study examining the same association (16, 17). For the largest study in each meta-analysis, the standard error (SE) of the effect size was calculated, and we examined whether the SE was <0.10. We used the I^2 metric to quantify the heterogeneity between studies. I^2 ranges from 0 to 100% and quantifies the variability in effect estimates that results from heterogeneity other than sampling error (18). When the I^2 exceeded 50% or 75%, the heterogeneity was judged to be large or very large, respectively.

We conducted Egger's regression asymmetry test, proposed by Egger and colleagues (19), to estimate the small-study effects, that is, whether small studies tended to present higher risk estimates than large studies. A P-value < 0.10 combined with more conservative effects in larger studies than in random-effects meta-analysis was considered to constitute adequate evidence of small-study effects.

We further evaluated whether the observed number of studies (O) with nominally significant results (positive studies, $P < 0.05$) included in a meta-analysis was larger than the expected number (E), by using the excess statistical significance test (20). We used the effect size of the largest study (with the smallest SE) in each meta-analysis to investigate the power of the component studies by using a non-central t-distribution. A P-value < 0.10 (one-sided $P < 0.05$ combined with O > E as early suggested) was considered to indicate excess statistical significance for each meta-analysis (20).

Assessment of the Quality and Grading of Evidence

The 11-item AMSTAR (21) checklist was used by two independent authors to assess the methodological quality of systematic reviews and meta-analyses. The AMSTAR checklist is a strict, reliable, and valid measurement tool to evaluate systematic reviews and meta-analyses, which includes the quality of the search, analysis, and transparency of meta-analyses. The AMSTAR score is graded as high, moderate, low, or critically low quality.

According to previous umbrella reviews (22, 23), we categorized the evidence from meta-analyses with nominally significant summary results ($P < 0.05$) as convincing, highly suggestive, suggestive, weak, or non-significant associations. We considered convincing associations to have a statistical significance of $P < 10^{-6}$ in a random-effects model based on >1,000 cases (or >20,000 participants for continuous outcomes), $P < 0.05$ for the largest component study, a 95% PI excluding the null value, no heterogeneity ($I^2 < 50\%$), and no evidence of small-study effects ($P > 0.10$) or excess significance bias ($P > 0.10$). Highly suggestive evidence had a significance threshold of $P < 10^{-6}$, a number of cases >1,000 (or > 20,000 participants for continuous outcomes), and a statistically significant effect observed in the largest study. Suggestive evidence was indicated by >1,000 cases (or >20,000 participants for continuous outcomes) and $P < 10^{-3}$ for random effects. Weak evidence was indicated by $P < 0.05$ for a significant association. No association was indicated by a P-value not reaching the significance threshold ($P > 0.05$).

Association does not necessarily indicate causation. For associations with convincing or highly suggestive evidence, we performed a sensitivity analysis of only prospective cohort studies to investigate the temporality of the relationship between DII and any health outcome. All analyses were conducted in STATA, version 12.0.

RESULTS

Study Selection

Overall, 10,154 publications were retrieved through the database search, and 45 were deemed eligible. Twenty-nine publications were excluded after full-text screening for different reasons (**Figure 1** and **Supplementary Table 2**). The final selection yielded 16 articles to be included for analysis (9, 24–38).

Characteristics of Meta-Analyses

Table 1 shows the 35 independent meta-analyses, which included 261 primary studies in 16 articles (9, 24–38). These 16 articles were published between 2018 and 2020. Cohort, case–control, and cross-sectional studies were included in the meta-analyses, and the median number of studies per meta-analysis was seven (range: 3–44). The case numbers exceeded 1,000 in 30 meta-analyses. A wide range of outcomes were investigated: 24 (69%) of 35 meta-analyses studied associations between DII and cancers, including digestive tract cancer, respiratory tract cancer, hormone-dependent cancer, rectal cancer, colon cancer, breast and prostate cancer, gynecological cancers, breast cancer, ovarian cancer, colorectal cancer, prostate cancer, overall cancer, esophageal cancer, lung cancer, oral cavity cancer, pharynx cancer, larynx cancer, upper aerodigestive tract (UADT) cancer, and gastric cancer. Four (11%) of 35 meta-analyses examined mortality and metabolic outcomes. In addition, three meta-analyses investigated associations with CVD risk ($n = 2$) and depression ($n = 1$). Twenty-eight meta-analyses compared the highest vs. lowest DII score, and seven meta-analyses reported health effects associated with a one-unit increase in DII score.

Summary Effect Size

Of the 35 meta-analyses, the summary random effects estimates were significant at $P < 0.05$ in 31 (89%) meta-analyses, whereas the summary fixed effects estimates were significant in 32 (91%) meta-analyses. When $P < 0.001$ was taken as a threshold for significance, 21 (60%) and 29 (83%) meta-analyses generated significant summary results according to the random and fixed effects models, respectively. However, when a more stringent threshold of significance ($P < 1 \times 10^{-6}$) was applied, the summary random effects estimates were significant in nine (26%) meta-analyses, and the summary fixed effects estimates were significant in 20 (57%) meta-analyses (**Supplementary Table 3**). All nine meta-analyses with strongly significant significance under the random effects model reported an increased risk. Of these, seven associations (digestive tract cancer, overall cancer, esophageal cancer, oral cavity cancer, pharynx cancer, UADT cancer, and CVD mortality) were studied by comparison of the highest vs. lowest DII score, and two associations (colorectal cancer and overall cancer) were investigated for dose–response relationships. The magnitude of the observed summary random effect estimates ranged from 0.66 to 2.81 (**Supplementary Figure 1**).

The effect of the largest study included in each meta-analysis is reported in our analysis (**Supplementary Table 3**). Twenty-one (60%) of 35 meta-analyses reported that the largest study effect was nominally statistically significant, with a P-value < 0.05, and a more conservative effect than the summary random effects was observed in 25 (71%) of 35 meta-analyses.

Heterogeneity and Prediction Intervals

Of the 35 meta-analyses, 9 (26%) showed low heterogeneity ($I^2 < 50\%$), 13 (37%) meta-analyses showed high heterogeneity ($I^2 = 50–75\%$), and 13 (37%) showed very high heterogeneity ($I^2 > 75\%$) (**Supplementary Table 4**). When 95% PIs were evaluated, we found that seven meta-analyses (ovarian cancer, colorectal cancer, overall cancer, esophageal cancer, pharynx cancer, UADT cancer, and depression) excluded the null value (**Supplementary Table 4**).

Small-Study Effects and Excess Significance Bias

Evidence of small-study effects was observed in 19 (54%) of 35 meta-analyses on the basis of Egger's test (**Supplementary Table 4**). When taking the largest study estimate as the plausible effect size, we found that 19 (54%) of 35 meta-analyses showed evidence of excess significance (i.e., compared with larger studies, smaller studies tended to show substantially larger estimates of effect size) (**Supplementary Table 4**).

Methodological Quality of the Meta-Analyses

Among the 16 articles included in our umbrella review, only two (13%) were rated as high quality (≥8 points) and 14 (87%)

TABLE 1 | Characteristics and quantitative synthesis of the eligible meta-analyses of DII for health outcomes.

Outcomes (reference)	First author, year	Study design included in meta-analysis	No. of studies	No. of cases/participants	Level of comparison	Summary effect size (95% CI)	
						Random effects	Fixed effects
Cancer outcomes							
Breast and prostate cancer (26)	Moradi S, 2018	Cohort and Case–control study	9	9,972/52,203	Highest vs. lowest	1.70 (1.31–2.22)	1.40 (1.27–1.55)
Breast cancer (30)	Liu, 2019	Cohort and Case–control study	12	30,052/347,147	Highest vs. lowest	1.34 (1.14–1.56)	1.19 (1.14–1.24)
Breast cancer (31)	Jayedi A, 2018	Cohort and Case–control study	7	18,781/225,606	A 1-unit increment	1.04 (1.00–1.08)	1.01 (1.00–1.02)
Colon cancer (25)	Zhang, 2017	Cohort and Case–control study	6	8,210/389,847	Highest vs. lowest	1.37 (1.16–1.62)	1.26 (1.18–1.36)
Colorectal cancer (37)	Moazzen S, 2020	Cohort and Case–control study	11	28,645/1,037,658	Highest vs. lowest	0.66 (0.56–0.78)	0.79 (0.75–0.83)
Colorectal cancer (31)	Jayedi A, 2018	Cohort and Case–control study	9	18,888/878,912	A 1-unit increment	1.06 (1.04–1.09)	1.04 (1.01–1.05)
Digestive tract cancer (24)	Zahedi H, 2020	Cohort and Case–control study	14	15,399/694,894	Highest vs. lowest	1.83 (1.53–2.19)	1.29 (1.23–1.35)
Esophageal cancer (34)	Li, 2018	Cohort and Case–control study	5	891/3,598	Highest vs. lowest	2.81 (2.07–3.82)	2.74 (2.11–3.57)
Gastric cancer (36)	Liang, 2019	Cohort and Case–control study	3	700/2,118	Highest vs. lowest	2.12 (1.41–3.18)	1.95 (1.48–2.57)
Gastric cancer (36)	Liang, 2019	Cohort and Case–control study	3	475/101,835	A 1-unit increment	1.45 (1.04–2.03)	1.24 (1.12–1.38)
Gynecological cancers (30)	Liu, 2019	Cohort and Case–control study	18	33,907/357,095	Highest vs. lowest	1.38 (1.21–1.56)	1.21 (1.16–1.26)
Hormone-dependent cancer (24)	Zahedi H, 2020	Cohort and Case–control study	14	22,234/239,666	Highest vs. lowest	1.22 (1.10–1.34)	1.10 (1.06–1.15)
Larynx cancer (35)	Hua, 2020	Case–control study	3	997/2,805	Highest vs. lowest	2.05 (0.85–4.93)	2.67 (1.95–3.66)
Lung cancer (34)	Li, 2018	Cohort and Case–control study	6	2,162/7,707	Highest vs. lowest	1.56 (1.21–2.01)	1.45 (1.22–1.73)
Oral cavity cancer (35)	Hua, 2020	Case–control study	3	926/3,371	Highest vs. lowest	2.23 (1.73–2.86)	2.23 (1.73–2.86)
Overall cancer (34)	Li, 2018	Cohort and Case–control study	44	48,032/1,298,343	Highest vs. lowest	1.58 (1.45–1.72)	1.37 (1.32–1.42)
Overall cancer (34)	Li, 2018	Cohort and Case–control study	30	31,863/532,225	A 1-unit increment	1.13 (1.09–1.16)	1.08 (1.07–1.10)
Ovarian cancer (30)	Liu, 2019	Cohort and Case–control study	4	3,104/7,982	Highest vs. lowest	1.41 (1.21–1.65)	1.41 (1.21–1.65)
Pharynx cancer (35)	Hua, 2020	Case–control study	4	1,161/9,163	Highest vs. lowest	2.02 (1.54–2.64)	2.00 (1.59–2.51)
Prostate cancer (32)	Zhu, 2019	Cohort and Case–control study	10	5,326/52,873	Highest vs. lowest	1.73 (1.34–2.23)	1.28 (1.17–1.39)
Prostate cancer (32)	Zhu, 2019	Cohort and Case–control study	10	5,326/52,873	A 1-unit increment	1.10 (1.04–1.17)	1.04 (1.02–1.07)
Rectal cancer (25)	Zhang, 2017	Cohort and Case–control study	7	4,679/730,773	Highest vs. lowest	1.44 (1.23–1.69)	1.42 (1.29–1.57)
Respiratory tract cancer (24)	Zahedi H, 2020	Cohort and Case–control study	4	1,261/41,979	Highest vs. lowest	1.80 (1.21–2.67)	1.74 (1.40–2.16)
UADT cancer (35)	Hua, 2020	Case–control study	9	4,394/19,984	Highest vs. lowest	2.27 (1.89–2.73)	1.93 (1.78–2.10)
Mortality							
All-cause mortality (29)	Namazi N, 2018	Cohort and Cross-sectional study	6	32,677/107,306	Highest vs. lowest	1.21 (1.09–1.35)	1.13 (1.09–1.18)
Cancer mortality (24)	Zahedi H, 2020	Cohort and Case–control study	11	9,506/229,115	Highest vs. lowest	1.23 (1.07–1.42)	1.14 (1.07–1.22)
CVD mortality (27)	Ji, 2020	Cohort study	10	32,319/385,765	Highest vs. lowest	1.31 (1.19–1.44)	1.21 (1.16–1.27)
CVD mortality (9)	Shivappa N, 2017	Cohort and Cross-sectional study	6	11,094/93,866	A 1-unit increment	1.09 (1.03–1.15)	1.06 (1.04–1.08)
Metabolic outcomes							
Central obesity (38)	Farhangi MA, 2020	Cross-sectional study	10	6,904/25,435	Highest vs. lowest	1.16 (0.95–1.43)	1.06 (0.96–1.17)
Hypertension (33)	Farhangi MA, 2019	Cross-sectional study	12	20,126/44,102	Highest vs. lowest	1.13 (1.01–1.27)	1.15 (1.08–1.23)
Hyperglycemia (33)	Farhangi MA, 2019	Cross-sectional study	9	5,365/10,715	Highest vs. lowest	1.13 (0.95–1.35)	1.05 (0.95–1.16)
Metabolic syndrome (29)	Namazi N, 2018	Cohort and Cross-sectional study	5	2,242/15,161	Highest vs. lowest	1.01 (0.82–1.24)	1.01 (0.87–1.18)
Other outcomes							
CVD (27)	Ji, 2020	Cohort study	6	1,310/43,385	Highest vs. lowest	1.41 (1.12–1.78)	1.35 (1.13–1.61)
CVD (9)	Shivappa N, 2017	Cohort and Cross-sectional study	4	2,420/49,446	A 1-unit increment	1.08 (1.00–1.16)	1.03 (1.01–1.05)
Depression (28)	Wang, 2018	Cohort and Cross-sectional study	6	4,864/49,584	Highest vs. lowest	1.23 (1.12–1.35)	1.23 (1.12–1.35)

CVD, cardiovascular disease; DII, dietary inflammatory index; UADT, upper aerodigestive tract.

were defined as moderate quality (4–7 points), according to the AMSTAR criteria (**Supplementary Figure 2**). In summary, the common flaws were that gray literature was not considered in the literature search, the list of excluded studies was not presented, and the influence of the quality of the included studies was not discussed.

Evidence Grading

Figure 2 summarizes the strength of evidence of the meta-analyses that evaluated the DII on health outcomes. On the basis of the predefined methodological criteria, no association presented convincing evidence, whereas seven associations presented highly suggestive evidence. These associations are as follows: the effect of DII on the risk of digestive tract cancer (highest vs. lowest), colorectal cancer (a one-unit increment), overall cancer (highest vs. lowest and a one-unit increment), pharynx cancer (highest vs. lowest), UADT cancer (highest vs. lowest), and CVD mortality (highest vs. lowest). Eleven associations were supported by suggestive evidence: hormone-dependent cancer, rectal cancer, colon cancer, breast and prostate cancer, gynecological cancer, breast cancer, ovarian cancer, colorectal cancer, prostate cancer, all-cause mortality, and depression. Moreover, 13 associations were supported by weak evidence. Finally, for the other four associations, a non-significant result was found.

We performed a sensitivity analysis for associations supported by convincing and highly suggestive evidence, which was limited to meta-analyses of prospective cohort studies. Of the five associations included, three further associations met the criteria for highly suggestive evidence: the effect of DII on colorectal cancer (DII as a continuous variable), overall cancer, and CVD mortality. Two associations between DII and digestive tract cancer and overall cancer (DII as continuous variable) were downgraded to suggestive evidence (**Supplementary Table 6**).

DISCUSSION

Principal Findings

The present study is the first umbrella review to quantitatively estimate the existing evidence of the associations between DII and multiple health outcomes, including cancer, mortality, metabolic, and other outcomes (i.e., CVD and depression). We provided a comprehensive overview of the current meta-analyses of observational studies and examined the methodological quality of the included meta-analyses and the quality of evidence for all these associations.

The umbrella review comprised 16 published meta-analyses on a total population of more than 5.6 million participants. The methodological quality of the included meta-analyses was high/moderate. Highly suggestive evidence was observed for seven outcome variables, including digestive tract cancer, colorectal cancer, overall cancer, pharynx cancer, UADT cancer, and CVD mortality. Eleven outcomes associated with higher DII scores presented suggestive evidence. Additionally, 11 associations were supported by weak evidence.

Interpretation in Light of Evidence

The most notable associations identified in our umbrella review were those between DII and diverse cancers; harmful associations of DII with digestive tract cancer, colorectal cancer, overall cancer, pharynx cancer, and UADT cancer were observed. Our results were in accordance with those of prior studies. A population-based multi case–control study in Spain (39) showed that a one-unit DII score increment is associated with increased colorectal cancer risk. A meta-analysis of prospective studies (10), including more than 28,000 participants, reported an association between DII and elevated risk of cancer, although the dose–response association requires further investigation. However, the selected meta-analyses examining the above associations have some limitations, such as the substantial heterogeneity, the 95% PI containing the null value, and the presence of small-study effects and excess significance bias. Of particular interest is the relationship between DII and pharynx cancer. Our research included excess significance bias, whereas there was no evidence of the 95% PI including the null value or small-study effects. Compared with a previous umbrella review that explored the association between single risk factors and health-related outcomes (40, 41), the association between DII and pharynx cancer risk did not meet only one of our criteria for convincing evidence, thus suggesting that the present bias in the study of the association between DII and pharynx cancer risk might be relatively modest. The mechanisms underlying the harmful role of diet-related inflammation in increasing the risk of cancer have been widely explored. Systemic inflammation may cause an increase in insulin resistance, which may in turn affect the risk of digestive-tract cancers (42, 43). In addition, pro-inflammatory diets, such as a Western diet, may contribute to overweight, high BMI, and obesity (44). Previous studies have suggested that high BMI or obesity is correlated with increased cancer risk (45, 46). Furthermore, interactions between diet and the environment are considered to be associated with epigenetic changes and cancer (47, 48).

We found highly suggestive evidence that higher DII scores are associated with a higher risk of CVD mortality. Our results are in line with those from a published meta-analysis comprising 42,000 participants and 1,000 CVD cases, in which a higher DII score was found to increase the risk of CVD mortality (49). However, this result must be interpreted with caution, mainly because of the high heterogeneity, the 95% PI including the null value, and the evidence of small-study effects and excess significance bias. Further studies are therefore needed. The effect of a pro-inflammatory diet on insulin resistance may explain the observed relationship between DII with increased CVD mortality risk (50, 51). Insulin resistance is a common pathway for both cancer (52) and CVD (53). Moreover, the DII has been confirmed to be associated with higher levels of high-sensitivity C-reactive protein (hs-CRP) (a serum inflammatory marker) (54). High levels of hs-CRP predict the risk of CVD mortality. If hs-CRP is not controlled, progressive disease and death may result.

Furthermore, we observed suggestive evidence of a positive association between DII and depression. This association did not meet our criteria for convincing evidence, mainly because of the relatively low statistical significance. A systematic review examining DII and the risk of depression,

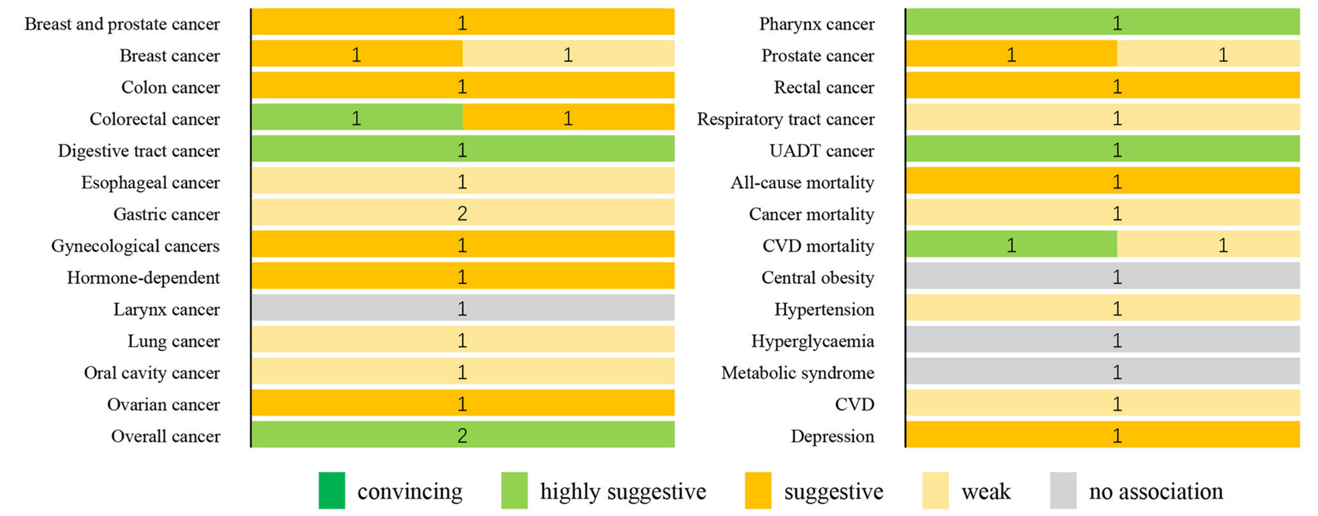

FIGURE 2 | Summary of the strength of evidence for the evaluated health outcomes. Numbers indicate the number of meta-analyses with convincing, highly suggestive, weak, or no association for each outcome. CVD, cardiovascular disease; UADT, upper aerodigestive tract.

published in 2019, has also reported that higher DII is associated with a higher risk of depression (55). Pro-inflammatory diets may increase inflammatory response system activation. Previous studies have also shown that in depressed people, inflammation is increased (56, 57), and the availability of brain-derived neurotrophic factor is decreased (58). Moreover, possible mechanisms underlying the effects of diet on depression include oxidative stress, the hypothalamic–pituitary–adrenal axis, and tryptophan depletion (59).

Strengths and Limitations

This umbrella review is the first to provide a comprehensive critical appraisal of published systematic reviews and meta-analyses on all health outcomes for DII. In addition, we searched three databases through a rigorous strategy, and two authors independently extracted the information. Moreover, we used the AMSTAR criteria to assess the methodological quality of selected in our umbrella review, and all investigated meta-analyses achieved a moderate-to-high quality score, thereby suggesting that current meta-analyses evaluating the effects of the DII on health outcomes partially or almost fully complied with standards of methodological quality. We used the criteria of evidence grading to evaluate the evidence categorization.

Nevertheless, some limitations of our study must be discussed. First, assessment criteria for credibility, which were based on established tools for observational evidence, were used in our umbrella review. Although none of the components of the assessment criteria presented definite evidence of absence of reliability, they together indicated the susceptibility of the results to uncertainty and bias. To account for the discrepancies in the populations, study designs, or other characteristics of the studies included in the meta-analyses, we used an $I^2 < 50\%$ as a criterion for convincing evidence, to assign the best grade of evidence to only robust associations without heterogeneity. Unfortunately, many of the meta-analyses included in our umbrella review showed high or very high heterogeneity. Second, fewer than 10 original studies were included in most (74%) of the meta-analyses in our study, thus potentially decreasing the power of Egger's tests and excess significance tests (22). Moreover, we used the random effects model proposed by DerSimonian and Laird (17) to calculate the adjusted summary effect size and corresponding 95% CIs, to ensure comparability with prior meta-analyses. However, a better approach to reflect the uncertainty in the variance between studies is recommended for future studies, such as the Hartung–Knapp approach (60), which shows the uncertainty of variance by wider CIs. Third, our work depended on prior meta-analyses, which might have missed some individual studies. However, this aspect is unlikely to have affected our findings, because the meta-analyses included in our study were those that included the largest number of research studies. Fourth, the results' validity depended on the quality of the data extracted from the meta-analyses included in the present umbrella review; those studies had the common limitations of observational studies, such as self-reported dietary information, misclassification, recall bias, or confounding bias. Fifth, few systematic reviews and meta-analyses included in our umbrella review performed analysis for confounding factors (**Supplementary Table 7**). However, most studies included in the meta-analyses in this umbrella review did adjust for potential confounding factors, including age, sex, and race.

CONCLUSIONS

In summary, highly suggestive evidence exists for associations between DII and digestive tract cancer, colorectal cancer, cancer, pharynx cancer, UADT cancer, and CVD mortality. Although

DII may be associated with an increased risk of other health outcomes, their relationships are uncertain according to our study. In the future, better designed studies are necessary to generate definite conclusions, and the association between inflammatory markers and health outcomes in a given population must be investigated.

TRANSPARENCY

The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this article can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

Q-JW, SG, and Y-HZ conceived the study. F-HL, SG, and T-TG contributed to the design. F-HL and MZ conducted the literature search, literature screening, and extracted the data. HS, Y-TJ, and J-YZ performed the quality assessment. X-YL and CG performed the statistical analysis. F-HL and T-TG wrote the first draft of the paper. CL revised the manuscript for important content. SG is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria were omitted. All authors interpreted the data, read the manuscript, and approved the final vision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.647122/full#supplementary-material

REFERENCES

1. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr.* (2014) 17:1689–96. doi: 10.1017/S1368980013002115
2. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr.* (2014) 17:1825–33. doi: 10.1017/S1368980013002565
3. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, et al. Construct validation of the dietary inflammatory index among postmenopausal women. *Ann Epidemiol.* (2015) 25:398–405. doi: 10.1016/j.annepidem.2015.03.009
4. Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, et al. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. *J Occup Environ Med.* (2014) 56:986–9. doi: 10.1097/JOM.0000000000000213
5. Ramallal R, Toledo E, Martinez-Gonzalez MA, Hernandez-Hernandez A, Garcia-Arellano A, Shivappa N, et al. Dietary inflammatory index and incidence of cardiovascular disease in the SUN cohort. *PLoS ONE.* (2015) 10:e135221. doi: 10.1371/journal.pone.0135221
6. Shivappa N, Hebert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. *Br J Nutr.* (2015) 113:665–71. doi: 10.1017/S000711451400395X
7. Neufcourt L, Assmann KE, Fezeu LK, Touvier M, Graffouillere L, Shivappa N, et al. Prospective association between the dietary inflammatory index and metabolic syndrome: findings from the SU.VI.MAX study. *Nutr Metab Cardiovasc Dis.* (2015) 25:988–96. doi: 10.1016/j.numecd.2015.09.002
8. Mazidi M, Shivappa N, Wirth MD, Hebert JR, Mikhailidis DP, Kengne AP, et al. Dietary inflammatory index and cardiometabolic risk in US adults. *Atherosclerosis.* (2018) 276:23–7. doi: 10.1016/j.atherosclerosis.2018.02.020
9. Shivappa N, Godos J, Hébert JR, Wirth MD, Piuri G, Speciani AF, et al. Dietary inflammatory index and cardiovascular risk and mortality-a meta-analysis. *Nutrients.* (2018) 10:nu10020200. doi: 10.3390/nu10020200
10. Canto-Osorio F, Denova-Gutierrez E, Sanchez-Romero LM, Salmeron J, Barrientos-Gutierrez T. Dietary Inflammatory Index and metabolic syndrome in Mexican adult population. *Am J Clin Nutr.* (2020) 112:373–80. doi: 10.1093/ajcn/nqaa135
11. Namazi N, Larijani B, Azadbakht L. Association between the dietary inflammatory index and the incidence of cancer: a systematic review and meta-analysis of prospective studies. *Public Health.* (2018) 164:148–56. doi: 10.1016/j.puhe.2018.04.015
12. Phillips CM, Chen LW, Heude B, Bernard JY, Harvey NC, Duijts L, et al. Dietary inflammatory index and non-communicable disease risk: a narrative review. *Nutrients.* (2019) 11:81873. doi: 10.3390/nu1108 1873
13. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc.* (2015) 13:132–40. doi: 10.1097/XEB.0000000000000055
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* (1986) 7:177–88. doi: 10.1016/0197-2456(86)90046-2
15. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med.* (1997) 127:820–6. doi: 10.7326/0003-4819-127-9-199711010-00008
16. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc.* (2009) 172:137–59. doi: 10.1111/j.1467-985X.2008.00552.x
17. Higgins JP. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol.* (2008) 37:1158–60. doi: 10.1093/ije/dyn204
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* (2002) 21:1539–58. doi: 10.1002/sim.1186

19. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ.* (2011) 343:d4002. doi: 10.1136/bmj.d4002
20. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials.* (2007) 4:245–53. doi: 10.1177/1740774507079441
21. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* (2007) 7:10. doi: 10.1186/1471-2288-7-10
22. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. *Parkinsonism Relat Disord.* (2016) 23:1–9. doi: 10.1016/j.parkreldis.2015.12.008
23. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol.* (2015) 14:263–73. doi: 10.1016/S1474-4422(14)70267-4
24. Zahedi H, Djalalinia S, Asayesh H, Mansourian M, Esmaeili AZ, Mahdavi GA, et al. A higher dietary inflammatory index score is associated with a higher risk of incidence and mortality of cancer: a comprehensive systematic review and meta-analysis. *Int J Prev Med.* (2020) 11:15. doi: 10.4103/ijpvm.IJPVM_332_18
25. Zhang C, Wang W, Zhang D. Association between dietary inflammation index and the risk of colorectal cancer: a meta-analysis. *Nutr Cancer.* (2018) 70:14–22. doi: 10.1080/01635581.2017.1374418
26. Moradi S, Issah A, Mohammadi H, Mirzaei K. Associations between dietary inflammatory index and incidence of breast and prostate cancer: a systematic review and meta-analysis. *Nutrition.* (2018) 55–6:168–78. doi: 10.1016/j.nut.2018.04.018
27. Ji M, Hong X, Chen M, Chen T, Wang J, Zhang N. Dietary inflammatory index and cardiovascular risk and mortality: a meta-analysis of cohort studies. *Medicine.* (2020) 99:e20303. doi: 10.1097/MD.0000000000020303
28. Wang J, Zhou Y, Chen K, Jing Y, He J, Sun H, et al. Dietary inflammatory index and depression: a meta-analysis. *Public Health Nutr.* (2018) 2018:1–7. doi: 10.1017/S1368980018002628
29. Namazi N, Larijani B, Azadbakht L. Dietary inflammatory index and its association with the risk of cardiovascular diseases, metabolic syndrome, and mortality: a systematic review and meta-analysis. *Horm Metab Res.* (2018) 50:345–58. doi: 10.1055/a-0596-8204
30. Liu ZY, Gao XP, Zhu S, Liu YH, Wang LJ, Jing CX, et al. Dietary inflammatory index and risk of gynecological cancers: a systematic review and meta-analysis of observational studies. *J Gynecol Oncol.* (2019) 30:e23. doi: 10.3802/jgo.2019.30.e23
31. Jayedi A, Emadi A, Shab-Bidar S. Dietary inflammatory index and site-specific cancer risk: a systematic review and dose-response meta-analysis. *Adv Nutr.* (2018) 9:388–403. doi: 10.1093/advances/nmy015
32. Zhu Y, Li Q, Xu X. Dietary inflammatory index and the risk of prostate cancer: a dose-response meta-analysis. *Eur J Clin Nutr.* (2020) 74:1001–8. doi: 10.1038/s41430-019-0500-3
33. Farhangi MA, Nikniaz L, Nikniaz Z, Dehghan P. Dietary inflammatory index potentially increases blood pressure and markers of glucose homeostasis among adults: findings from an updated systematic review and meta-analysis. *Public Health Nutr.* (2020) 23:1362–80. doi: 10.1017/S1368980019003070
34. Li D, Hao X, Li J, Wu Z, Chen S, Lin J, et al. Dose-response relation between dietary inflammatory index and human cancer risk: evidence from 44 epidemiologic studies involving 1,082,092 participants. *Am J Clin Nutr.* (2018) 107:371–88. doi: 10.1093/ajcn/nqx064
35. Hua R, Liang G, Yang F. Meta-analysis of the association between dietary inflammatory index (DII) and upper aerodigestive tract cancer risk. *Medicine.* (2020) 99:e19879. doi: 10.1097/MD.0000000000019879
36. Liang Y, Jiao H, Qu L, Liu H. Positive association between dietary inflammatory index and gastric cancer risk: a systematic review and meta-analysis. *Nutr Cancer.* (2019) 2019:1–7. doi: 10.1080/01635581.2019.1679197
37. Moazzen S, van der Sloot K, Bock GH, Alizadeh BZ. Systematic review and meta-analysis of diet quality and colorectal cancer risk: is the evidence of sufficient quality to develop recommendations? *Crit Rev Food Sci Nutr.* (2020) 2020:1–10. doi: 10.1080/10408398.2020.1786353
38. Farhangi MA, Vajdi M. The association between dietary inflammatory index and risk of central obesity in adults: an updated systematic review and meta-analysis. *Int J Vitam Nutr Res.* (2020) 90:535–52. doi: 10.1024/0300-9831/a000648
39. Obon-Santacana M, Romaguera D, Gracia-Lavedan E, Molinuevo A, Molina-Montes E, Shivappa N, et al. Dietary inflammatory index, dietary non-enzymatic antioxidant capacity, and colorectal and breast cancer risk (MCC-Spain Study). *Nutrients.* (2019) 11:61406. doi: 10.3390/nu11061406
40. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. *BMC Med.* (2016) 14:147. doi: 10.1186/s12916-016-0692-5
41. Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ.* (2017) 356:j477. doi: 10.1136/bmj.j477
42. Bruce WR, Giacca A, Medline A. Possible mechanisms relating diet and risk of colon cancer. *Cancer Epidemiol Biomarkers Prev.* (2000) 9:1271–9.
43. Bruce WR, Wolever TM, Giacca A. Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance. *Nutr Cancer.* (2000) 37:19–26. doi: 10.1207/S15327914NC3701_2
44. Fabiani R, Minelli L, Bertarelli G, Bacci S. A western dietary pattern increases prostate cancer risk: a systematic review and meta-analysis. *Nutrients.* (2016) 8:70. doi: 10.20944/preprints201608.0070.v1
45. Reynolds JV, Donohoe CL, Doyle SL. Diet, obesity and cancer. *Ir J Med Sci.* (2011) 180:521–7. doi: 10.1007/s11845-010-0653-5
46. Deng T, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA. Obesity, inflammation, and cancer. *Annu Rev Pathol.* (2016) 11:421–49. doi: 10.1146/annurev-pathol-012615-044359
47. Sapienza C, Issa JP. Diet, nutrition, and cancer epigenetics. *Annu Rev Nutr.* (2016) 36:665–81. doi: 10.1146/annurev-nutr-121415-112634
48. Shankar E, Kanwal R, Candamo M, Gupta S. Dietary phytochemicals as epigenetic modifiers in cancer: promise and challenges. *Semin Cancer Biol.* (2016) 40–41:82–99. doi: 10.1016/j.semcancer.2016.04.002
49. Zhong X, Guo L, Zhang L, Li Y, He R, Cheng G. Inflammatory potential of diet and risk of cardiovascular disease or mortality: a meta-analysis. *Sci Rep.* (2017) 7:6367. doi: 10.1038/s41598-017-06455-x
50. Esmaillzadeh A, Kimiagar M, Mehrabi Y, Azadbakht L, Hu FB, Willett WC. Dietary patterns and markers of systemic inflammation among Iranian women. *J Nutr.* (2007) 137:992–8. doi: 10.1093/jn/137.4.992
51. Festa A, D'Agostino RJ, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation.* (2000) 102:42–7. doi: 10.1161/01.CIR.102.1.42
52. Djiogue S, Nwabo KA, Vecchio L, Kipanyula MJ, Farahna M, Aldebasi Y, et al. Insulin resistance and cancer: the role of insulin and IGFs. *Endocr Relat Cancer.* (2013) 20:R1–17. doi: 10.1530/ERC-12-0324
53. Pihlajamaki J, Gylling H, Miettinen TA, Laakso M. Insulin resistance is associated with increased cholesterol synthesis and decreased cholesterol absorption in normoglycemic men. *J Lipid Res.* (2004) 45:507–12. doi: 10.1194/jlr.M300368-JLR200
54. Li Y, Zhong X, Cheng G, Zhao C, Zhang L, Hong Y, et al. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: a meta-analysis. *Atherosclerosis.* (2017) 259:75–82. doi: 10.1016/j.atherosclerosis.2017.02.003
55. Kheirouri S, Alizadeh M. Dietary inflammatory potential and the risk of incident depression in adults: a systematic review. *Adv Nutr.* (2019) 10:9–18. doi: 10.1093/advances/nmy100
56. Hegarty BD, Parker GB. Marine omega-3 fatty acids and mood disorders–linking the sea and the soul. "Food for Thought" I. *Acta Psychiatr Scand.* (2011) 124:42–51. doi: 10.1111/j.1600-0447.2011.01703.x

57. Parker G, Gibson NA, Brotchie H, Heruc G, Rees AM, Hadzi-Pavlovic D. Omega-3 fatty acids and mood disorders. *Am J Psychiatry*. (2006) 163:969–78. doi: 10.1176/ajp.2006.163.6.969
58. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. (2008) 358:55–68. doi: 10.1056/NEJMra073096
59. Lopresti AL, Hood SD, Drummond PD. A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. *J Affect Disord*. (2013) 148:12–27. doi: 10.1016/j.jad.2013.01.014
60. Langan D, Higgins J, Jackson D, Bowden J, Veroniki AA, Kontopantelis E, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods*. (2019) 10:83–98. doi: 10.1002/jrsm.1316

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Predicting Obesity in Adults Using Machine Learning Techniques: An Analysis of Indonesian Basic Health Research 2018

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Obesity is strongly associated with multiple risk factors. It is significantly contributing to an increased risk of chronic disease morbidity and mortality worldwide. There are various challenges to better understand the association between risk factors and the occurrence of obesity. The traditional regression approach limits analysis to a small number of predictors and imposes assumptions of independence and linearity. Machine Learning (ML) methods are an alternative that provide information with a unique approach to the application stage of data analysis on obesity. This study aims to assess the ability of ML methods, namely Logistic Regression, Classification and Regression Trees (CART), and Naïve Bayes to identify the presence of obesity using publicly available health data, using a novel approach with sophisticated ML methods to predict obesity as an attempt to go beyond traditional prediction models, and to compare the performance of three different methods. Meanwhile, the main objective of this study is to establish a set of risk factors for obesity in adults among the available study variables. Furthermore, we address data imbalance using Synthetic Minority Oversampling Technique (SMOTE) to predict obesity status based on risk factors available in the dataset. This study indicates that the Logistic Regression method shows the highest performance. Nevertheless, kappa coefficients show only moderate concordance between predicted and measured obesity. Location, marital status, age groups, education, sweet drinks, fatty/oily foods, grilled foods, preserved foods, seasoning powders, soft/carbonated drinks, alcoholic drinks, mental emotional disorders, diagnosed hypertension, physical activity, smoking, and fruit and vegetables consumptions are significant in predicting obesity status in adults. Identifying these risk factors could inform health authorities in designing or modifying existing policies for better controlling chronic diseases especially in relation to risk factors associated with obesity. Moreover, applying ML methods on publicly available health data, such as Indonesian Basic Health Research (RISKESDAS) is a promising strategy to fill the gap for a more robust understanding of the associations of multiple risk factors in predicting health outcomes.

Keywords: classification, Logistic Regression, machine learning, Naive Bayes, obesity status

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INTRODUCTION

Obesity is a major health problem strongly associated with many chronic illnesses with negative effects and long-term consequences, not only for the patients but also their families. In Southeast Asia, problems related to nutrition or malnutrition are a double burden because the number of cases of malnutrition and malnourishment is still relatively high and the number of cases of obesity has also increased significantly over time (1).

Data from the 2013 national-level survey of Indonesian Basic Health Research (RISKESDAS) showed the prevalence of obesity in Indonesia has increased over the years. Obesity among adult men was 13.9% in 2007, 7.8% in 2010, and 19.7% in 2013, whereas for adult women the prevalence was 14.8% in 2007, 15.5% in 2010, and increased drastically to 32.9% in 2013 (2). By 2018, the same survey (RISKESDAS 2018) showed that the prevalence of obesity in men and women had decreased slightly to 14.5 and 29.3%, respectively (3).

Risk factors for obesity have been studied extensively, and in general, they are divided into several categories: demographic and socio-economic factors (gender, age, education, income, marital status, and urban areas) (4–6); lifestyle factors (consumption of fast food, stress, smoking, alcoholic drinks, and low level of physical activity) (6, 7); and genetic factors (obese parents) (4, 5). Among these risk factors, some can be changed or modified, while others cannot. Identifying modifiable risk factors for obesity at the individual and the population level is urgently required in order to implement an effective risk reduction strategy. Numerous studies have explored better approaches to predicting obesity using available data. A novel method recently introduced to answer this question uses Machine Learning (ML), which is currently one of the most popular topics in the scientific community for large-scale datasets.

Epidemiological data modeling using ML approaches is becoming increasingly popular in the published scientific literature. These methods have the potential to improve our understanding of general health regarding disease distribution, detection, and the identification of risk factors for health problems, and thus, opportunities for intervention. Various ML methods and algorithms have been applied to various aspects of health data including obesity (8). In the case of obesity, it is essential to develop a precise data classification to facilitate the process of finding predictive risk factors from the given data, in efforts to control these risk factors and eventually to decrease morbidity and mortality linked to obesity.

For the purpose of obesity prevention, ML has been used to predict the probability of obesity based on data encoding adherence to dietary recommendations and several other factors (9). The ML has also been applied for the prediction of obesity in children using electronic health records before the age of 2 (10); prediction of obesogenic environments for children (11); and for the aggregation of metabolomics, lipidomics, and other clinical data to modeling drug dose responses (12).

Based on previous research, ML approaches can increase the risk prediction of health outcomes compared to conventional approaches (13). Prediction of obesity using ML has been investigated by many researchers: Zhang et al. (14), Adnan et al. (15), Toschke et al. (16), Golino et al. (17), Dugan et al. (10), Zheng and Ruggiero (18), Chatterjee et al. (19), Singh and Tawfik (20), and Colmenarejo (21). The ML approach provides an alternative in providing information with a unique approach at the application stage of data analysis on obesity which is important in providing a better predictive solution to the likelihood of obesity (22).

MATERIALS AND METHODS

Data Source

The dataset used to develop the classification model in this study is publicly available data from an Indonesia national scale survey with a cross-sectional and non-intervention design, the RISKESDAS survey, which was conducted by the Indonesian Ministry of Health. The RISKESDAS report is a community-based health survey whose indicators can be generalized with variables described from the national level down to the district/city level. It is conducted every 5 years across 34 provinces and 514 districts/cities in order to track important indicators of public health status, diseases risk factors, and to evaluate healthcare services delivery programs. The methodology and detailed protocols of the survey are described elsewhere (3). Briefly, the target sample for this study is 300,000 households from 30,000 Census Block (CBs) in 34 provinces and 514 district-cities throughout Indonesia. The sampling frame lists are provided by the Central Bureau of Statistics (BPS) using a two-stage sampling method. In the first stage, 180,000 CBs (25%) were selected from 720,000 CBs from the national socio-economic survey (SUSENAS) as a sampling frame using a proportionate to population size (PPS) method and stratified by prosperity level, continued by systematically selecting 30,000 CBs from 180,000 CBs priorly selected and stratified by urban and rural for each district or city. In the second stage, 10 households were selected systematically using implicit stratification for the education level of the head of household to maintain variation of education among households. Household members who were eligible according to the inclusion criteria were invited to participate in the interview.

The dataset can be accessed by request at the Institute of Health Research and Development of the Indonesian Ministry of Health (https://www.litbang.kemkes.go.id/layanan-permintaan-data-riset/).

Pre-processing Data

Data Cleaning or Filtering

The sample used in this study included all the data from the RISKESDAS dataset for individuals aged 18 or above; in total there was data for 634,709 respondents. We conducted data cleaning by excluding all records with incomplete or missing values for the variable/feature Body Mass Index (BMI), a core feature used to categorize obesity status. The number of samples included for the analysis process after cleaning was 618,898 records. Data cleaning was performed by using the *dplyr* package of R version 3.5.1 to perform filtering (23).

Feature Selection

After removing missing values, we proceeded to variable or feature selection. Variable selection is a process of reducing the data dimensions to reduce processing time as well as computation costs (24). We selected a subset of variables that contributed significantly to the target class to improve the overall predictive performance of the classification using the Chi-Square (χ^2) test between obesity status with each of the variables and including those with a p-value < 0.05. All features that met these criteria (a total of 21 features) were selected for developing the classification model. These variables or features were location (X1), marital status (X2), age group (X3), education (X4), work category (X5), sugary foods (X6), sweet drinks (X7), salty foods (X8), fatty/oily foods (X9), grilled foods (X10), preserved foods (X11), seasoning powders (X12), soft/carbonated drinks (X13), energy drinks (X14), instant foods (X15), alcoholic drinks (X16), mental-emotional disorders (X17), diagnosed hypertension (X18), physical activity (X19), smoking (X20), and fruit and vegetables consumptions (X21). A list of these features and how it was generated from the questionnaire (for composited and calculated feature, i.e., obesity, fruit and vegetables consumption, physical activity, and mental-emotional disorders) can be found in the **Supplementary Table 1**. The process of developing a classification model was carried out by using the R Statistical Software version 3.5.1 (25).

Dealing With Imbalanced Datasets

Data imbalance occurs when there are one or more classes that dominate the whole data as major classes, and other classes are rare occurrences or minor classes. Imbalanced data will produce a good classification prediction accuracy against the major class, but in the minor class, the resulting accuracy is poor.

The Synthetic Minority Oversampling Technique (SMOTE) was introduced by Chawla et al. (26) and Chawla (27), as a way of dealing with the effect of the lack of information on minority classes in a data set. SMOTE is an algorithm with an oversampling approach, which generates artificial data for minority data classes (28) so that the proportions of major and minor data classes are more balanced (29). Artificial data or synthetic data are made based on the k-nearest neighbor. All attributes used in this study were categorical features so that the calculation of the distance between the minor class samples was carried out using the Modify Value Difference Metric (MVDM) method (30). In this method, several steps are taken, namely calculating the distance between two observations at a nominal scale and choosing the majority category between the minority class observations with its k-closest neighbors for a nominal value, and if the same value occurs, it is chosen randomly. Furthermore, the selected value is a new observation. In this study, the SMOTE technique with oversampling of 200% and 300% was used which resulted in two new datasets.

Machine Learning Classification Methods

Logistic Regression

One of the basic linear models developed with a probabilistic approach to classification problems is Logistic Regression (31) and is one of the supervised learning models widely used in ML. Logistic Regression can be seen as a development of Linear Regression models with a logistic function for data with a target in the form of classes (32) as follows:

$$y(x) = \sigma\left(\beta_0 + \beta^T x\right),$$

where $x = (x_1, x_2, \ldots, x_D)^T$ is the D-dimensional data, $\beta = (\beta_1, \beta_2, \ldots, \beta_D)^T$ are the weight parameters, β_0 is the bias parameter, and σ is a logistic function that is shaped as $\sigma(a) = \frac{1}{1+e^{-a}}$.

The weights of β can be obtained by using probabilistic concepts. For example, if $y_n = y(x_n)$ and $t_n \in \{0, 1\}$ are an independent identical distribution. The joint probabilistic or likelihood function for all the data can be expressed by the Bernoulli distribution $p(t|\beta)$,where $t = (t_1, t_2, \ldots, t_N)^T$. Therefore, the Logistic Regression learning and bias (β) is to maximize $p(t \vee \beta)$. The learning method for determining the weight and bias (β) parameters is known as the maximum likelihood method. Generally, the solution to the maximum likelihood problem is done by minimizing the negative of the logarithm of the likelihood function, namely $\min_\beta E(\beta)$, where $E(\beta) = -\ln\left(p(t \vee \beta)\right)$. Logistic Regression models can use regularization techniques to solve the problem of overfitting by adding the weight norm ||w|| in the error function, namely $E(\beta) = \frac{1}{2}\|\beta\|^2 + C\sum_{n=1}^{N}\left\{t_n \ln\left(y_n\right) + (1-t_n)\ln\left(1-y_n\right)\right\}$, where $C > 0$ is the inverse parameter of the regulation.

Simultaneous and partial parameter testing is performed to examine the role of predictor variables in the model. Simultaneous parameter testing uses the G test.

Classification and Regression Trees

Breiman et al. (33) proposes a new algorithm for tree arrangement, namely Classification and Regression Tree (CART). CART is a non-parametric statistical method used for classification analysis, both for categorical and continuous response variables, and for explanatory variables which may consist of nominal, ordinal, or continuous features. The resulting tree model depends on the scale of the response attribute. CART generates a classification tree if the response variables are categorical, and generates a regression tree if the response variables are continuous (33).

The tree structure in the CART method is obtained through a binary recursive partitioning algorithm against its explanatory variables (31, 32). The binding is carried out by dividing the data set into two subclusters called nodes. The impurity value at node t is a measurement of the heterogeneity level of a class from a particular node in the classification tree. The process of forming a classification tree is carried out in three stages; selecting a classifier, determining the final node, and marking the class label (31). In selecting the classifier, each partitioning depends on the value that comes from only one explanatory variable. For categorical variables, the partitioning that occurs comes from all the possible partitioning based on the formation of two subgroups that are mutually exclusive (disjoint). In addition, in solving classification tree problems, the Gini Splitting Rule (also known as the Gini Index) is the most common rule to be used (32). Then, the partitioning evaluation is performed using the goodness of split $\varphi(s, t)$ of the s partition at t node. The partitioning function is defined as decreased heterogeneity. A sort that produces a higher value is a better sort because it reduces the impurity value more significantly. If the resulting node is of a non-homogeneous class, the same procedure will be repeated until the tree $\varphi(s, t)\, \varphi(s^{*}, t) = \max_{s \in S} \varphi(s, t)$. Determination of child nodes is carried out recursively by using the same method as determining the main node.

After selecting the classifier, the end node is determined. The minimum number of cases in a node is generally five. If this is fulfilled, tree development will be stopped and continued with the marking of class labels. Class label marking at the end node is carried out based on the highest number rule. The process of forming classification trees stops when there is only one observation in each child node. One of the ways to get the optimal tree is by consecutively pruning the tree that is less important. In random pruning, the observations are divided into two parts, namely training data L_1 and test data L_2. Through the pruning process, a row of trees is formed from L_1. Next, L_2 is used to form the total proportion of misclassification $(R|ts(G))$. The optimal tree that meets the criteria as $R^{ts}\left(G^{0}\right) = \min\ R^{ts}(G_t)$.

Naïve Bayesian

Naïve Bayesian classification is a statistical approach which attempts to predict the probability of each class (14). The advantage of this Bayes grouping is that it has a high level of accuracy and speed when using large data sets. Naïve Bayesian grouping assumes that the values of the variables on the class labels are independent of other attribute values, which can facilitate the calculation (10, 34).

Naïve Bayesian Classification is achieved by applying the Bayes rule to calculate the probability of each attribute and predicting the class based on the highest prior probability (34).

Model Validation

The validation process in this study used *k*-fold cross-validation (35). Cross-Validation (CV) divides the dataset into two parts: one part is used as the training data and the other is used as testing data. In this study, the data were divided into 10 parts, 90% of which was used as training and the rest was used for testing. This process was done repeatedly, a maximum of 10 times, until all data records were part of the testing data. This process is also known as the 10-fold CV. The 10-fold CV process has been used in several previous health care- and medical-related studies (36).

Evaluation of Classification Performance

Measuring accuracy is a diagnostic step to test the level of performance of an algorithm against the dataset used. A matrix, known as the confusion matrix, is used to evaluate the learning algorithm (37). Each column in the matrix shows the number of observations in the predicted class. The rows in the matrix represent the actual number of observations in the class.

In ML, the term metric refers to a value that can be used to represent the performance of the resulting model. In classification modeling, the model output is a label/class. There are several metrics that are commonly used, namely accuracy,

TABLE 1 | General description of obesity data from Indonesian RISKESDAS 2018.

Variables	Categories	Frequency	Percentage
Obesity status (Y)	Non-obese	484,189	78.23
	Obese	134,709	21.77
Location (X1)	Urban	267,913	43.29
	Rural	350,985	56.71
Marital status (X2)	Not married	84,792	13.70
	Married	472,269	76.31
	Divorced	14,333	2.32
	Widowed	47,504	7.68
Age groups (X3)	18–24 years	69,532	11.23
	25–29 years	60,380	9.76
	30–34 years	68,683	11.10
	35–39 years	77,538	12.53
	40–44 years	73,775	11.92
	45–49 years	70,503	11.39
	50–54 years	58,618	9.47
	55–59 years	49,632	8.02
	60–64 years	35,471	5.73
	>64 years	54,766	8.85
Education (X4)	Not/Never schooled	40,861	6.60
	Not finished basic school	84,637	13.68
	Finished basic school	157,391	25.43
	Finished Junior High School	104,435	16.87
	Finished Senior High School	170,246	27.51
	Finished Academy/College	20,005	3.23
	Finished higher education	41,323	6.68
Work types (X5)	Not working	171,984	27.79
	School	12,238	1.98
	Government employee	27,703	4.48
	Private employee	50,049	8.09
	Entrepreneur	91,011	14.71
	Farmer	163,009	26.34
	Fisherman	8,344	1.35
	Daily waged labors	52,379	8.46
	Others	42,181	6.82
Sugary foods (X6)	>1 time per day	82,775	13.37
	1 time per day	125,754	20.32
	3–6 times per week	138,685	22.41
	1–2 times per week	177,173	28.63
	<3 times per month	62,972	10.17
	Never	31,539	5.10
Sweet drinks (X7)	>1 time per day	176,096	28.45
	1 time per day	195,361	31.57
	3–6 times per week	87,827	14.19
	1–2 times per week	95,409	15.42
	<3 times per month	33,666	5.44
	Never	30,539	4.93
Salty foods (X8)	>1 time per day	64,660	10.45

(Continued)

TABLE 1 | Continued

Variables	Categories	Frequency	Percentage
	1 time per day	78,744	12.72
	3–6 times per week	105,363	17.02
	1–2 times per week	170,442	27.54
	<3 times per month	107,318	17.34
	Never	92,371	14.93
Fatty/Oily foods (X9)	>1 time per day	103,634	16.74
	1 time per day	113,057	18.27
	3–6 times per week	133,552	21.58
	1–2 times per week	164,703	26.61
	<3 times per month	72,739	11.75
	Never	31,213	5.04
Grilled foods (X10)	>1 time per day	12,948	2.09
	1 time per day	22,189	3.59
	3–6 times per week	63,967	10.34
	1–2 times per week	161,356	26.07
	<3 times per month	202,251	32.68
	Never	156,187	25.24
Preserved foods (X11)	>1 time per day	6,310	1.02
	1 time per day	12,024	1.94
	3–6 times per week	31,993	5.17
	1–2 times per week	72,618	11.73
	<3 times per month	145,068	23.44
	Never	350,885	56.70
Seasonings powders (X12)	>1 time per day	227,357	36.74
	1 time per day	226,628	36.62
	3–6 times per week	42,598	6.88
	1–2 times per week	34,030	5.50
	<3 times per month	20,887	3.37
	Never	67,398	10.89
Soft/Carbonated drinks (X13)	>1 time per day	3,689	0.60
	1 time per day	7,857	1.27
	3–6 times per week	16,470	2.66
	1–2 times per week	43,686	7.06
	<3 times per month	100,398	16.22
	Never	446,798	72.19
Energy drinks (X14)	>1 time per day	3,654	0.59
	1 time per day	7,761	1.25
	3–6 times per week	12,888	2.08
	1–2 times per week	31,045	5.02
	<3 times per month	58,659	9.48
	Never	504,891	81.58
Instant foods (X15)	>1 time per day	12,144	1.96
	1 time per day	28,943	4.68
	3–6 times per week	108,287	17.50
	1–2 times per week	220,125	35.57
	<3 times per month	149,066	24.09
	Never	100,333	16.21
Alcoholic drinks (X16)	Yes	30,240	4.89
	No	588,658	95.11
Mental-emotional disorders (X17)	Yes	61,092	9.87
	No	557,806	90.13
Diagnosed hypertension (X18)	Yes	55,640	8.99
	No	315,467	50.97
	Unknown	247,791	40.04
Physical activity (X19)	Adequate	73,736	11.91
	Not adequate	545,162	88.09
Smoking (X20)	Yes	233,306	37.70
	No	385,592	62.30
Fruit and vegetables consumptions (X21)	Adequate	29,321	4.74
	Not adequate	589,577	95.26

(Continued)

precision, sensitivity, specificity, recall, F1-score, kappa, and F_β. In terms of the confusion matrix, accuracy is the ratio of the number of diagonal elements to the total number of matrix elements. The accuracy of the method is only considered adequate when the comparison of the actual number of data labels is nearly identical with the confusion matrix. If the comparison is imbalanced, then other metrics can be used. Precision is an appropriate metric when false positives are to be avoided. Sensitivity can be interpreted as the degree of reliability of the model to detect data labeled positive correctly. Sensitivity is an appropriate metric when false negatives are to be avoided (high risk). Specificity is the degree of model reliability for detecting data labeled negative correctly. This metric is closely related to sensitivity. This metric is appropriate when the true negative rate is to be maximized. To minimize both (false positive and false negative) outcomes at the same time, precision and sensitivity need to be summarized by using the F1-score. Recall is a valid choice of evaluation metric when we want to capture as many positives (obese) as possible. In this study, we want to be sure that the sample we catch is obese (precision) and we also want to capture as many obese (recall) as possible. The F1-score manages this trade-off. However, the main problem with the F1-score is that it gives equal weight to precision and recall. Sometimes we may need to include domain knowledge in our evaluations where we want more recall or more precision. To solve this, we can create a weighted F1 metric, where beta (β) sets the balance between precision and recall. This is called F_β. In this study, we used $\beta = 0.5$ to measure more weight on precision and less weight on recall.

Kappa is used to test the inter reliability. Kappa values range from 0 to 1.0 which can be divided into several classifications, namely 0–0.20 (slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.0 (perfect) (38).

The Area Under ROC Curve, also known as AUC, has a range between 0.5 (50%) and 1 (100%). The interpretation of AUC

TABLE 2 | Comparison of classification accuracy with 10-fold CV based on the obesity test data using three models with confusion matrix.

ML methods	Classification prediction	Fold 1 Test		Fold 2 Test		Fold 3 Test		Fold 4 Test		Fold 5 Test	
		Real circumstances									
		Non-obese	Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese
CART	Non-obese	360,554	193,472	360,260	193,579	360,791	193,595	360,325	193,504	360,459	193,685
	Obese	75,298	291,411	75,283	291,744	75,227	291,362	75,294	291,335	75,401	291,611
Naïve-Bayes	Non-obese	314,384	141,264	313,957	141,209	314,357	141,167	314,080	141,106	314,273	141,413
	Obese	121,468	343,619	121,586	344,114	121,661	343,790	121,539	343,733	121,587	343,883
Logistic Regression	Non-obese	320,456	140,260	319,952	140,279	320,628	140,336	320,202	140,144	320,285	140,474
	Obese	115,396	344,623	115,591	345,044	115,390	344,621	115,417	344,695	115,575	344,822

ML methods	Classification prediction	Fold 6 Test		Fold 7 Test		Fold 8 Test		Fold 9 Test		Fold 10 Test	
		Real circumstances									
		Non-obese	Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese
CART	Non-obese	360,531	193,271	360,426	193,360	360,177	193,275	360,566	193,586	360,411	193,430
	Obese	75,312	291,645	75,410	291,447	75,351	291,331	75,308	291,504	75,317	291,377
Naïve-Bayes	Non-obese	314,356	141,221	314,273	141,183	314,030	141,113	314,239	141,296	314,234	141,345
	Obese	121,487	343,695	121,563	343,624	121,498	343,493	121,635	343,794	121,494	343,462
Logistic Regression	Non-obese	320,479	140,281	320,423	140,220	320,206	140,253	320,464	140,277	320,355	140,328
	Obese	115,364	344,635	115,413	344,587	115,322	344,353	115,410	344,813	115,373	344,479

TABLE 3 | Evaluation of classification prediction performance with 10-fold CV based on the obesity test data using 3 ML methods.

ML methods	Test	Accuracy (%)	Sensitivity (%)	Specificity (%)	Precision (%)	F1-Score (%)	Kappa (%)	AUC (%)	$F_{\beta=0.5}$ (%)
CART	1-Fold	70.81	**82.72**	60.10	65.08	**72.85**	42.24	74.57	67.98
	2-Fold	70.80	**82.72**	60.11	65.05	**72.83**	42.24	74.56	67.95
	3-Fold	70.81	**82.75**	60.08	65.08	**72.86**	42.25	74.56	67.98
	4-Fold	70.80	**82.72**	60.09	65.06	**72.83**	42.22	74.55	67.96
	5-Fold	70.79	**82.70**	60.09	65.05	**72.82**	42.21	74.54	67.95
	6-Fold	70.83	**82.72**	60.14	65.10	**72.86**	42.28	74.55	68.00
	7-Fold	70.81	**82.70**	60.12	65.08	**72.84**	42.24	74.55	67.98
	8-Fold	70.81	**82.70**	60.12	65.08	**72.84**	42.24	74.56	67.97
	9-Fold	70.80	**82.72**	60.09	65.07	**72.84**	42.23	74.56	67.97
	10-Fold	70.81	**82.71**	60.10	65.07	**72.84**	42.24	74.54	67.97
Naïve-Bayes	1-Fold	71.46	72.13	70.87	69.00	70.53	42.90	78.47	69.60
	2-Fold	71.46	72.08	70.90	68.98	70.50	42.89	78.47	69.58
	3-Fold	71.46	72.10	70.89	69.01	70.52	42.89	78.47	69.61
	4-Fold	71.47	72.10	70.90	69.00	70.52	42.90	78.47	69.60
	5-Fold	71.45	72.10	70.86	68.97	70.50	42.87	78.45	69.57
	6-Fold	71.47	72.13	70.88	69.00	70.53	42.90	78.48	69.60
	7-Fold	71.46	72.11	70.88	69.00	70.52	42.89	78.46	69.60
	8-Fold	71.46	72.10	70.88	69.00	70.52	42.89	78.45	69.60
	9-Fold	71.45	72.09	70.87	68.98	70.50	42.87	78.48	69.58
	10-Fold	71.45	72.12	70.85	68.97	70.51	42.86	78.47	69.58
Logistic Regression	1-Fold	**72.23**	73.52	**71.07**	**69.56**	71.49	**44.47**	**79.80**	**70.32**
	2-Fold	**72.21**	73.46	**71.10**	**69.52**	71.44	**44.43**	**79.79**	**70.27**
	3-Fold	**72.23**	73.54	**71.06**	**69.56**	71.49	**44.47**	**79.80**	**70.32**
	4-Fold	**72.24**	73.51	**71.09**	**69.56**	71.48	**44.47**	**79.80**	**70.31**
	5-Fold	**72.20**	73.48	**71.05**	**69.51**	71.44	**44.41**	**79.77**	**70.27**
	6-Fold	**72.24**	73.53	**71.07**	**69.55**	71.49	**44.47**	**79.80**	**70.31**
	7-Fold	**72.23**	73.52	**71.08**	**69.56**	71.48	**44.47**	**79.78**	**70.32**
	8-Fold	**72.22**	73.52	**71.06**	**69.54**	71.48	**44.45**	**79.78**	**70.30**
	9-Fold	**72.24**	73.52	**71.08**	**69.55**	71.48	**44.48**	**79.81**	**70.31**
	10-Fold	**72.22**	73.52	**71.05**	**69.54**	71.48	**44.45**	**79.79**	**70.30**

Bold values shows in which aspect does the ML methods performed best.

values can be classified into five different sections, namely 0.5–0.6 (false accuracy), 0.6–0.7 (poor accuracy), 0.7–0.8 (moderate accuracy), 0.8–0.9 (high accuracy), and 0.9–1 (very high level of accuracy) (39).

RESULTS

An overview of the explanatory variables contained in the obesity data of the Indonesia RISKESDAS 2018 survey is given in **Table 1**. As can be seen from **Table 1**, out of 618,898 respondents, there are 134,709 (21.77%) people who are classified as obese, 484,189 (78.23%) people are non-obese. In **Table 1**, it can also be seen that the number of obese (21.77%) and non-obese classes (78.23%) seems imbalanced. Based on **Table 1**, the respondents in this study lived in rural areas (56.71%), married (76.31%), aged 35–39 years (12.53%), finished senior high school (25.43%), unemployed (27.79%), consumed sugary foods 1–2 times per week (28.63%), drank sweet drinks one time per day (31.57%), consumed salty foods 1–2 times per week (27.54%), consumed fatty/oily foods 1–2 times per week (26.61%), consumed grilled foods more than 3 times per month (32.68%), never consumed preserved foods (56.70%), consumed seasoning powders less that one time per day (36.74%), never drank soft/carbonated drinks (72.19%), never drank energy drinks (81.58%), experienced no mental emotional disorders (90.13%), consumed instant foods 1–2 times per week (35.57%), drank non-alcoholic drinks (95.11%), diagnosed with no hypertension (50.97%), not adequate physical activity (88.09%), not a smoker (62.30%), and consumed inadequate fruit and vegetables (95.26%). This general description of the obesity data can be seen in detail in **Table 1**. Moreover, the obesity status description can be seen in detail in the **Supplementary Table 2**.

To overcome the oversampling of the prediction of this obesity status classification due to class imbalance in the dataset (**Table 1**), the SMOTE technique was used. In this study, the SMOTE technique used two different percentages, namely 200% and 300%. SMOTE with 300% can improve minor class data

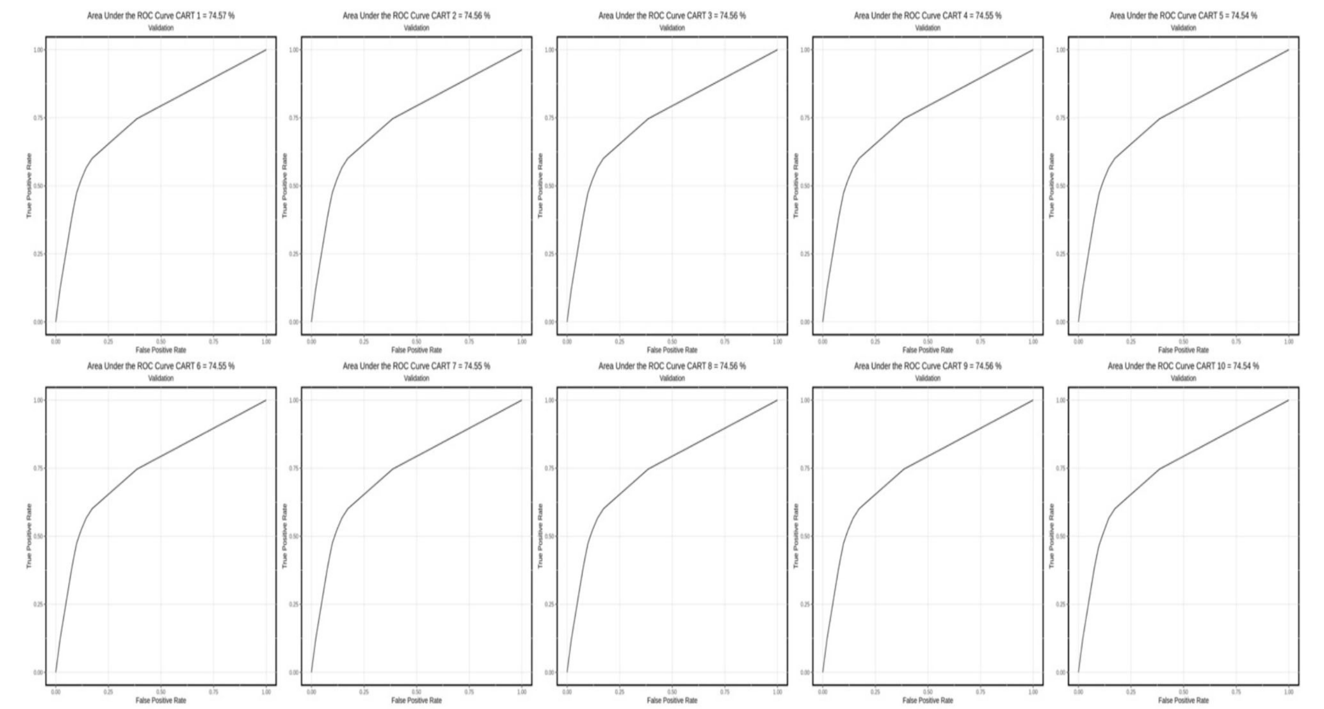

FIGURE 1 | AUC performance of the classification methods with 10-fold CV using the CART method.

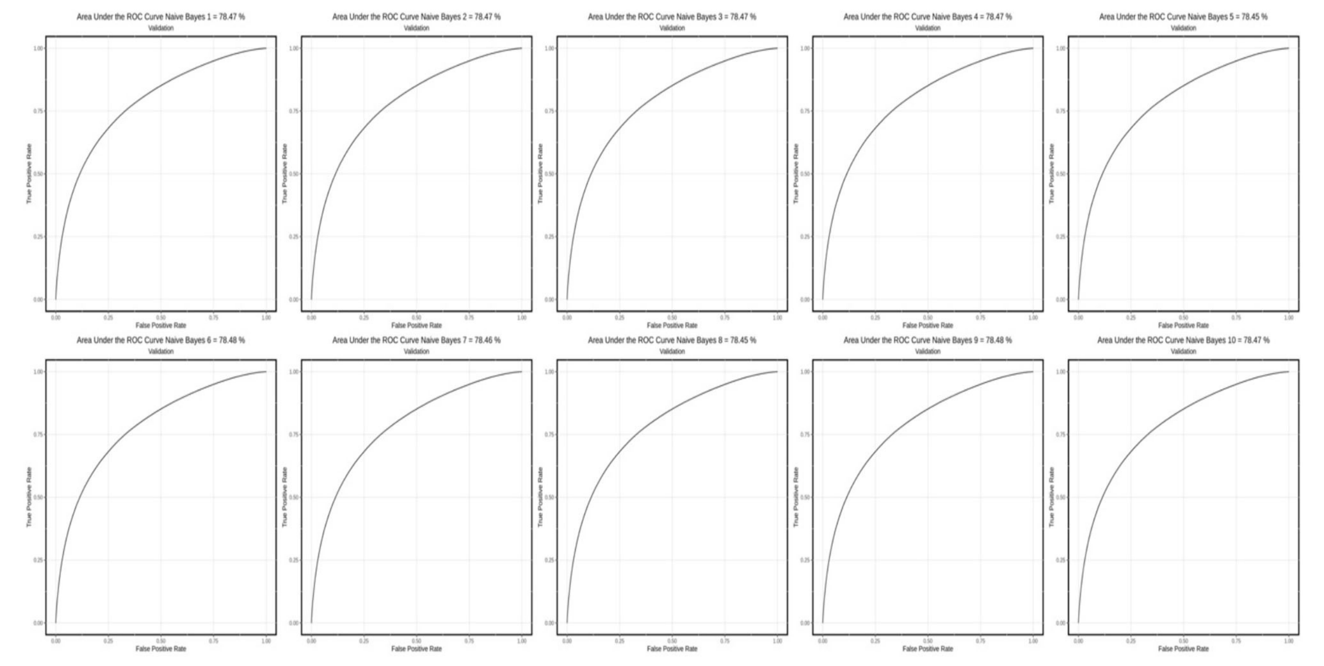

FIGURE 2 | AUC performance on the classification method with the 10-fold CV using the Naïve Bayes method.

better (from 21.77%, in the original dataset, to 47.3%). As a result, the comparison between major class (non-obese) and minor class (obese) is balanced, namely 47.3% and 52.7%, respectively. The new dataset resulting from the SMOTE technique with 300% was used to build a classification model and prediction of obesity risk factors.

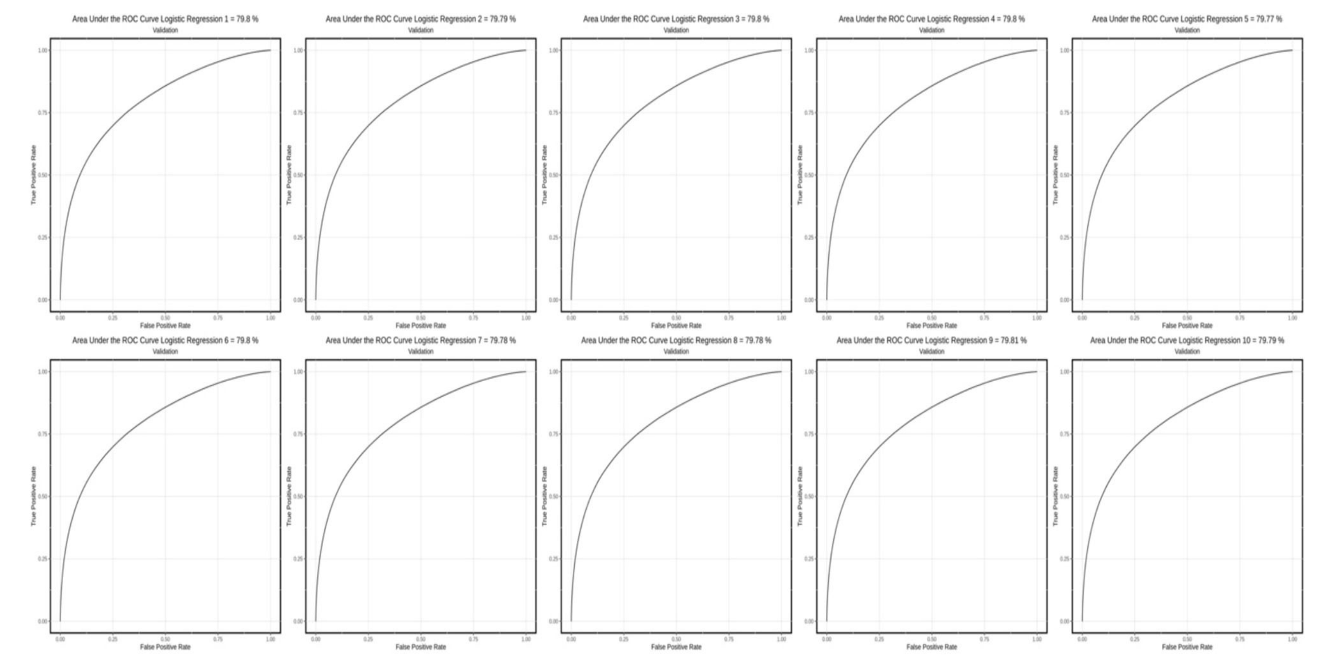

FIGURE 3 | AUC performance on the classification method with the 10-fold CV using the Logistic Regression method.

Using the three models (Logistic Regression model, CART, and Naïve Bayes), 10-fold CV was carried out to train and see which model performed better in predicting test set points on all data (**Tables 2**, **3**). This is also to ensure that all these new data resulting from the SMOTE technique are not bias in the result.

The prediction performance for the classification of obesity status from these methods is also assessed based on accuracy, sensitivity, specificity, precision, recall, F1-score, kappa, and F_β. The measurement results of these metrics based on the 10-fold CV using ML methods for the obesity data set can be seen in **Table 3**. Based on **Table 3**, the classification prediction using the Logistic Regression method achieves the best performance based on the accuracy metric (72%), specificity (71%), precision (69%), Kappa (44%), and F_β (70%). Classification prediction by the CART method achieves the highest sensitivity (82%) and the highest F1-score (72%).

Figures 1–**3** show AUC performance of the respective classification methods with 10-fold CV. The results show that the Logistic Regression classifier has the highest average AUC values (0.798) (**Figure 3**). In addition to comparing the AUC values obtained, the accuracy, sensitivity, specificity, precision, F1-Score, and F_β values of each method can also be considered. The AUC is a classification threshold invariant metric that measures the predictive quality of a model regardless of which classification threshold is selected.

After calculating the classification performance for correctly determining the obesity status for each of the 3 different models, it is also necessary to estimate a set of risk factors for obesity among the available study variables. Based on the evaluation of classification prediction performance, the Logistic Regression method had the better performance compared with the CART method and the Naïve Bayes method. Overall, fold 6 out of 10-fold CV showed the best accuracy for the classification performance of the obesity status. Partial testing of parameters of the Logistic Regression model using the Wald test showed that all explanatory variables qualify as factors that can affect the obesity status (**Table 4**). From **Table 4**, the variables that have the greatest effect on the obesity status in adults (p-value < 0.05) included location (X1), marital status (X2), age groups (X3), education (X4), sweet drinks (X7), fatty/oily foods (X9), grilled foods (X10), preserved foods (X11), seasoning powders (X12), soft/carbonated drinks (X13), alcoholic drinks (X16), mental emotional disorders (X17), diagnosed hypertension (X18), physical activity (X19), smoking (X20), and fruit and vegetables consumptions (X21).

In addition to the Logistic Regression method, prediction of obesity classification also used CART and Naïve Bayes methods. From **Figure 4**, it can be seen that the characteristics of the variables that influence the occurrence of obesity in the Indonesia RISKESDAS 2018 are significant variables that function as the main partitioning of all the trees produced. In this case, the main partitioning variables for 10% test data with fold 6 out of the 10-fold CV are alcoholic drinks (X16). The order of important variables in this CART model are alcoholic drinks (X16), energy drinks (X14), soft/carbonated drinks (X13), mental-emotional disorders (X17), fruit and vegetables consumptions (X21), diagnosed hypertension (X18), physical activity (X19), and marital status (X2).

Obesity prediction using the Naïve Bayes model was also done by looking for values of $P\left(C_i\right)$ for the obese class and $P\left(C_j\right)$ for

TABLE 4 | Estimation of the Logistic Regression parameters based on fold 6 out of the 10-fold CV for obesity dataset in Indonesian RISKESDAS 2018 survey.

Descriptive of variables		**Fold 6 out of 10-fold CV Test**				
		β	**SE**	**Wald**	***p*-Value**	**Odd Ratio**
Constant		6.510	0.046	142.754	0.000	671.976
Location (X1)	Rural	−0.305	0.005	−59.121	0.000	0.737
Marital status (X2)	Married	−0.363	0.007	−50.033	0.000	0.695
	Divorced	0.271	0.015	18.000	0.000	1.311
	Widowed	0.289	0.012	24.963	0.000	1.335
Age groups (X3)	25–29 years	0.488	0.010	46.674	0.000	1.630
	30–34 years	0.560	0.011	52.679	0.000	1.750
	35–39 years	0.680	0.011	64.375	0.000	1.975
	40–44 years	0.746	0.011	69.255	0.000	2.110
	45–49 years	0.741	0.011	67.743	0.000	2.097
	50–54 years	0.549	0.012	46.783	0.000	1.731
	55–59 years	0.333	0.013	26.349	0.000	1.396
	60–64 years	0.304	0.014	21.859	0.000	1.355
	>64 years	−0.457	0.014	−32.580	0.000	0.633
Education (X4)	Not finished basic school	0.313	0.013	24.156	0.000	1.367
	Finished basic school	0.361	0.012	29.692	0.000	1.435
	Finished Junior High School	0.456	0.013	35.808	0.000	1.577
	Finished Senior High School	0.469	0.012	38.083	0.000	1.598
	Finished Academy/College	0.502	0.018	28.496	0.000	1.652
	Finished higher education	0.506	0.015	33.432	0.000	1.659
Work types (X5)	School	−0.356	0.018	−19.850	0.000	0.700
	Government employee	0.197	0.013	15.224	0.000	1.218
	Private employee	−0.117	0.010	−12.055	0.000	0.889
	Entrepreneur	0.069	0.008	8.797	0.000	1.072
	Farmer	−0.548	0.007	−74.090	0.000	0.578
	Fisherman	−0.838	0.024	−35.437	0.000	0.432
	Daily waged labors	−0.389	0.010	−39.463	0.000	0.678
	Others	0.010	0.010	0.987	0.324	1.010
Sugary foods (X6)	1 times per day	−0.135	0.009	−15.096	0.000	0.874
	3–6 times per week	−0.141	0.009	−15.938	0.000	0.869
	1–2 times per week	−0.158	0.009	−18.457	0.000	0.854
	<3 times per month	0.013	0.011	1.189	0.234	1.013
	Never	−0.101	0.014	−7.308	0.000	0.904
Sweet drinks (X7)	1 times per day	0.094	0.007	13.815	0.000	1.099
	3–6 times per week	0.148	0.008	17.454	0.000	1.159
	1–2 times per week	0.189	0.008	22.735	0.000	1.208
	<3 times per month	0.313	0.012	26.572	0.000	1.368
	Never	0.297	0.013	23.106	0.000	1.346
Salty foods (X8)	1 times per day	0.070	0.010	6.824	0.000	1.073
	3–6 times per week	−0.077	0.010	−7.773	0.000	0.926
	1–2 times per week	−0.113	0.009	−12.268	0.000	0.893
	<3 times per month	−0.056	0.010	−5.640	0.000	0.946
	Never	−0.016	0.010	−1.568	0.117	0.984
Fatty/Oily foods (X9)	1 times per day	−0.092	0.009	−10.707	0.000	0.913
	3–6 times per week	−0.158	0.008	−19.229	0.000	0.854
	1–2 times per week	−0.165	0.008	−20.722	0.000	0.848
	<3 times per month	−0.184	0.010	−18.937	0.000	0.832
	Never	−0.495	0.014	−35.457	0.000	0.609
Grilled foods (X10)	1 times per day	−0.184	0.019	−9.749	0.000	0.832
	3–6 times per week	−0.311	0.016	−18.881	0.000	0.733

(Continued)

TABLE 4 | Continued

Descriptive of variables		Fold 6 out of 10-fold CV Test				
		β	SE	Wald	*p*-Value	Odd Ratio
	1–2 times per week	−0.419	0.016	−26.825	0.000	0.658
	<3 times per month	−0.430	0.016	−27.690	0.000	0.651
	Never	−0.452	0.016	−28.697	0.000	0.636
Preserved foods (X11)	1 times per day	−0.465	0.025	−18.674	0.000	0.628
	3–6 times per week	−0.550	0.022	−25.115	0.000	0.577
	1–2 times per week	−0.597	0.021	−28.800	0.000	0.551
	<3 times per month	−0.694	0.020	−34.273	0.000	0.499
	Never	−0.856	0.020	−42.964	0.000	0.425
Seasonings powders (X12)	1 times per day	0.117	0.006	19.308	0.000	1.124
	3–6 times per week	0.276	0.010	27.709	0.000	1.318
	1–2 times per week	0.229	0.011	20.837	0.000	1.257
	<3 times per month	0.582	0.013	46.073	0.000	1.789
	Never	0.399	0.008	47.027	0.000	1.491
Soft/Carbonated drinks (X13)	1 times per day	0.313	0.032	9.805	0.000	1.368
	3–6 times per week	0.156	0.029	5.284	0.000	1.169
	1–2 times per week	0.073	0.028	2.621	0.009	1.076
	<3 times per month	−0.158	0.027	−5.753	0.000	0.854
	Never	−0.457	0.027	−16.900	0.000	0.633
Energy drinks (X14)	1 times per day	0.046	0.031	1.476	0.140	1.047
	3–6 times per week	0.020	0.029	0.681	0.496	1.020
	1–2 times per week	−0.032	0.027	−1.185	0.236	0.968
	<3 times per month	−0.095	0.027	−3.549	0.000	0.909
	Never	−0.713	0.026	−27.394	0.000	0.490
Instant foods (X15)	1 times per day	0.010	0.019	0.512	0.609	1.010
	3–6 times per week	0.048	0.017	2.767	0.006	1.049
	1–2 times per week	−0.063	0.017	−3.710	0.000	0.939
	<3 times per month	0.084	0.017	4.901	0.000	1.088
	Never	−0.009	0.018	−0.533	0.594	0.991
Alcoholic drinks (X16)	No	−1.576	0.008	−190.048	0.000	0.207
Mental-emotional disorders (X17)	No	−1.029	0.007	−150.755	0.000	0.357
Diagnosed hypertension (X18)	No	−0.867	0.009	−100.728	0.000	0.420
	Unknown	−0.982	0.009	−110.600	0.000	0.375
Physical activity (X19)	Not adequate	−0.852	0.007	−128.275	0.000	0.427
Smoking (X20)	No	0.219	0.005	41.165	0.000	1.244
Fruit and vegetables consumptions (X21)	Not adequate	−1.248	0.009	−135.504	0.000	0.287

the non-obese class. In this case, the value of $i = 1$ and the value of $j = 2$. The probability value for each variable on the class label is presented in detail in the **Supplementary Table 3**.

DISCUSSION

We have conducted a study to establish a set of risk factors for obesity in adults among the available study variables using ML methods using publicly available data on RISKESDAS (RISKESDAS 2018). In this study, three methods (Logistic Regression, CART, and Naïve Bayes) were used in the ML approach to select a method that produces predictions with high accuracy. The result revealed that the Logistic Regression method shows a better accuracy compared to the other methods with AUC = 0.798 using 21 variables, namely location (X1), marital status (X2), age groups (X3), education (X4), work types (X5), sugary foods (X6), sweet drinks (X7), fatty/oily foods (X9), grilled foods (X10), preserved foods (X11), seasoning powders (X12), soft/carbonated drinks (X13), energy drinks (X14), instant foods (X15), alcoholic drinks (X16), mental emotional disorders (X17), diagnosed hypertension (X18), physical activity (X19), smoking (X20), and fruit and vegetables consumptions (X21).

With the accelerated economic growth and lifestyle changes around the world, including in Indonesia, it is important to evaluate and build predictive models for obesity using common risk factors. Based on RISKESDAS 2013 and 2018, Indonesia as a middle-income country seems to underestimate the significance of actual obesity cases even though there has

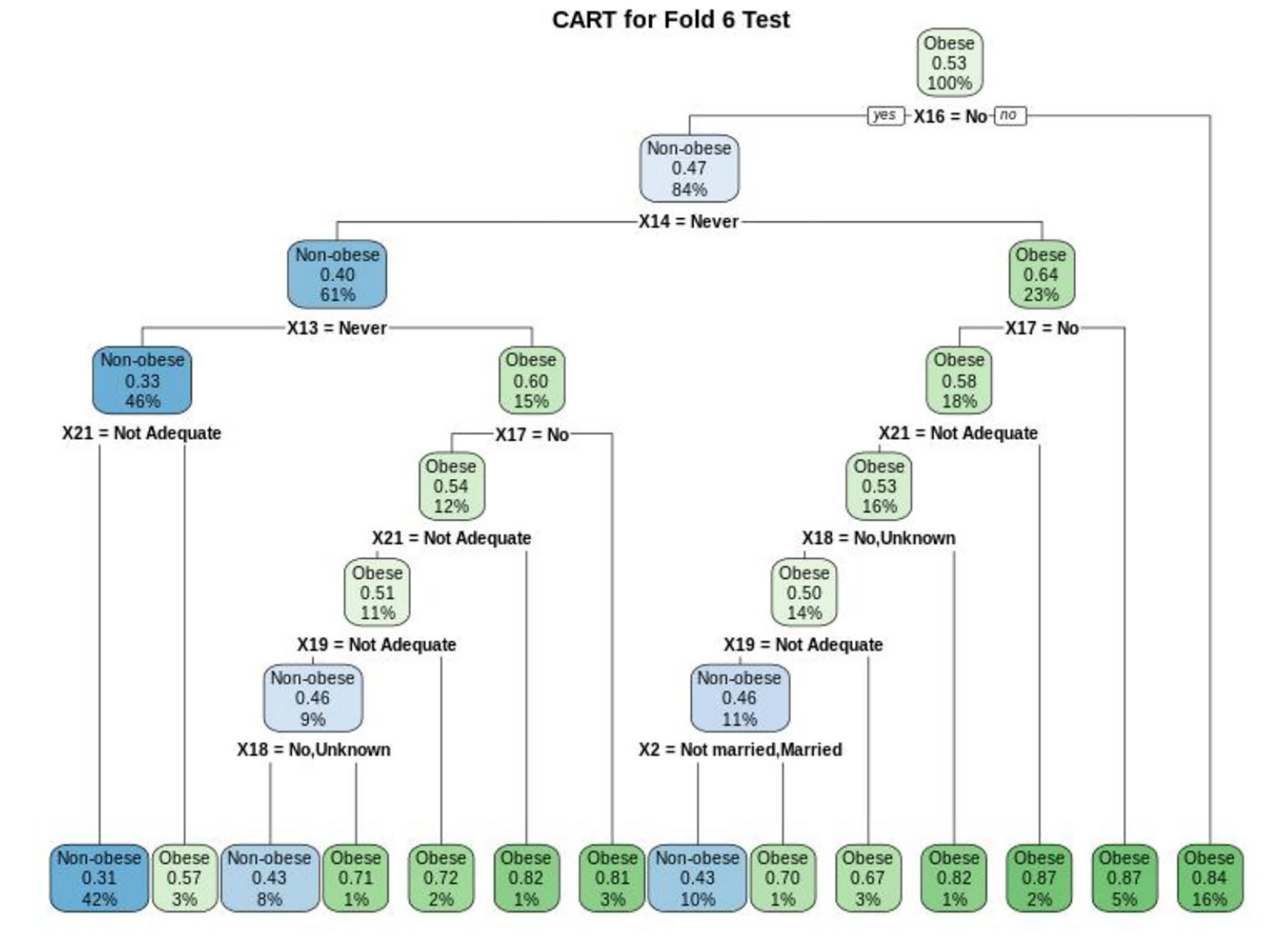

FIGURE 4 | Obesity data classification tree for fold 6 out of the 10-fold CV for CART model based on the variables of alcoholic drinks (X16), energy drinks (X14), soft/carbonated drinks (X13), mental-emotional disorders (X17), Fruit and Vegetables Consumptions (X21), diagnosed hypertension (X18), Physical Activity (X19), and Marital Status (X2).

been a significant increase in cases. As shown in this study, the 21 selected measures play a prominent role in increasing the risk for obesity in adults. This is in parallel with some previous studies. In their study, Roemling and Qaim (4) found that obesity risk in Indonesia occurred both in rural and urban areas and was closely associated with food consumption pattern changes coupled with physical activity decreases. Rachmi et al. (5) showed that the increasing prevalence of overweight children, adolescents, and adults in Indonesia over the past two decades coincides with higher numbers of obesity in urban areas. Similarly, Oddo et al. (6) demonstrated that there were more obesity cases in rural areas compared to the past even though the overall case numbers are still higher in urban areas in Indonesia. They also showed that highly processed foods are mostly consumed and decreased physical activities have led to the higher prevalence of obesity. Dewi et al. (7) found that the consumption of oil and fat, animal source foods, and low physical activities are some of the significant determinants of obesity in Indonesia. Emery et al. (40) revealed that there was a relationship between less healthy food consumption with obesity. Sinha and Jastreboff (41) found that eating habits and the increased consumption of food result from stress. Koski and Naukkarinen (42) strengthened the fact that the development of obesity is significantly due to persistent stress. The difference in confounding factors involved in the analysis is one of the reasons for the differences found in this study with previous studies.

In this study, we employed the metrics for accuracy, sensitivity, specificity, precision, recall, F1-score, kappa, and F_β with 10-fold CV for performance evaluation of the three classification methods. The results obtained are the prediction of the classification with 10-fold CV using the Logistic Regression method, which achieved the best performance as assessed by the accuracy metric (72%), specificity (71%), precision (69%), kappa (44%), and $F_{\beta=0.5}$ (70%). Classification prediction by the CART method achieved the highest sensitivity (82%), and F1-score (72%). The Naïve Bayes method had an accuracy of 71% and a $F_{\beta=0.5}$ of 69%.

In general, this ML approach is an alternative to the classical methods used so far (22). Using ML methods on public health data can help to improve predictions and find a rich structure among available data and increase understanding of complex problems in public health, including risk factors for obesity with ML. The ML method could inform the design of more appropriate health policies and programs to address Non-Communicable Diseases, most notably in predicting obesity incidence/prevalence, and in turn, reducing severity as well as the cost of treating obesity and obesity-related condition which eventually could improve the health and well-being of the population. Apart from that, the ML method as shown in the current study could be utilized to identify the most significant risk factors for predicting obesity status can be applied to publicly available data, such as RISKESDAS data.

In general, RISKESDAS provides an overview of Indonesian health indicators, such as health status, health services, health behavior, and environmental health. RISKESDAS is supposedly the best data available on health in Indonesia but its main limitation is the fact that the purpose and nature of RISKESDAS are based on a periodic study (every 5 years) examining a broad range of health issues and health behaviors. This then results in a data set that lacks depth.

In Indonesia, policies on obesity prevention and control in adults are related to limiting consumption of fats and oils, sugary foods and carbohydrates, and increasing vegetable intake are carried out through the Health Community Movement, known as GERMAS and the Food Label with the inclusion of sugar, salt, and fat content on food labels (7). Yet, these efforts seem to be ineffective as the increase in the proportion of obesity remains relatively high. The findings of this study in predicting the risk factor for obesity among the available study variables on RISKESDAS 2018 can then convince the policy makers in Indonesia (primarily the government) to put more attention into the pressing obesity problems. As a result, the effectiveness of existing program policies could be further improved and the financing of the health care system can be made more efficient (43).

This study provides an overview of the methods available for predicting risk factors for obesity in adults among the available study variables in Indonesia. Several factors that might influence obesity (e.g., sex, dietary quality, clinical and physiological, wealth, genetic and cultural influences) were not included in this study, and thereby, the relationship between these factors and obesity cannot be explained further. Further research needs to be carried out using large datasets with individual subjects to confirm the results of this study and to describe the variation in the results for individual regions.

CONCLUSION

The Logistic Regression method showed better results on the accuracy, specificity, precision, kappa, and F_β metrics. Meanwhile, the CART method showed better results on the sensitivity, recall, and F1-score. For the 10-fold CV, the Logistic Regression method had the highest AUC performance which was 0.798. Then, from the Logistic Regression method, it can also be seen that the variables that affect the prediction of obesity status in adults are location, marital status, age groups, education, sweet drinks, fatty/oily foods, grilled foods, preserved foods, seasoning powders, soft/carbonated drinks, alcoholic drinks, mental emotional disorders, diagnosed hypertension, physical activity, smoking, and fruit and vegetables consumptions. The constructed obesity classification model can evaluate and predict the risk of obesity using ML methods for the population of Indonesia which can then be applied to publicly available open data, such as the RISKESDAS survey data. In general, this study has been able to establish a set of risk factors for obesity in adults among the available study variables. However, more studies should be done to further improve the quality of predictions by exploring other ML models. In the future work, we will validate the results with other relevant groups. Additionally, we will also evaluate differences in the prediction of obesity status at the district/city or province level in Indonesia with regional disaggregation.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://www.litbang.kemkes.go.id/layanan-permintaan-data-riset.

AUTHOR CONTRIBUTIONS

ST contributed to the concept and design of the study, carried out the statistical analysis, and wrote the manuscript. DA interpreted the data, analyzed, and wrote the manuscript. HK collected the necessary data and carried out the statistical analysis. AL interpreted the data and analyzed the manuscript. SN analyzed and wrote the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.669155/full#supplementary-material

REFERENCES

1. ASEAN/UNICEF/WHO Regional Report. *World Health Statistics* 2016*: Monitoring Health for the SDGs, Sustainable Development Goals*. (2016). Available online at: https://www.who.int/about/licensing/copyright_form/en/index.html
2. Institute of Health Research and Development. *Basic Health Research Reports*. (2013). Available online at: https://www.litbang.kemkes.go.id/laporan-riset-kesehatan-dasar-riskesdas/
3. Institute of Health Research and Development. *Basic Health Research Reports*. (2018). Available online at: http://labdata.litbang.kemkes.go.id/images/download/laporan/RKD/2013/Laporan_riskesdas_2013_final.pdf
4. Roemling C, Qaim M. Obesity trends and determinants in Indonesia. *Appetite*. (2012) 58:1005–13. doi: 10.1016/j.appet.2012.02.053
5. Rachmi CN, Li M, Alison Baur L. Overweight and obesity in Indonesia: prevalence and risk factors-a literature review. *Public Health*. (2017) 147:20–9. doi: 10.1016/j.puhe.2017.02.002
6. Oddo VM, Maehara M, Rah JH. Overweight in Indonesia: an observational study of trends and risk factors among adults and children. *BMJ Open*. (2019) 9:e031198. doi: 10.1136/bmjopen-2019-031198
7. Dewi NU, Tanziha I, Solechah SA, Bohari B. Obesity determinants and the policy implications for the prevention and management of obesity in Indonesia. *Curr Res Nutr Food Sci J*. (2020) 8:942–55. doi: 10.12944/CRNFS.8.3.22
8. Wiemken TL, Kelley RR. Machine learning in epidemiology and health outcomes research. *Annu Rev Public Health*. (2020) 41:21–36. doi: 10.1146/annurev-publhealth-040119-094437
9. Giabbanelli PJ, Adams J. Identifying small groups of foods that can predict achievement of key dietary recommendations: data mining of the UK National Diet and Nutrition Survey, 2008–12. *Public Health Nutr*. (2016) 19:1543–51. doi: 10.1017/S1368980016000185
10. Dugan TM, Mukhopadhyay S, Carroll A, Downs S. Machine learning techniques for prediction of early childhood obesity. *Appl Clin Inform*. (2015) 6:506–20. doi: 10.4338/ACI-2015-03-RA-0036
11. Nau C, Ellis H, Huang H, Schwartz BS, Hirsch A, Bailey-Davis L, et al. Exploring the forest instead of the trees: an innovative method for defining obesogenic and obesoprotective environments. *Health Place*. (2015) 35:136–46. doi: 10.1016/j.healthplace.2015.08.002
12. Acharjee A, Ament Z, West JA, Stanley E, Griffin JL. Integration of metabolomics, lipidomics and clinical data using a machine learning method. *BMC Bioinformatics*. (2016) 17:440. doi: 10.1186/s12859-016-1292-2
13. Selya AS, Anshutz D. Machine learning for the classification of obesity from dietary and physical activity patterns. In: Giabbanelli P, Mago V, Papageorgiou E, editors. *Advanced Data Analytics in Health*. Springer (2018). p. 77–97. Available online at: http://doi-org-443.webvpn.fjmu.edu.cn/10.1007/978-3-319-77911-9_5
14. Zhang S, Tjortjis C, Zeng X, Qiao H, Buchan I, Keane J. Comparing data mining methods with logistic regression in childhood obesity prediction. *Inform Syst Front*. (2009) 11:449–60. doi: 10.1007/s10796-009-9157-0
15. Adnan MHBM, Husain W, Rashid NA. Parameter identification and selection for childhood obesity prediction using data mining. In: *2nd International Conference on Management and Artificial Intelligence*. Singapore (2012). p. 7.
16. Toschke AM, Beyerlein A, Von Kries R. Children at high risk for overweight: a classification and regression trees analysis approach. *Obes Res*. (2005) 13:1270–4. doi: 10.1038/oby.2005.151
17. Golino HF, Amaral LSB, Duarte SFP, Gomes CMA, Soares J, Reis LA, et al. Predicting increased blood pressure using machine learning. *J Obes*. (2014) 2014:637635. doi: 10.1155/2014/637635
18. Zheng Z, Ruggiero K. Using machine learning to predict obesity in high school students. In: *2017 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*. Kansas (2017). p. 2132–2138. doi: 10.1109/BIBM.2017.8217988
19. Chatterjee A, Gerdes MW, Martinez SG. Identification of risk factors associated with obesity and overweight–a machine learning overview. *Sensors*. (2020) 20:2734. doi: 10.3390/s20092734
20. Singh B, Tawfik H. Machine learning approach for the early prediction of the risk of overweight and obesity in young people. *Comput Sci ICCS 2020*. (2020). 12140:523–35. doi: 10.1007/978-3-030-50423-6_39
21. Colmenarejo G. Machine learning models to predict childhood and adolescent obesity: a review. *Nutrients*. (2020) 12:2466. doi: 10.3390/nu12082466
22. DeGregory KW, Kuiper P, DeSilvio T, Pleuss JD, Miller R, Roginski JW, et al. A review of machine learning in obesity. *Obes Rev*. (2018) 19:668–85. doi: 10.1111/obr.12667
23. Wickham H, François R, Henry L, Müller K. *dplyr: A Grammar of Data Manipulation*. R package version 0.7.6 (2018). Available online at: https://cran.r-project.org/package=dplyr
24. Blum AL, Langley P. Selection of relevant features and examples in machine learning. *Artif Intell*. (1997) 97:245–71. doi: 10.1016/S0004-3702(97)00063-5
25. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2020).
26. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. SMOTE: synthetic minority over-sampling technique. *J Artif Intell Res*. (2002) 16:321–57. doi: 10.1613/jair.953
27. Chawla NV. Data mining for imbalanced datasets: an overview. In: Maimon O, Rokach L, editors. *Data Mining and Knowledge Discovery Handbook*. Boston, MA: Springer (2005). p. 853–67. doi: 10.1007/0-387-25465-X_40
28. Blagus R, Lusa L. Joint use of over- and under-sampling techniques and cross-validation for the development and assessment of prediction models. *BMC Bioinformatics*. (2015) 16:363. doi: 10.1186/s12859-015-0784-9
29. Alghamdi M, Al-Mallah M, Keteyian S, Brawner C, Ehrman J, Sakr S. Predicting diabetes mellitus using SMOTE and ensemble machine learning approach: the Henry Ford ExercIse Testing (FIT) project. *PLoS ONE*. (2017) 12:e0179805. doi: 10.1371/journal.pone.0179805
30. Cost S, Salzberg S. A weighted nearest neighbor algorithm for learning with symbolic features. *Mach Learn*. (1993) 10:57–78. doi: 10.1023/A:1022664626993
31. Hastie T, Tibshirani R, Friedman J. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*. Springer-Verlag (2009). Available online at: https://web.stanford.edu/~hastie/ElemStatLearn/
32. Bishop C. *Pattern Recognition and Machine Learning*. Springer-Verlag New York (2006). Available online at: https://www.springer.com/gp/book/9780387310732
33. Breiman L, Friedman JH, Olshen RA, Stone CJ. *Classification and Regression Trees*. Washington, DC: Chapman & Hall; CRC (1984).
34. Han J, Kamber M, Pei J. *Data mining: Concepts and Techniques*, 3rd ed. Morgan Kaufmann Publishers (2012). Available online at: http://myweb.sabanciuniv.edu/rdehkharghani/files/2016/02/The-Morgan-Kaufmann-Series-in-Data-Management-Systems-Jiawei-Han-Micheline-Kamber-Jian-Pei-Data-Mining.-Concepts-and-Techniques-3rd-Edition-Morgan-Kaufmann-2011.pdf
35. Refaeilzadeh P, Tang L, Liu H. Cross-validation. In: LIU L, ÖZSU MT, editors. *Encyclopedia of Database Systems*. Boston, MA: Springer (2009). p. 24. doi: 10.1007/978-0-387-39940-9
36. Liu B, Fang L, Liu F, Wang X, Chen J, Chou KC. Identification of real microRNA precursors with a pseudo structure status composition approach. *PLoS ONE*. (2015) 10:e0121501. doi: 10.1371/journal.pone.0121501
37. Nguyen GH, Bouzerdoum A, Phung SL. *Learning Pattern Classification Tasks with Imbalanced Data Sets*. London: IntechOpen (2009). doi: 10.5772/7544
38. Landis J, Koch G. The measurement of observer agreement for categorical data. *Biometrics*. (1977) 33:159–74. doi: 10.2307/2529310
39. Brefeld U, Scheffer T. AUC maximizing support vector learning. In: Ferri C, Lachiche N, Macskassy S, Rakotomamonjy A, editors. *Proceedings of the 2nd Workshop on ROC Analysis in Machine Learning (ROCML 2005)*. (2005). Available online at: https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.59.7864&rep=rep1&type=pdf
40. Emery CF, Olson KL, Lee VS, Habash DL, Nasar JL, Bodine A. Home environment and psychosocial predictors of obesity status among community-residing men and women. *Int J Obes*. (2015) 39:1401–7. doi: 10.1038/ijo.2015.70

41. Sinha R, Jastreboff AM. Stress as a common risk factor for obesity and addiction. *Biol Psychiatry*. (2013) 73:827–35. doi: 10.1016/j.biopsych.2013.01.032
42. Koski M, Naukkarinen H. The relationship between stress and severe obesity: a case-control study. *Biomed Hub*. (2017) 2:1–13. doi: 10.1159/000458771
43. Yu H, Chris K, Junxiu L, Yujin L, Jonathan PS, Brendan C. Cost-effectiveness of the US food and drug administration added sugar labeling policy for improving diet and health. *Circulation*. (2019) 139:2613–24. doi: 10.1161/CIRCULATIONAHA.118.036751

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Associations of Whole Grain and Refined Grain Consumption With Metabolic Syndrome. A Meta-Analysis of Observational Studies

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Background: The associations of whole grain and refined grain consumption with metabolic syndrome (MetS) has been evaluated in several epidemiological studies with conflicting results. This meta-analysis was therefore employed to further investigate the above associations.

Method: We searched the PubMed, Web of Science and Embase database until March 2021 (without restriction for inclusion time), for observational studies on the associations of whole grain and refined grain consumption with MetS. The pooled relative risk (RR) of MetS for the highest vs. lowest category of whole grain and refined grain consumption, as well as their corresponding 95% confidence interval (CI) were calculated.

Results: A total of 14 observational studies, which involved seven cross-sectional and seven prospective cohort studies, were identified. Specifically, nine studies were related to whole grain consumption, and the overall multi-variable adjusted RR demonstrated that the whole grain consumption was inversely associated with MetS (RR = 0.80, 95%CI: 0.67–0.97; $P = 0.021$). With regard to refined grain consumption, 13 studies were included. The overall multi-variable adjusted RR indicated that refined grain consumption was positively associated with MetS (RR = 1.37, 95%CI: 1.02–1.84; $P = 0.036$).

Conclusions: The existing evidence suggests that whole grain consumption is negatively associated with MetS, whereas refined grain consumption is positively associated with MetS. Our result might be helpful to better consider the diet effect on MetS. However, more well-designed prospective cohort studies are needed to elaborate the concerned issues further.

Keywords: whole grain, refined grain, metabolic syndrome, meta-analysis, observational study

INTRODUCTION

The metabolic syndrome is a complex of interrelated risk factors for cardiovascular disease (CVD), diabetes and all-cause mortality. These factors include dysglycemia, raised blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, and obesity (particularly central adiposity) (1). Affecting about 25% of the population in developed countries in parallel with obesity and diabetes, MetS has been known as an important public health issue in the 21st century (2). Although the etiology of MetS is still not well-understood yet, dietary factors are considered to be associated with MetS (3–5).

Grain, a small, hard and dry seed, is composed of the endosperm, germ, and bran (6). Grain is served as the primary source of carbohydrates and global staples of diets (7). Whole grain contains more abundant and diverse nutrients with potential health benefits (fiber, vitamins, and minerals) than refined grains (8). Indeed, a potential different biological effect of whole grain and refined grain on health issues has been reported, e.g., gastric cancer (6), chronic kidney disease (9) or all-cause mortality (10), etc. Moreover, whole grain consumption was indicated to be associated with a lower risk of hypertension (11) and diabetes (12, 13), whereas refined grain consumption was associated with higher risk of diabetes (13). Moreover, some randomized control trials demonstrated that whole grain (replacing refined grain) within a weight-loss diet could reduce blood glucose (14). A whole grain-based diet could also lower the postprandial plasma insulin and triglyceride level in MetS (15). With regard to the fundamental research, the pre-germinated brown rice extract was also proved to ameliorate MetS model (16, 17).

As far as we know, the associations of whole grain and refined grain consumption with MetS has been investigated by numerous observational studies (18–31). However, their results are still controversial. The present meta-analysis of observational studies was therefore employed to examine the issues further. It was hypothesized that whole grain consumption was inversely associated with MetS, whereas refined grain consumption was positively associated with MetS.

MATERIALS AND METHODS

Search Strategy

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic review and Meta-analyses (PRISMA) guidelines (32). The PubMed, Web of Science and Embase database were searched until March 2021 (without restriction for inclusion time), by a series of logic combinations of keywords related to metabolic syndrome ("metabolic syndrome") and grain ("grain," "grains," "rice," "bread," "breads," "wheat," "wheats," "rye," "cereal," "cereals"). No language restrictions were set in the search strategy. We first screened the titles and abstracts of all of the articles to identify eligible studies and then read the full articles to include eligible studies. Moreover, the reference lists from retrieved articles were reviewed to identify additional studies.

Study Selection

Two researchers (YZ and JD) reviewed the titles, abstracts and full texts of all retrieved studies independently. Disagreements were resolved by discussions and mutual-consultations. The potentially eligible articles were selected through full text review in line with the inclusion and exclusion criteria according to PICOS strategy. The included studies were required to meet the following criteria: (1) the participants were general population; (2) the exposure of interest was the consumption of whole grain or refined grain; (3) the comparison was the highest vs. lowest category of exposure; (4) the outcomes included the MetS; (5) observational studies in general population. The exclusion criteria were as follows: (1) duplicated or irrelevant articles; (2) reviews, letters or case reports; (3) randomized controlled trials; (4) non-human studies.

Data Extraction

Two researchers extracted the data (YZ and JD) independently. Disagreements were resolved by consensus. The information about first author, year of publication, location, age, gender, sample size, study design, exposure assessment, category of exposure, effect estimates for MetS, adjustments, and diagnostic criteria of MetS was collected. The corresponding effect estimates adjusted for the maximum number of confounding variables with corresponding 95% CIs for the highest vs. lowest level were extracted. For the studies that reported the effect estimates by gender, the pooled effect estimates were calculated. In addition, Huang presented the data as southern and northern China, and they were processed independently (30). Rice/white rice was also processed as refined grain (23, 25–27).

Quality Assessment

Quality assessment was conducted according to the Newcastle-Ottawa (NOS) criteria for non-randomized studies, which is based on three broad perspectives: the selection process of study cohorts, the comparability among different cohorts, and the identification of either the exposure or outcome of study cohorts. Disagreements with respect to the methodological quality were resolved by discussion and mutual-consultation. In the current study, we considered a study awarded seven or more stars as a high-quality study (33).

Statistical Analyses

RR was considered as the common measure of the associations of whole grain or refined grain consumption with MetS, and OR and HR was directly converted into RR. The I^2 statistic, which measures the percentage of the total variation across studies due to heterogeneity, was also examined ($I^2 > 50\%$ was considered heterogeneity). If significant heterogeneity was observed among studies, the random-effects model was used; otherwise, the fixed effects model was utilized. Begg's tests were performed to assess the publication bias (34), and statistical analyses were performed using STATA version 11.0 (StataCorp LP, College Station, Texas). A p-value < 0.05 was accepted as statistically significant. Subgroup analysis for study design, diagnostic criteria of MetS, sample size, exposure assessment, study quality and adjustment of BMI and energy, were conducted.

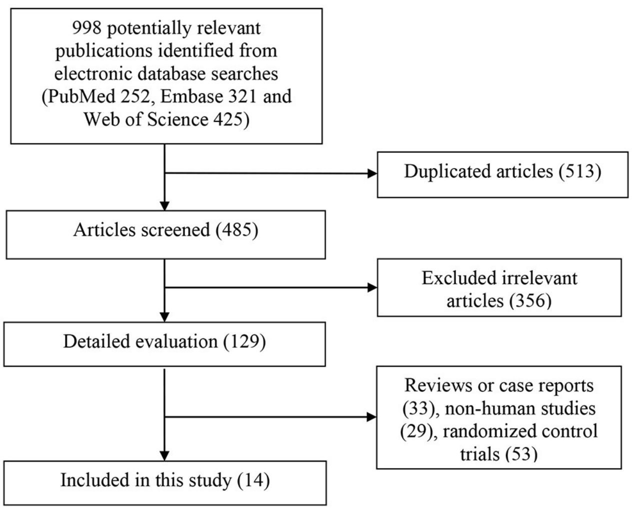

FIGURE 1 | Flow chart for the identification of studies that were included in this meta-analysis.

RESULTS

Study Identification and Selection

The detailed flow diagram of study identification and selection was presented in **Figure 1**. A total of 998 potentially relevant articles (PubMed 252, Embase 321 and Web of Science 425) were retrieved during the initial literature search. After eliminating 513 duplicated articles, 485 articles were screened by titles and abstracts. Three hundred fifty six irrelevant studies were excluded thereafter. Then, 33 reviews, case reports or letters, 29 non-human studies, and 53 randomized control trials were removed. Eventually, a total of 14 studies were identified for this meta-analysis.

Study Characteristics

Table 1 shows the main characteristics of the included studies. These studies were published between 2004 and 2020, which involved seven cross-sectional and seven prospective cohort studies. Ten studies were performed in the Asian countries [Korea (24, 25, 28, 31), Iran (19, 27), Japan (26), India (22) and China (23, 30)], three studies were conducted in US (18, 20, 21), and one study was conducted in Chile (29). Thirteen articles included both male and female participants (18–25, 27–31), whereas 1 study included only male participants (26). The sample size ranged from 535 to 15,972 for a total number of 61,431. Food frequency questionnaire (FFQ) was utilized in 11 studies (18, 19, 21–24, 26, 27, 29–31) and three studies employed recall record (24 h or 3 days) (20, 25, 28). Ten (18–22, 24, 25, 28, 30, 31) and four (23, 26, 27, 29) studies were defined as high and low-quality study, respectively. The diagnostic criteria for MetS were National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) in nine (18–20, 22, 26–29, 31), International Diabetes Foundation (IDF) in three (23, 24, 30), American Heart Association (AHA) (21, 25) in two studies, respectively.

Association Between Whole Grain Consumption and MetS

The overall multi-variable adjusted RR evidenced an inverse association between whole grain consumption and MetS (RR = 0.80, 95%CI: 0.67–0.97; $P = 0.02$) (**Figure 2**). A substantial level of heterogeneity was observed among studies ($P < 0.001$, $I^2 =$ 81.9%). No evidence of publication bias was observed among the included studies according to the Begg rank-correlation test ($P = 0.152$). In addition, such findings were obtained only in cross-sectional (RR = 0.71, 95%CI: 0.53–0.95; $P = 0.02$), NCEP ATP III (RR = 0.69, 95%CI: 0.54–0.89; $P = 0.004$), FFQ (RR = 0.80, 95%CI: 0.65–0.97; $P = 0.03$), adjustment of BMI (RR = 0.69, 95%CI: 0.49–0.98; $P = 0.04$) and energy intake (RR = 0.75, 95%CI: 0.59–0.96; $P = 0.01$) studies (**Table 2**).

Association Between Refined Grain Consumption and MetS

The overall multi-variable adjusted RR demonstrated that refined grain consumption was positively associated with MetS (RR = 1.37, 95%CI: 1.02–1.84 $P = 0.036$) (**Figure 3**). A substantial level of heterogeneity was observed among studies ($P < 0.001$, $I^2 =$ 90.4%). No evidence of publication bias was observed among the included studies according to the Begg rank-correlation test ($P = 0.324$). In addition, such findings were obtained only in cross-sectional (RR = 1.84, 95%CI: 1.03–3.28; $P = 0.04$), NCEP ATP III (RR = 1.84, 95%CI: 1.22–2.79; $P = 0.004$), high-quality studies (RR = 1.44 95%CI: 1.01–2.04; $P = 0.04$), adjustment of BMI (RR = 1.82, 95%CI: 1.10–3.02; $P = 0.02$) and energy intake (RR = 1.54, 95%CI: 1.04–2.28; $P = 0.02$) studies (**Table 3**).

DISCUSSIONS

In this study, a total of 14 observational studies were identified. Our pooled analysis showed that whole grain consumption was negatively associated with MetS, whereas refined grain consumption was positively associated with MetS.

The opposite results with regard to the whole grain and refined grain consumption could be explained by several biological mechanisms. First, the glycemic index (GI) and the glycemic load (GL), which are both determined by the amount of carbohydrates consumed, contribute to the glycemic response directly (35). It was reported that GIs and GLs were associated with a higher risk of MetS, which was independent of diabetes mellitus (36). Compared with refined grain, whole grain tends to be absorbed slowly with a relatively low GI. On the contrary, refined grain is abundant in carbohydrate content, which leads to a higher dietary GL (37). Second, whole grain is rich in dietary fiber, trace minerals, and phytochemicals (37). These nutrients and food components were considered to be beneficial for MetS (38, 39). However, the nutrient components of refined grain were lost during the refining process (22).

Our results were supported by several randomized control trials directly. Jackson et al. (14) showed that the replacing refined grain by whole grain in weight-loss diet could reduce glucose directly. Moreover, Giacco et al. (15) further indicated that a 12-weeks of whole grain intervention could reduce postprandial

TABLE 1 | Characteristics of the individual studies included in this meta-analysis.

First author year of publication	Location	Age years	Gender	Sample Size	Study design	Exposure assessment	Category of Exposure	Effect estimates for MetS (95%CI)	Adjustments	Diagnostic criteria of MetS	NOS
Mckeown (18)	US	26–82	Both	2,834	Cross-sectional	126-item FFQ	Whole grain		Sex, age, cigarette dose, total energy intake, alcohol intake, percentage saturated fat, percentage polyunsaturated fat, multivitamin use, and physical activity	NCEP ATP III	7
							Quintile 1	1.0			
							Quintile 2	0.81 (0.60, 1.08)			
							Quintile 3	1.09 (0.82, 1.44)			
							Quintile 4	0.82 (0.61, 1.10)			
							Quintile 5	0.67 (0.48, 0.91)			
							Refined grain				
							Quintile 1	1.0			
							Quintile 2	1.13 (0.84, 1.52)			
							Quintile 3	1.01 (0.74, 1.38)			
							Quintile 4	1.03 (0.75, 1.42)			
							Quintile 5	0.76 (0.53, 1.09)			
Esmaillzadeh (19)	Iran	18–74	Both	827	Cross-sectional	132-item FFQ	Whole grain		Age, total energy intake, energy from fat, use of blood pressure medication, use of estrogen, smoking, physical activity, consumption of meats and fish, fruit and vegetables	NCEP ATP III	8
							Quartile 1	1.0			
							Quartile 2	0.84 (0.79, 0.89)			
							Quartile 3	0.76 (0.69, 0.82)			
							Quartile 4	0.68 (0.60, 0.78)			
							Refined grain				
							Quartile 1	1.0			
							Quartile 2	1.68 (1.26, 2.31)			
							Quartile 3	1.92 (1.48, 2.58)			
							Quartile 4	2.25 (1.80, 2.84)			
Sahyoun (20)	US	60–98	Both	535	Cross-sectional	3-day food record (single recall)	Whole grain		Age, sex, race, educational attainment, marital status, smoking, alcohol intake, exercise, BMI, energy intake, percentage saturated fatty acid intake and use of antihypertensive or lipid-lowering medication	NCEP ATP III	7
							Quartile 1	1.0			
							Quartile 2	0.58 (0.35, 0.97)			
							Quartile 3	0.41 (0.24, 0.69)			
							Quartile 4	0.46 (0.27, 0.79)			
							Refined grain				
							Quartile 1	1.0			
							Quartile 2	1.17 (0.69, 1.97)			
							Quartile 3	1.57 (0.91, 2.68)			
							Quartile 4	2.16 (1.20, 3.87)			
Lutsey (21)	US	45–64	Both	15,972	Cohort	66-item FFQ	Whole grain		Age, sex, race, education, center, and total calories, smoking status, pack-years, physical activity, meat, dairy, fruits and vegetables.	AHA	8
							Quintile 1	1.0			
							Quintile 2	1.02 (0.92, 1.13)			
							Quintile 3	1.06 (0.96, 1.18)			
							Quintile 4	1.02 (0.92, 1.14)			
							Quintile 5	1.02 (0.92, 1.14)			
							Refined grain				
							Quintile 1	1.0			
							Quintile 2	0.92 (0.83, 1.02)			
							Quintile 3	0.95 (0.86, 1.06)			
							Quintile 4	0.95 (0.85, 1.06)			
							Quintile 5	0.89 (0.78, 1.01)			

(Continued)

TABLE 1 | Continued

First author year of publication	Location	Age years	Gender	Sample Size	Study design	Exposure assessment	Category of Exposure	Effect estimates for MetS (95%CI)	Adjustments	Diagnostic criteria of MetS	NOS
Radhika (22)	India	≥20	Both	2,042	Cross-sectional	222-item FFQ	Refined grain Quartile 1 Quartile 2 Quartile 3 Quartile 4	 1.0 3.37 (2.13, 5.31) 4.33 (2.72, 6.90) 7.83 (4.72, 12.99)	Age, sex, smoking, alcohol, BMI, total energy, legumes, visible fats and oils, dairy products, sugars, fruits and vegetables, tubers, fish and seafoods, and nuts and oil seeds	NCEP ATP III	8
Shi (23)	China	>20	Both	1,231	Cohort	33-item FFQ	Refined grain <200 g 201–400 g >401 g	 1.0 0.70 (0.39, 1.26) 0.76 (0.43, 1.36)	Smoking, drinking, active commuting, leisure time physical activity, education, occupation, energy intake	IDF	6
Baik (24)	Korea	40–69	Both	5,251	Cohort	103-item FFQ	Whole grain Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5 Refined grain Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	 1.0 NA 0.96 (0.81, 1.14) 1.10 (0.84, 1.45) 0.96 (0.75, 1.22) 1.0 0.82 (0.68, 0.99) 1.00 (0.80, 1.25) 0.87 (0.68, 1.12) 0.79 (0.59, 1.04)	Age, sex, income, occupation, education, smoking status, alcohol intake, quartiles of MET-hours/day, study sites, FTO genotypes, quartiles of energy intake	IDF	7
Son (25)	Korea	20–64	Both	5,830	Cross-sectional	24 h recall (single recall)	Refined grain Quartile 1 Quartile 2 Quartile 3 Quartile 4	 1.0 1.02 (0.73, 1.42) 1.01 (0.73, 1.40) 1.09 (0.77, 1.53)	Age, energy, sex, BMI, alcohol, smoke, income, activity	AHA	7
Watanabe (26)	Japan	40–74	Male	6,095	Cohort	29-item FFQ	Refined grain <300 g/day 300–450 g/day >450 g/day	 1.0 1.05 (0.92, 1.21) 1.19 (0.79, 1.81)	Age, egg intake, vegetable intake, milk intake, sugary beverage intake, alcoholic beverage intake, family structure, daily physical activity, checking body weight <3 times per week, a gain of ≥10 kg in body weight since the age of 20, eating quickly, having dinner within 2 h of going to bed more than three times a week, snacking after dinner three or more times per week and skipping breakfast three or more times per week	NCEP ATP III	5
Bahadoran (27)	Iran	19–70	Both	2,799	Cohort	168-item FFQ	Refined grain Quartile 1 Quartile 2 Quartile 3 Quartile 4	 1.0 1.11 (0.72, 1.72) 1.23 (0.79, 1.89) 1.66 (1.04, 2.66)	Age, sex, BMI, energy intake, carbohydrate, protein and fiber	NCEP ATP III	6
Song (28)	Korea	30–65	Both	6,845	Cross-sectional	24 h recall (single recall)	Whole grain Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	 1.0 0.99 (0.70, 1.41) 1.26 (0.88, 1.79) 1.25 (0.88, 1.76) 1.15 (0.82, 1.61)	Age, living area, education, smoking status, current alcohol intake, vigorous physical activity and total energy intake.	NCEP ATP III	8

(Continued)

TABLE 1 | Continued

First author year of publication	Location	Age years	Gender	Sample Size	Study design	Exposure assessment	Category of Exposure	Effect estimates for MetS (95%CI)	Adjustments	Diagnostic criteria of MetS	NOS
							Refined grain				
							Quintile 1	1.0			
							Quintile 2	0.87 (0.62, 1.21)			
							Quintile 3	1.12 (0.80, 1.56)			
							Quintile 4	1.21 (0.87, 1.70)			
							Quintile 5	1.02 (0.75, 1.40)			
Dussaillant (29)	Chile	>18	Both	2,561	Cross-sectional	FFQ	Whole grain		Age, gender, education, physical activity, BMI	NCEP ATP III	6
							<1 serving/day	1.0			
							≥1 serving/day	1.78 (1.09, 2.92)			
Huang South (30)	China	18–75	Both	1,804	Cohort	74-item FFQ	Whole grain		Gender, age, marital status, income level, urbanicity index, BMI, smoking, alcohol, physical activity, TEI, vegetable, fruit, red meat consumption	IDF	8
							Quartile 1	1.0			
							Quartile 2	1.02 (0.70,1.47)			
							Quartile 3	1.19 (0.82,1.72)			
							Quartile 4	1.28 (0.87,1.90)			
							Refined grain				
							Quartile 1	1.0			
							Quartile 2	1.01 (0.41, 2.49)			
							Quartile 3	1.05 (0.53, 2.06)			
							Quartile 4	1.18 (0.44, 3.16)			
Huang North (30)	China	18–75	Both	1,088	Cohort	74-item FFQ	Whole grain		Gender, age, marital status, income level, urbanicity index, BMI, smoking, alcohol, physical activity, TEI, vegetable, fruit, red meat consumption	IDF	8
							Quartile 1	1.0			
							Quartile 2	1.06 (0.71,1.58)			
							Quartile 3	0.77 (0.50,1.14)			
							Quartile 4	0.72 (0.47,1.11)			
							Refined grain				
							Quartile 1	1.0			
							Quartile 2	0.80 (0.59, 1.07)			
							Quartile 3	0.93 (0.69, 1.26)			
							Quartile 4	0.95 (0.68, 1.33)			
Kang (31)	Korea	40–69	Both	5,717	Cohort	103-item FFQ	Male		Age, education level, household income, smoking status, alcohol intake, physical activity, BMI, LDL cholesterol, total energy intake, vegetable intake, fruit intake, meat intake and dairy intake	NCEP ATP III	9
							Whole grain				
							<1 servings/day	1.0			
							1–3 servings/day	0.51 (0.43, 0.61)			
							≥3 servings/day	0.51 (0.41, 0.63)			
							Refined grain				
							<1 servings/day	1.0			
							1–3 servings/day	1.15 (0.98, 1.36)			
							≥3 servings/day	1.63 (1.31, 2.03)			
							Female				
							Whole grain				
							<1 servings/day	1.0			
							1-3 servings/day	0.58 (0.49, 0.68)			
							≥3 servings/day	0.73 (0.60, 0.90)			
							Refined grain				
							<1 servings/day	1.0			
							1-3 servings/day	0.96 (0.82, 1.12)			
							≥3 servings/day	2.25 (1.82, 2.78)			

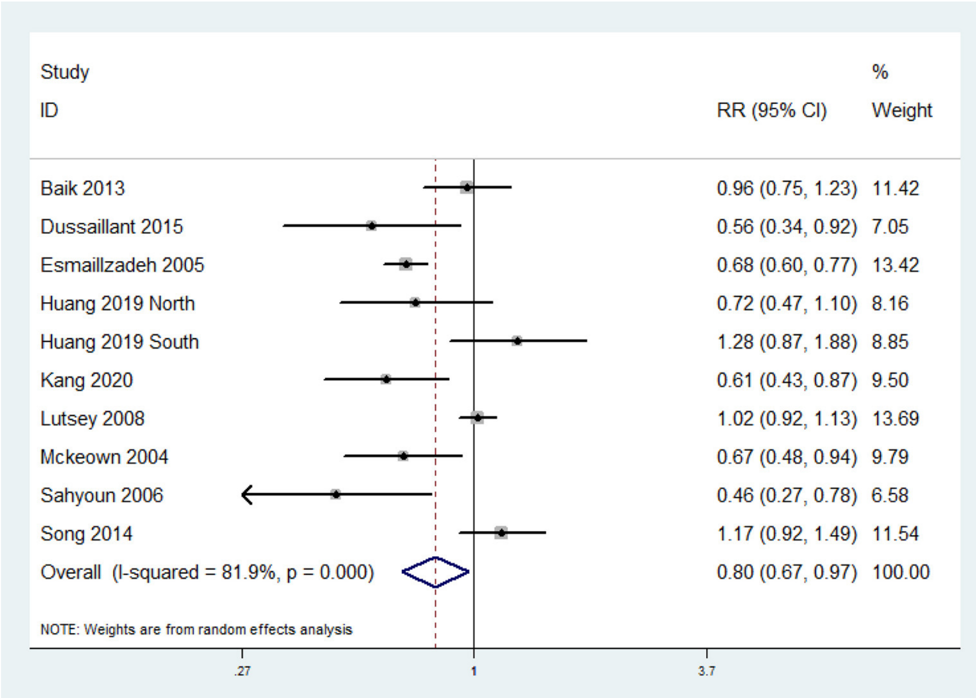

FIGURE 2 | Forest plot of meta-analysis: Overall multi-variable adjusted RR of MetS for the highest vs. the lowest category of whole grain consumption.

insulin and triglycerides responses in MetS (also compared to refined grain) (15). On the other hand, some fundamental experimental study should also be emphasized. Both Hao et al. (16) and Yen et al. (17) demonstrated that pre-germinated brown rice extract could ameliorate high-fat diet-induced MetS model. Above all, the results of our study were partly supported by the corresponding clinical and experimental evidence.

Generally speaking, whole grain referred to barley, multigrain and ground mixed grain, whereas refined grain included white rice, noodles and bread. Interestingly, several studies have considered the grain consumption as a whole (without subtype specification). Unsurprisingly, no significant relationship was obtained in these studies (40–43). It could be attributed to the synergistic effect of whole grain and refined grain consumption on MetS. Of note, our result was only confirmed in cross-sectional studies both for whole grain and refined grain. Although the reliability of our results may be influenced by the substantial level of heterogeneity, the potential different effect of grain consumption on the prevalence or risk of MetS could not be ignored, it was still an open question for MetS prevention. Moreover, the inconsistent result with regard to diagnostic criteria of MetS, exposure assessment and study quality (for refined grain) was also acquired. FFQ seems to be more reliable and precise for dietary assessment, and the NCEP ATP III criteria may be suitable for considering the effect of grain consumption. In addition, the quality of study may also influence the results. High consumption of whole-grain foods is associated with lower BMI in a dose-dependent manner (44), and BMI is considered as an important factor in MetS (1). Moreover, grain consumption is closely associated with appetite and energy intake (45), and a low reported energy intake is also reported to be associated with MetS (46). Indeed, the inconsistent result with regard to the adjustment of BMI and energy intake was obtained in our study. Therefore, further studies are required to consider BMI and energy intake as confounding factors. It should also be noted that the heterogeneity of our study cannot be ignored, especially for the exposure assessment. A semi-quantitative FFQ was utilized in most studies (18, 19, 21–24, 26, 27, 29–31), whereas several studies used recall record (20, 25, 28). On the other hand, the definition of whole grain or refined grain may vary greatly among individuals. For example, refined grain always refers to rice, noodles or bread etc, but several studies only considered rice/white rice (23, 25–27). These inconsistent exposure assessments could cause significant heterogeneity and inaccuracies in the interpretation of the results. Of note, the plasma level of alkylresorcinols, which was served as a reliable marker of whole grain consumption (14), was unfortunately ignored in all the included studies. Therefore, more well-designed prospective cohort studies are still needed.

Our study has several strengths. First, this is the first meta-analysis of observational study aiming at the associations of whole grain and refined grain consumption with MetS. Second, the included studies were analyzed based on adjusted results and large samples. Third, our result might be helpful to better consider the diet effect on MetS. We should also acknowledge the limitations of the present study. First, the substantial level of heterogeneity might have distorted the results. Second, due to the limitation of relevant literature, only a

TABLE 2 | Subgroup analyses of whole grain consumption and MetS.

Stratification	Number of studies	Pooled RR	95% CI	*P*-value	Heterogeneity
All	9	0.80	0.67, 0.97	$P = 0.02$	$P < 0.001$; $I^2 = 82\%$
Study design					
Cross-sectional	5	0.71	0.53, 0.95	$P = 0.02$	$P < 0.001$; $I^2 = 80\%$
Cohort	4	0.91	0.74, 1.12	$P = 0.37$	$P = 0.02$; $I^2 = 65\%$
Diagnostic criteria of MetS					
NCEP ATP III	6	0.69	0.54, 0.89	$P = 0.004$	$P = 0.001$; $I^2 = 76\%$
Other	3	1.01	0.92, 1.10	$P = 0.85$	$P = 0.25$; $I^2 = 26\%$
Exposure assessment					
FFQ	7	0.80	0.65, 0.97	$P = 0.03$	$P < 0.001$; $I^2 = 82\%$
Other	2	0.76	0.30, 1.89	$P = 0.55$	$P = 0.002$; $I^2 = 90\%$
Study quality					
High-quality	8	0.83	0.68, 1.00	$P = 0.05$	$P < 0.001$; $I^2 = 83\%$
Low-quality	1	0.56	0.34, 0.92	/	/
Adjustment of BMI					
Adjusted	4	0.69	0.49, 0.98	$P = 0.04$	$P = 0.01$; $I^2 = 69\%$
Unadjusted	5	0.88	0.70, 1.11	$P = 0.29$	$P < 0.001$; $I^2 = 88\%$
Adjustment of energy intake					
Adjusted	6	0.75	0.59, 0.96	$P = 0.01$	$P < 0.001$; $I^2 = 79\%$
Unadjusted	3	0.90	0.67, 1.20	$P = 0.45$	$P = 0.03$; $I^2 = 67\%$

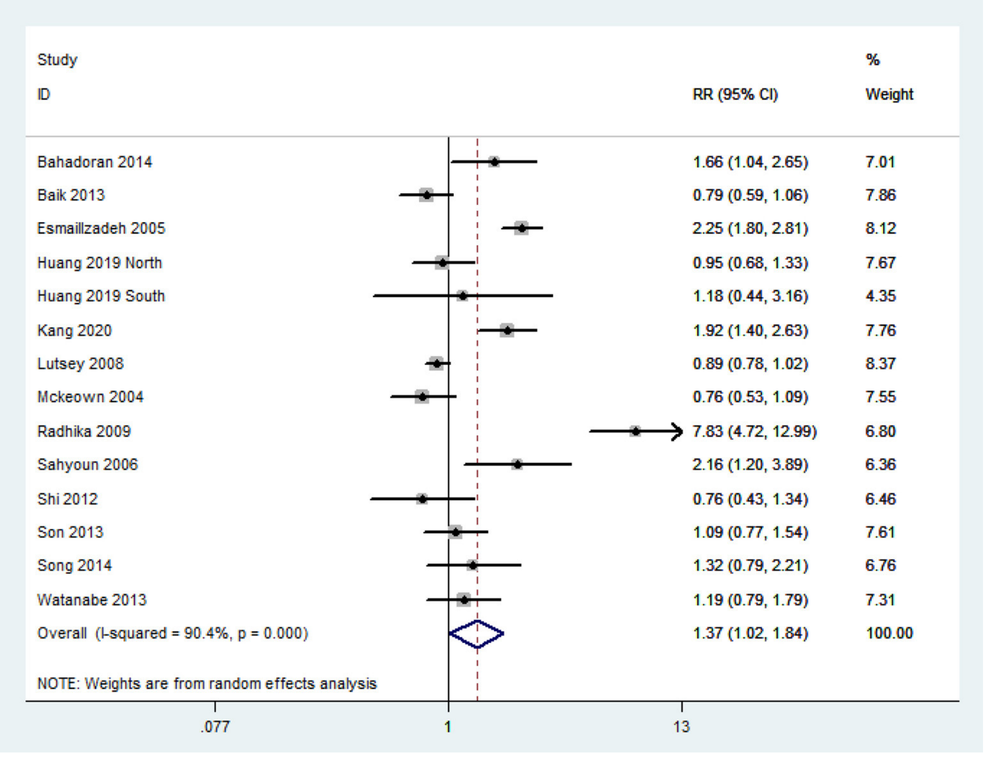

FIGURE 3 | Forest plot of meta-analysis: Overall multi-variable adjusted RR of MetS for the highest vs. the lowest category of refined grain consumption.

limited number of observational studies were identified for this meta-analysis. Third, the classification of exposure may vary greatly among individuals. Fourth, the diagnostic criteria of MetS and the selection of adjusted factors were not uniform. Last but not the least, a subgroup for gender could not be performed since very limited study specified the effect estimates by gender. These limitations might weaken the significance of this study.

TABLE 3 | Subgroup analyses of refined grain consumption and MetS.

Stratification	Number of studies	Pooled RR	95% CI	*P*-value	Heterogeneity
All studies	13	1.37	1.02, 1.84	$P = 0.04$	$P < 0.001$; $I^2 = 90\%$
Study design					
Cross-sectional	6	1.84	1.03, 3.28	$P = 0.04$	$P < 0.001$; $I^2 = 93\%$
Cohort	7	1.10	0.86, 1.40	$P = 0.46$	$P < 0.001$; $I^2 = 75\%$
Diagnostic criteria of MetS					
NCEP ATP III	8	1.84	1.22, 2.79	$P = 0.004$	$P < 0.001$; $I^2 = 89\%$
Other	5	1.02	1.00, 1.04	$P = 0.12$	$P = 0.22$; $I^2 = 27\%$
Exposure assessment					
FFQ	10	1.36	0.95, 1.93	$P = 0.09$	$P < 0.001$; $I^2 = 92\%$
Other	3	1.31	1.01, 1.69	$P = 0.04$	$P = 0.15$; $I^2 = 48\%$
Study quality					
High-quality	10	1.44	1.01, 2.04	$P = 0.04$	$P < 0.001$; $I^2 = 92\%$
Low-quality	3	1.18	0.78, 1.76	$P = 0.43$	$P = 0.12$; $I^2 = 54\%$
Adjustment of BMI					
Adjusted	6	1.82	1.10, 3.02	$P = 0.02$	$P < 0.001$; $I^2 = 89\%$
Unadjusted	7	1.06	0.75, 1.51	$P = 0.74$	$P < 0.001$; $I^2 = 90\%$
Adjustment of energy intake					
Adjusted	10	1.54	1.04, 2.28	$P = 0.03$	$P < 0.001$; $I^2 = 91\%$
Unadjusted	3	0.92	0.82, 1.04	$P = 0.17$	$P = 0.56$; $I^2 = 0\%$

CONCLUSIONS

The existing evidence suggests that whole grain consumption is negatively associated with MetS, whereas refined grain consumption is positively associated with MetS. More well-designed prospective cohort studies are needed to elaborate the concerned issues further.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

YZ conceived the idea and performed the statistical analysis. YZ, HG, and JD drafted this meta-analysis. HG and JD selected retrieved relevant papers. HG and JL assessed each study. YZ was the guarantor of the overall content. All authors revised and approved the final manuscript.

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REFERENCES

1. Alberti K, Eckel R, Grundy S, Zimmet P, Cleeman J, Donato K, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* (2009) 120:1640–5. doi: 10.1161/CIRCULATIONAHA.109.192644
2. Athyros V, Ganotakis E, Elisaf M, Mikhailidis D. The prevalence of the metabolic syndrome using the National Cholesterol Educational Program and International Diabetes Federation definitions. *Curr Med Res Opin.* (2005) 21:1157–9. doi: 10.1185/030079905X53333
3. Zhang Y, Zhang D. Associations of vegetable and fruit consumption with metabolic syndrome. A meta-analysis of observational studies. *Public Health Nutr.* (2018) 21:1693–703. doi: 10.1017/S1368980018000381
4. Zhang Y, Zhang D. Relationship between nut consumption and metabolic syndrome: a meta-analysis of observational studies. *J Am Coll Nutr.* (2019) 38:499–505. doi: 10.1080/07315724.2018.1561341
5. Zhang Y, Zhang D. Relationship between serum zinc level and metabolic syndrome: a meta-analysis of observational studies. *J Am Coll Nutr.* (2018) 37:708–15. doi: 10.1080/07315724.2018.1463876
6. Xu Y, Yang J, Du L, Li K, Zhou Y. Association of whole grain, refined grain, and cereal consumption with gastric cancer risk: a meta- analysis of observational studies. *Food Sci Nutr.* (2018) 7:256–65. doi: 10.1002/fsn3.878
7. Slavin J. Whole grains and human health. *Nutr Res Rev.* (2004) 17:99–110. doi: 10.1079/NRR200374
8. Kashino I, Eguchi M, Miki T, Kochi T, Nanri A, Kabe I, et al. Prospective association between whole grain consumption and hypertension: the Furukawa Nutrition and Health Study. *Nutrients.* (2020) 12:902. doi: 10.3390/nu12040902
9. Mazidi M, Katsiki N, Mikhailidis D, Banach M. A higher ratio of refined grain to whole grain is associated with a greater likelihood of chronic kidney disease: a population-based study. *Br J Nutr.* (2019) 121:1294–302. doi: 10.1017/S0007114518003124
10. Steffen L, Jacobs D, Stevens J, Shahar E, Carithers T, Folsom A. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke:

the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr.* (2003) 78:383–90. doi: 10.1093/ajcn/78.3.383
11. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, Andriolo V, et al. Food groups and risk of hypertension: a systematic review and dose-response meta-analysis of prospective studies. *Adv Nutr.* (2017) 8:793–803. doi: 10.3945/an.117.017178
12. Aune D, Norat T, Romundstad P, Vatten L. Whole grain and refined grain consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *Eur J Epidemiol.* (2013) 28:845–58. doi: 10.1007/s10654-013-9852-5
13. Liu S, Manson J, Stampfer M, Hu F, Giovannucci E, Colditz G, et al. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health.* (2000) 90:1409–15. doi: 10.2105/AJPH.90.9.1409
14. Jackson K, West S, Heuvel J, Jonnalagadda S, Ross A, Hill A, et al. Effects of whole and refined grains in a weight-loss diet on markers of metabolic syndrome in individuals with increased waist circumference: a randomized controlled-feeding trial. *Am J Clin Nutr.* (2014) 100:577–86. doi: 10.3945/ajcn.113.078048
15. Giacco R, Costabile G, Pepa G, Anniballi G, Griffo E, Mangione A, et al. A whole-grain cereal-based diet lowers postprandial plasma insulin and triglyceride levels in individuals with metabolic syndrome. *Nutr Metab Cardiovasc Dis.* (2014) 24:837–44. doi: 10.1016/j.numecd.2014.01.007
16. Hao C, Lin H, Ke L, Yen H, Shen K. Pre-germinated brown rice extract ameliorates high-fat diet-induced metabolic syndrome. *J Food Biochem.* (2019) 43:e12769. doi: 10.1111/jfbc.12769
17. Yen H, Lin H, Hao C, Chen F, Chen C, Chen J, et al. Effects of pre-germinated brown rice treatment high-fat diet-induced metabolic syndrome in C57BL/6J mice. *Biosci Biotechnol Biochem.* (2017) 81:979–86. doi: 10.1080/09168451.2017.1279848
18. McKeown N, Meigs J, Liu S, Saltzman E, Wilson P, Jacques P. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the framingham offspring cohort. *Diabetes Care.* (2004) 27:538–46. doi: 10.2337/diacare.27.2.538
19. Esmaillzadeh A, Mirmiran P, Azizi F. Whole-grain consumption and the metabolic syndrome: a favorable association in Tehranian adults. *Eur J Clin Nutr.* (2005) 59:353–62. doi: 10.1038/sj.ejcn.1602080
20. Sahyoun N, Jacques P, Zhang X, Juan W, McKeown N. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr.* (2006) 83:124–31. doi: 10.1093/ajcn/83.1.124
21. Lutsey P, Steffen L, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation.* (2008) 117:754–61. doi: 10.1111/j.0030-1299.2008.16455.x
22. Radhika G, Dam R, Sudha V, Ganesan A, Mohan V. Refined grain consumption and the metabolic syndrome in urban Asian Indians (Chennai Urban Rural Epidemiology Study 57). *Metabolism.* (2009) 58:675–81. doi: 10.1016/j.metabol.2009.01.008
23. Shi Z, Taylor A, Hu G, Gill T, Wittert G. Rice intake, weight change and risk of the metabolic syndrome development among Chinese adults: the Jiangsu Nutrition Study (JIN). *Asia Pac J Clin Nutr.* (2012) 21:35–43.
24. Baik I, Lee M, Jun N, Lee J, Shin C. A healthy dietary pattern consisting of a variety of food choices is inversely associated with the development of metabolic syndrome. *Nutr Res Pract.* (2013) 7:233–41. doi: 10.4162/nrp.2013.7.3.233
25. Son S, Lee H, Park K, Ha T, Seo J. Nutritional evaluation and its relation to the risk of metabolic syndrome according to the consumption of cooked rice and cooked rice with multi-grains in Korean adults: based on 2007-2008 Korean National Health and Nutrition Examination Survey. *Korean J Commun Nutr.* (2013) 18:77–87. doi: 10.5720/kjcn.2013.18.1.77
26. Watanabe Y, Saito I, Asada Y, Kishida T, Matsuo T, Yamaizumi M, et al. Daily rice intake strongly influences the incidence of metabolic syndrome in japanese men aged 40–59 years. *J Rural Med.* (2013) 8:161–70. doi: 10.2185/jrm.8.161
27. Bahadoran Z, Mirmiran P, Delshad H, Azizi F. White rice consumption is a risk factor for metabolic syndrome in Tehrani adults: a prospective approach in Tehran lipid and glucose study. *Arch Iran Med.* (2014) 17:435–40.
28. Song S, Lee J, Song W, Paik H, Song Y. Carbohydrate intake and refined-grain consumption are associated with metabolic syndrome in the Korean adult population. *J Acad Nutr Diet.* (2014) 114:54–62. doi: 10.1016/j.jand.2013.08.025
29. Dussaillant C, Echeverría G, Villarroel L, Marin P, Rigotti A. Uuhealthy food intake is linked to higher prevalence of metabolic syndrome in children adult population: cross-sectional study in 2009-2010 national health survey. *Nutr Hosp.* (2015) 32:2098–104. doi: 10.3305/nh.2015.32.5.9657
30. Huang L, Wang H, Wang Z, Zhang J, Zhang B, Ding G. Regional disparities in the association between cereal consumption and metabolic syndrome: results from the china health and nutrition survey. *Nutrients.* (2019) 11:764. doi: 10.3390/nu11040764
31. Kang Y, Lee K, Lee J, Kim J. Grain subtype and the combination of grains consumed are associated with the risk of metabolic syndrome: analysis of a community-based prospective cohort. *J Nutr.* (2020) 150:118–27. doi: 10.1093/jn/nxz179
32. Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* (2009) 339:b2700. doi: 10.1136/bmj.b2700
33. Yuhara H, Steinmaus C, Cohen S, Corley D, Tei Y, Buffler P. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *Am J Gastroenterol.* (2011) 106:1911–22. doi: 10.1038/ajg.2011.301
34. Begg C, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* (1994) 50:1088–101. doi: 10.2307/2533446
35. Augustin L, Kendall C, Jenkins D, Willett W, Astrup A, Barclay A, et al. Glycemic index, glycemic load and glycemic response: an International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr Metab Cardiovasc Dis.* (2015) 25:795–815. doi: 10.1016/j.numecd.2015.05.005
36. Juanola-Falgarona M, Salas-Salvadó J, Buil-Cosiales P, Corella D, Estruch R, Ros E, et al. Dietary glycemic index and glycemic load are positively associated with risk of developing metabolic syndrome in middle-aged and elderly adults. *J Am Geriatr Soc.* (2015) 63:1991–2000. doi: 10.1111/jgs.13668
37. Slavin J, Martini M, Jacobs D, Marquart L. Plausible mechanisms for the protectiveness of whole grains. Plausible mechanisms for the protectiveness of whole grains. *Am J Clin Nutr.* (1999) 70:459S—63S. doi: 10.1093/ajcn/70.3.459s
38. Grooms K, Ommerborn M, Pham D, Djoussé L, Clark C. Dietary fiber intake and cardiometabolic risks among US adults, NHANES 1999-2010. *Am J Med.* (2013) 126:1059–67.e1-4. doi: 10.1016/j.amjmed.2013.07.023
39. Ju S, Choi W, Ock S, Kim C, Kim D. Dietary magnesium intake and metabolic syndrome in the adult population: dose-response meta-analysis and meta-regression. *Nutrients.* (2014) 6:6005–19. doi: 10.3390/nu6126005
40. Ruidavets J, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, et al. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. *J Epidemiol Commun Health.* (2007) 61:810–7. doi: 10.1136/jech.2006.052126
41. Jung H, Han S, Song S, Paik H, Baik H, Joung H. Association between adherence to the Korean Food Guidance System and the risk of metabolic abnormalities in Koreans. *Nutr Res Pract.* (2011) 5:560–8. doi: 10.4162/nrp.2011.5.6.560
42. Oliveira E, McLellan K, Silveira L, Burini R. Dietary factors associated with metabolic syndrome in Brazilian adults. *Nutr J.* (2012) 11:13. doi: 10.1186/1475-2891-11-13
43. Pasdar Y, Moradi S, Moludi J, Darbandi M, Niazi P, Nachvak S, et al. Risk of metabolic syndrome in non-alcoholic fatty liver disease patients. *Mediterr J Nutr Metab.* (2019) 12:353–63. doi: 10.3233/MNM-190290
44. McKeown N, Yoshida M, Shea M, Jacques P, Lichtenstein A, Rogers G, et al. Whole-grain intake and cereal fiber are associated with lower abdominal adiposity in older adults. *J Nutr.* (2009) 139:1950–5. doi: 10.3945/jn.108.103762
45. Sanders L, Zhu Y, Wilcox M, Koecher K, Maki K. Effects of whole grain intake, compared with refined grain, on appetite and energy intake: a systematic review and meta-analysis. *Adv Nutr.* (2021) nmaa178. doi: 10.1093/advances/nmaa178

46. Buscemi S, Verga S, Donatelli M, D'Orio L, Mattina A, Tranchina M, et al. A low reported energy intake is associated with metabolic syndrome. *J Endocrinol Invest.* (2009) 32:538–41. doi: 10.1007/BF03346503

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Frequency of Boiled Potato Consumption and All-Cause and Cardiovascular Disease Mortality in the Prospective Population-Based HUNT Study

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Few studies have assessed the association between potato consumption and mortality, especially cardiovascular disease (CVD) mortality. Our objective was to investigate the association between consumption of boiled potatoes and all-cause and CVD mortality in a Norwegian population. We used data from the population based HUNT3 study in Norway, with data on boiled potato consumption frequency in 2006–2008 from 49,926 males and females aged 20 years or above. All-cause and CVD mortality were identified during 10 years follow-up through the national Cause of Death Registry, which is virtually complete. We used Cox regression to estimate hazard ratio (HR) with a 95% confidence interval (CI) for death controlling for potential confounders, and conducted additional analyses stratified by sex, body mass index (BMI) ±25 kg/m^2, and age ±65 years. There were 4,084 deaths and 1,284 of these were due to CVD. Frequency of boiled potato consumption was not associated with all-cause mortality, nor with CVD mortality. Compared to those individuals who consumed boiled potatoes less than once weekly, those who reported to consume boiled potatoes 1–3 times per week had an adjusted HR (95% CI) of 1.12 (0.89, 1.41) for all-cause mortality and 1.20 (0.78, 1.86) for CVD mortality. Individuals who consumed boiled potatoes 4–6 times per week had HRs of 0.97 (0.78, 1.21) and 1.03 (0.68, 1.55), for all-cause and CVD mortality, respectively, whereas those who consumed boiled potatoes more than once daily had HRs of 1.04 (0.83, 1.29) and 1.09 (0.73, 1.63) for all-cause and CVD mortality, respectively. There was no evidence of differential associations for males vs. females, nor between people with BMI ± 25 kg/m^2. The associations between frequency of boiled potato consumption and all-cause mortality showed different patterns between those younger vs. older than 65 years, with a tendency of increased risk only in the oldest age group. In conclusion, frequency of consumption of boiled potatoes was not associated with all-cause or CVD mortality in the HUNT population in Norway.

Keywords: diet, survival, heart disease, vegetables, nutrients

INTRODUCTION

Europe has the highest level of potato consumption in the world, with almost 90 kg per capita per year (1). Potatoes contain several key nutrients, including potassium, dietary fiber, and vitamin C. On the other hand, potatoes have high carbohydrate content and are considered to be a high glycaemic index food, making the nutritional value of potatoes uncertain (2). Some prospective observational studies have reported positive associations between potato consumption and incidence of type 2 diabetes (3, 4) and hypertension (5), whereas others have reported no such associations (6, 7). Two recent systematic reviews and dose-response meta-analyses of prospective cohort studies found no associations between total potato consumption and risk of all-cause mortality (8, 9). However, frequent consumption of fried potatoes was associated with all-cause mortality in a North American cohort (10). So far, there have been too few studies to perform meta-analyses about the association between potato intake and CVD mortality. Pietinen et al. (11) reported an inverse association between intake of potatoes and coronary heart disease mortality in a cohort of 21,930 middle-aged, smoking Finnish males. Contrary, another study in 69,313 Swedish males and females, reported no associations between potato consumption and CVD mortality (6). Data from the National Health and Nutrition Examination Surveys (NHANES) 1999–2010 showed an association between total potato consumption and all-cause and CVD mortality in crude analyses, but the association was largely attenuated after adjusting for hypertension and diabetes (12). These inconsistent findings may be due to different preparation methods of potatoes used in the different cohorts and available evidence is insufficient to reach a conclusion about the association between potato consumption and mortality. There are some data showing that individuals with a high potato consumption have a less favorable profile of metabolic and cardiovascular risk factors, such as circulating lipids, abdominal obesity, blood pressure profiles, and the metabolic syndrome (12, 13). The aim of this study was to investigate the associations between the frequency of consumption of boiled potatoes and risk of all-cause and CVD mortality in a Norwegian population.

SUBJECTS AND METHODS

Study Population

We included participants from the HUNT3 Study, undertaken in 2006–2008. The HUNT Study is a longitudinal population-based health study among residents who are 20 years or older in one county in Norway and 50,807 participated in HUNT3. Detailed information about the HUNT-studies and cohort profile is available at http://www.ntnu.edu/hunt. We included participants with valid data on potato consumption ($n = 49{,}926$) in this study (**Figure 1**). All participants provided informed, written consent. The study was approved by the Regional Committee for Ethics in Medical Research (no. 2017/1503 REK midt).

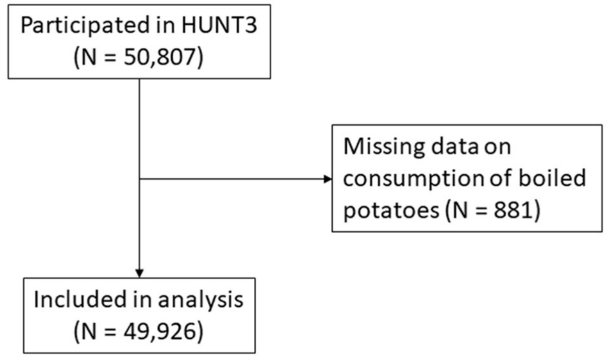

FIGURE 1 | Flow diagram of participants included in the analysis.

Assessment of Potato Consumption and Possible Confounders

The participants completed questionnaires about their habitual intake of various food groups, including vegetables, fruits, fish, meat, pasta, and rice. Consumption of boiled potatoes was assessed by the questions "How often do you normally eat boiled potatoes?" and this question had four response alternatives; (1) <once per week, (2) 1–3 times per week, (3), 4–6 times per week, and (4) at least once daily.

The HUNT3 study includes survey questionnaires on a range of other health and lifestyle-related topics and a clinical examination of standardized measures of height, body weight and blood pressure. Height and body weight were measured with the participants wearing light clothes (without shoes). Height was measured to the nearest centimetre and weight to the nearest half kilogram. Body mass index (BMI) was calculated as kg/m^2. CVD, diabetes, and cancer at baseline were self-reported. Blood pressure was measured three times using a Dinamap 845XT (Critikon), and we used the mean of the second and third measurements in the analyses. We categorised those with systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg and/or currently taking blood pressure medication as having hypertension. Participants also reported their smoking status, leisure time physical activity, occupational physical activity, alcohol consumption, and consumption of vegetables, high-fat fish, pasta/rice, and sausages/hamburgers in detailed questionnaires.

Follow-Up

We used the unique personal identification number of all Norwegian citizens to link data from HUNT to information from the national Cause of Death Registry on primary cause of death classified according to the International Classification of Disease (ICD). Mortality from all causes and from CVD (i.e., ICD-10: I00-I99) were recorded from baseline in 2006-2008 until the date of death or end of follow-up 31.12.2016, whichever occurred first.

Statistical Analyses

We used Cox regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of death from all causes and from CVD within each category of boiled potato consumption, compared to the reference category of individuals who reported to eat potatoes less than once weekly. All estimates were adjusted for age and sex, as well as for CVD at baseline (yes or no), cancer at baseline (yes or no), hypertension at baseline (yes or no), BMI (<18.5, 18.5–24.9, 25.0–29.9, or ≥30.0 kg/m^2), leisure time physical activity (none, <1, 1, 2–3, or ≥4 times per week), occupational physical activity (mostly sitting, much walking, much walking and lifting, heavy physical work, or unknown/not employed), smoking (never, former, current, or unknown), and habitual intake of alcohol (≤1 per month, ≤1 per week, ≥2 per week, or abstainer), vegetables (≤3 times per week, 4–6 times per week, ≥1 times per day), high-fat fish (≤3 times per month, 1–3 times per week, ≥4 times per week), pasta/rice (≤3 times per month, 1–3 times per week, ≥4 times per week), and sausages/hamburgers (≤3 times per month, 1–3 times per week, ≥4 times per week). The proportional hazard assumption was assessed by tests of Schoenfeld residuals and inspection of log-log plots. Additional analyses were stratified by sex (male, female), by BMI (±25 kg/m^2) and by age (±65 years). We also conducted three sensitivity analyses: (1) (we did not adjust for intake of pasta/rice) since this may be a mediator of the association under study, (2) we excluded participants with CVD at baseline to reduce possible confounding by ill health, and for the same reason, we (3) excluded participants who died within the first 2 years of follow-up. Statistical tests were two-sided, and all analyses were performed using Stata for Windows (Version 15 © StataCorp LP, 1985-2017).

RESULTS

Table 1 shows the baseline characteristics of the participants according to boiled potato consumption. About two thirds of the participants reported to eat boiled potatoes four times or more per week. Compared with those who had a low intake of boiled potatoes, those with a high consumption were older, had more often a sedentary work type, were less physically active, had higher prevalence of hypertension and CVD, and had a lower intake of pasta/rice.

A total of 4,084 deaths occurred with 1,284 from CVD over 10 years of follow-up. There were no associations between intake of boiled potatoes and all-cause mortality or CVD mortality (**Table 2**). The same was true also when the analyses were stratified by sex (**Table 3**) and by BMI (**Table 4**). In the analyses stratified for BMI ± 25 kg/m^2, the HRs suggest lower CVD mortality in those who had a healthy BMI and who consumed boiled potatoes once per week or more often compared to the reference group, whereas the opposite was evident for those with overweight/obesity (**Table 4**). When the analyses were stratified for age ±65 years, we observed a tendency of increased all-cause mortality associated with frequent consumption of boiled potatoes among those in the oldest age group, whereas for those below 65 years the HR was highest for those in the reference group (<once weekly consumption) (**Table 5**).

TABLE 1 | Selected participant characteristics according to boiled potato consumption.

Variable	Boiled potato consumption per week			
	<1	1–3	4–6	Daily
Number of participants	2,712	12,808	19,942	14,464
Age, years, mean (SD)	38.8 (15.5)	43.9 (13.8)	53.4 (14.2)	63.3 (13.3)
Women/men	1,633/1,079	7,354/5,454	10,583/9,359	7,677/6,787
Body mass index, kg/m^2	26.4 (4.7)	26.7 (4.4)	27.3 (4.3)	27.6 (4.4)
Cigarette smoking, current smoker	27%	25%	23%	25%
Alcohol consumption, >1/week	13%	16%	17%	12%
Work type, sedentary	31%	32%	25%	14%
Physical activity, <1/week	23%	21%	21%	24%
Hypertension	21%	24%	40%	57%
Cardiovascular disease	4%	4%	8%	15%
Pasta/rice consumption, ≥4/week	23%	9%	4%	3%

TABLE 2 | Boiled potato consumption in relation to mortality from all causes and from cardiovascular diseases (CVD).

Frequency of boiled potato consumption	No. of persons years	No. of cases	Crude HR	Adjusted HR[a]	95% CI[a]
All-Cause Mortality					
<1 per week	257,933	90	1.00	1.00	Reference
1–3 per week	1,220,518	419	0.98	1.12	0.89–1.41
4–6 per week	1,889,300	1,328	0.83	0.97	0.78–1.21
≥1 per day	1,321,989	2,247	0.90	1.04	0.83–1.29
CVD Mortality					
<1 per week	257,933	26	1.00	1.00	Reference
1–3 per week	1,220,518	109	0.97	1.20	0.78–1.86
4–6 per week	1,889,300	402	0.85	1.03	0.68–1.55
≥1 per day	1,321,989	747	0.93	1.09	0.73–1.63

[a]Adjusted for age (time scale), sex (woman, man), CVD at baseline (no, yes), diabetes at baseline (no, yes), hypertension at baseline (no, yes), cancer at baseline (no, yes), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m^2), work type (sitting, waling, walking and lifting, heavy work, unknown/not employed), frequency of physical activity (none, <1, 1, 2–3, ≥4 times per week), smoking (never, former, current, unknown), alcohol past year (≤1 month, 1–3 per month, ≥1 per week, never), and intake of vegetables (≤3 times per week, 4–6 times per week, ≥1 times per day), high-fat fish (≤3 times per month, 1–3 times per week, ≥4 times per week), pasta/rice (≤3 times per month, 1–3 times per week, ≥4 times per week), and sausages/hamburgers (≤3 times per month, 1–3 times per week, ≥4 times per week).

Sensitivity Analyses

We observed only minor changes to the estimates when we repeated the analyses without adjusting for intake of pasta/rice (**Supplementary Table 1**). Neither did excluding individuals with CVD at baseline (**Supplementary Table 2**)

TABLE 3 | Boiled potato consumption in relation to mortality from all causes and from cardiovascular diseases (CVD), stratified by sex.

	Males					Females				
Frequency of boiled potato consumption	**No. of person years**	**No. of cases**	**Crude HR**	**Adjusted HR[a]**	**95% CI[a]**	**No. of person years**	**No. of cases**	**Crude HR**	**Adjusted HR[a]**	**95% CI[a]**
All-Cause Mortality										
<1 per week	102,013	46	1.00	1.00	Reference	155,920	44	1.00	1.00	Reference
1–3 per week	519,144	200	0.84	0.98	0.71-1.35	701,374	219	1.14	1.29	0.92–1.79
4–6 per week	880,403	747	0.71	0.85	0.62-1.15	1,008,897	581	0.96	1.10	0.80–1.52
≥1 per day	611,966	1,214	0.77	0.88	0.65-1.20	710,022	1,033	1.05	1.21	0.88–1.65
CVD Mortality										
<1 per week	102,013	14	1.00	1.00	Reference	155,920	12	1.00	1.00	Reference
1–3 per week	519,144	54	0.77	1.02	0.56-1.86	701,374	55	1.23	1.44	0.76–2.74
4–6 per week	880,403	233	0.67	0.90	0.51-1.57	1,008,897	169	1.06	1.15	0.63–2.11
≥1 per day	611,966	415	0.77	0.95	0.55-1.65	710,022	332	1.12	1.23	0.67–2.24

[a]Adjusted for age (time scale), CVD at baseline (no, yes), diabetes at baseline (no, yes), hypertension at baseline (no, yes), cancer at baseline (no, yes), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥ 30.0 kg/m^2), work type (sitting, walking, walking and lifting, heavy work, unknown/not employed), frequency of physical activity (none, <1, 1, 2–3, ≥4 times per week), smoking (never, former, current, unknown), alcohol past year (≤1 month, 1–3 per month, ≥1 per week, never), and intake of vegetables (≤3 times per week, 4–6 times per week, ≥1 times per day), high-fat fish (≤3 times per month, 1–3 times per week, ≥4 times per week), pasta/rice (≤3 times per month, 1–3 times per week, ≥4 times per week), and sausages/hamburgers (≤3 times per month, 1–3 times per week, ≥4 times per week).

TABLE 4 | Boiled potato consumption in relation to mortality from all causes and from cardiovascular diseases (CVD), stratified by body mass index (BMI) ±25 kg/m^2.

	<25 kg/m^2					≥25 kg/m^2				
Frequency of boiled potato consumption	**No. of person years**	**No. of cases**	**Crude HR**	**Adjusted HR[a]**	**95% CI[a]**	**No. of person years**	**No. of cases**	**Crude HR**	**Adjusted HR[a]**	**95% CI[a]**
All-Cause Mortality										
<1 per week	111,966	31	1.00	1.00	Reference	144,374	56	1.00	1.00	Reference
1–3 per week	461,224	110	0.73	0.92	0.61–1.39	751,762	299	1.13	1.26	0.94–1.69
4–6 per week	584,260	407	0.73	0.85	0.58–1.25	1,294,031	880	0.95	1.08	0.82–1.43
≥1 per day	365,624	674	0.75	0.87	0.59–1.27	946,898	1,496	1.06	1.15	0.87–1.51
CVD Mortality										
<1 per week	111,966	11	1.00	1.00	Reference	144,374	14	1.00	1.00	Reference
1–3 per week	461,224	28	0.65	0.92	0.44–1.95	751,762	77	1.25	1.60	0.89–2.87
4–6 per week	584,260	108	0.53	0.64	0.33–1.27	1,294,031	279	1.21	1.50	0.86–2.61
≥1 per day	365,624	229	0.62	0.75	0.39–1.46	946,898	491	1.27	1.50	0.87–2.61

[a]Adjusted for age (time scale), sex (woman, man), CVD at baseline (no, yes), diabetes at baseline (no, yes), hypertension at baseline (no, yes), cancer at baseline (no, yes),work type (sitting, walking, walking and lifting, heavy work, unknown/not employed), frequency of physical activity (none, <1, 1, 2–3, ≥4 times per week), smoking (never, former, current, unknown), alcohol past year (≤1 month, 1–3 per month, ≥1 per week, never), and intake of vegetables (≤3 times per week, 4–6 times per week, ≥1 times per day), high-fat fish (≤3 times per month, 1–3 times per week, ≥4 times per week), pasta/rice (≤3 times per month, 1–3 times per week, ≥4 times per week), and sausages/hamburgers (≤3 times per month, 1–3 times per week, ≥4 times per week).

nor excluding individuals who died during the first 2 years of follow-up (**Supplementary Table 3**) change the estimates substantially.

DISCUSSION

We examined the association between the frequency of boiled potato consumption and all-cause and CVD mortality in a Norwegian population. Boiled potatoes are a principal element in the traditional diet for this population, with two thirds of the participants reporting to eat boiled potatoes four times or more per week. We observed no clear associations between intake of boiled potatoes and mortality, neither from all causes nor from CVD. The associations were similar in males and females. Among individuals with BMI <25 kg/m^2, the HRs were lower for those with frequent consumption of boiled potatoes, whereas there was an opposite trend for those with BMI ≥25 kg/m^2. Opposite associations between frequency of potato consumption and mortality were also evident in those who were below and above 65 years of age. We are unsure how to interpret these differing associations for BMI categories and for age, and it is worth noticing that for neither stratification was there any clear dose-response between frequency of consumption and mortality.

Previous studies on the associations between consumption of potatoes and risk of type 2 diabetes, hypertension, and CVD, as well as CVD and all-cause mortality have shown

TABLE 5 | Boiled potato consumption in relation to mortality from all causes and from cardiovascular diseases (CVD), stratified by age ±65 years.

	<65 years					≥65 years				
Frequency of boiled potato consumption	**No. of person years**	**No. of cases**	**Crude HR**	**Adjusted HR[a]**	**95% CI[a]**	**No. of person years**	**No. of cases**	**Crude HR**	**Adjusted HR[a]**	**95% CI[a]**
All-cause mortality										
<1 per week	243,270	39	1.00	1.00	Reference	14,663	56	1.00	1.00	Reference
1–3 per week	1,145,140	181	0.76	0.82	0.57–1.16	75,379	299	1.16	1.36	1.00–1.85
4–6 per week	1,525,805	344	0.67	0.74	0.53–1.04	363,495	880	1.02	1.16	0.87–1.55
≥1 per day	737,430	279	0.75	0.71	0.50–1.01	584,559	1,496	1.10	1.24	0.93–1.64
CVD mortality										
<1 per week	243,270	11	1.00	1.00	Reference	14,663	14	1.00	1.00	Reference
1–3 per week	1,145,140	28	0.64	0.67	0.27–1.66	75,379	77	1.13	1.41	0.86–2.31
4–6 per week	1,525,805	108	0.83	0.86	0.36–2.03	363,495	279	0.94	1.07	0.67–1.70
≥1 per day	737,430	229	0.90	0.78	0.32–1.87	584,559	491	1.03	1.14	0.72–1.80

[a]Adjusted for age (time scale), sex (woman, man), CVD at baseline (no, yes), diabetes at baseline (no, yes), hypertension at baseline (no, yes), cancer at baseline (no, yes),work type (sitting, walking, walking and lifting, heavy work, unknown/not employed), frequency of physical activity (none, <1, 1, 2–3, ≥4 times per week), smoking (never, former, current, unknown), alcohol past year (≤1 month, 1–3 per month, ≥1 per week, never), and intake of vegetables (≤3 times per week, 4–6 times per week, ≥1 times per day), high-fat fish (≤3 times per month, 1–3 times per week, ≥4 times per week), pasta/rice (≤3 times per month, 1–3 times per week, ≥4 times per week), and sausages/hamburgers (≤3 times per month, 1–3 times per week, ≥4 times per week).

conflicting results. Some prospective observational studies report that potato consumption is positively associated with the risk of type 2 diabetes and hypertension (3–5, 14). One of these studies is from the China Health and Nutrition Survey (CHNS) (14). However, in the same population, researchers found that low and moderate, but not high, levels of total potato consumption were inversely associated with all-cause mortality (15). We previously reported some weak positive associations between boiled potato consumption and several CVD risk factors (high waist circumference, high circulating triglycerides, and prevalence of the metabolic syndrome) in a cross-sectional investigation of the HUNT population (13). Here we observe that these associations do not transfer to increased mortality in this population. Our data are also consistent with findings from two prospective cohort studies in Swedish adults, who also have a high consumption of boiled potatoes (6). Larsson and Wolk (6) observed no evidence that consumption of boiled potatoes associated with the risk of major CVD events or mortality form CVD.

Different preparation methods of potatoes used in the different cohorts may partly explain the diverse findings. In our study, we investigated boiled potato consumption, which is assumed to be the healthiest preparation method. Roasted and fried potatoes carry more salt and fats, with acrylamide formation as an additional problem if the potatoes are prepared at temperatures above 120°C (16). The unfavorable cardiometabolic effects of potatoes are generally attributed to their high content of starch, leading to an exceptionally high glycaemic index (17). The glycaemic index of potatoes is, however, dependent on the preparation method, with boiled potatoes eliciting higher glycaemic response than french fries (18). Foods with high glycaemic index induce a rapid rise in blood glucose (19) and such foods are suggested to cause weight gain by redirecting nutrition from oxidation in insulin-sensitive tissue to storage as fat (20). Postprandial hyperglycaemia is an important risk factor for incident CVD events and this relationship extends below the diabetic threshold (21). However, there were no indications for an increased CVD mortality with high consumption of boiled potatoes in this Norwegian population. Potatoes are typically part of a complex meal (2), together with other foods with lower glycaemic index and which reduces the overall postprandial glucose response of the meal (22).

The strengths of this study are the population-based nature of the data, the prospective design, detailed information on lifestyle and health-related factors, and the completeness of follow-up by linkage with the population-based Norwegian Cause of Death Registry. There are also some limitations to our study. The diet questionnaire in HUNT did not capture information about the portion sizes, so we were not able to calculate the total consumption of potatoes, only the frequency of intake. Neither could we calculate the total energy intake or the distribution of macronutrients in the diet of the participants based on the questionnaire, and the lack of these data represents a main limitation. Additionally, we had no information about consumption of potatoes prepared by different cooking methods, as for example frying. It is likely that the frequency of boiled potato consumption could be inversely correlated with intake of potatoes prepared otherwise. Finally, we cannot rule out residual confounding due to poorly or unmeasured lifestyle and health related factors or confounding by ill health that causes both dietary changes and increase mortality.

In conclusion, the frequency of boiled potato consumption was not associated with all-cause or CVD mortality in this population.

DATA AVAILABILITY STATEMENT

Data described in the article, code book, and analytic code will not be made available because the Trøndelag Health Study

(HUNT) does not allow for such sharing. The data are stored in HUNT databank and biological material in HUNT biobank. HUNT Research Centre has permission from the Norwegian Data Inspectorate to store and handle these data. The key identification in the data base is the personal identification number given to all Norwegians at birth or immigration, whilst de-identified data are sent to researchers upon approval of a research protocol by the Regional Ethical Committee and HUNT Research Centre. To protect participants' privacy, HUNT Research Centre aims to limit storage of data outside HUNT databank, and cannot deposit data in open repositories. HUNT databank has precise information on all data exported to different projects and are able to reproduce these on request. There are no restrictions regarding data export given approval of applications to HUNT Research Centre. For more information see: http://www.ntnu.edu/hunt/data.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Committee for Ethics in Medical Research, Central Norway. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TM designed research (project conception, development of overall research plan, and study oversight) and had primary responsibility for final content. TM and TN conducted research and wrote the manuscript. TN analyzed data and performed statistical analyses. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.681365/full#supplementary-material

REFERENCES

1. Potatopro (2019). Available online at: https://www.potatopro.com/europe/potato-statistics (accessed November 19, 2019).
2. McGill CR, Kurilich AC, Davignon J. The role of potatoes and potato components in cardiometabolic health: a review. *Ann Med.* (2013) 45:467–73. doi: 10.3109/07853890.2013.813633
3. Halton TL, Willett WC, Liu S, Manson JE, Stampfer MJ, Hu FB. Potato and french fry consumption and risk of type 2 diabetes in women. *Am J Clin Nutr.* (2006) 83:284–90. doi: 10.1093/ajcn/83.2.284
4. Muraki I, Rimm EB, Willett WC, Manson JE, Hu FB, Sun Q. Potato consumption and risk of type 2 diabetes: results from three prospective cohort studies. *Diabetes Care.* (2016) 39:376–84. doi: 10.2337/dc15-0547
5. Borgi L, Rimm EB, Willett WC, Forman JP. Potato intake and incidence of hypertension: results from three prospective US cohort studies. *BMJ.* (2016) 353:i2351. doi: 10.1136/bmj.i2351
6. Larsson SC, Wolk A. Potato consumption and risk of cardiovascular disease: 2 prospective cohort studies. *Am J Clin Nutr.* (2016) 104:1245–52. doi: 10.3945/ajcn.116.142422
7. Borch D, Juul-Hindsgaul N, Veller M, Astrup A, Jaskolowski J, Raben A. Potatoes and risk of obesity, type 2 diabetes, and cardiovascular disease in apparently healthy adults: a systematic review of clinical intervention and observational studies. *Am J Clin Nutr.* (2016) 104:489–98. doi: 10.3945/ajcn.116.132332
8. Darooghegi Mofrad M, Milajerdi A, Sheikhi A, Azadbakht L. Potato consumption and risk of all cause, cancer and cardiovascular mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Crit Rev Food Sci Nutr.* (2019) 60:1–14. doi: 10.1080/10408398.2018.1557102
9. Schwingshackl L, Schwedhelm C, Hoffmann G, Boeing H. Potatoes and risk of chronic disease: a systematic review and dose-response meta-analysis. *Eur J Nutr.* (2019) 58:2243–51. doi: 10.1007/s00394-018-1774-2
10. Veronese N, Stubbs B, Noale M, Solmi M, Vaona A, Demurtas J, et al. Fried potato consumption is associated with elevated mortality: an 8-y longitudinal cohort study. *Am J Clin Nutr.* (2017) 106:162–7. doi: 10.3945/ajcn.117.154872
11. Pietinen P, Rimm EB, Korhonen P, Hartman AM, Willett WC, Albanes D, et al. Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation.* (1996) 94:2720–7. doi: 10.1161/01.CIR.94.11.2720
12. Mazidi M, Katsiki N, Mikhailidis DP, Pella D, Banach M. Potato consumption is associated with total and cause-specific mortality: a population-based cohort study and pooling of prospective studies with 98,569 participants. *Arch Med Sci.* (2020) 16:260–72. doi: 10.5114/aoms.2020.92890
13. Moholdt T, Devlin BL, Nilsen TIL. Intake of boiled potato in relation to cardiovascular disease risk factors in a large norwegian cohort: the HUNT study. *Nutrients.* (2019) 12:73. doi: 10.3390/nu12010073
14. Huang M, Zhuang P, Jiao J, Wang J, Chen X, Zhang Y. Potato consumption is prospectively associated with risk of hypertension: an 11.3-year longitudinal cohort study. *Clin Nutr.* (2019) 38:1936–44. doi: 10.1016/j.clnu.2018.06.973
15. Chen X, Jiao J, Zhuang P, Wu F, Mao L, Zhang Y, et al. Current intake levels of potatoes and all-cause mortality in China: a population-based nationwide study. *Nutrition.* (2021) 81:110902. doi: 10.1016/j.nut.2020.110902
16. Mottram DS, Wedzicha BL, Dodson AT. Acrylamide is formed in the Maillard reaction. *Nature.* (2002) 419:448–9. doi: 10.1038/419448a
17. Soh NL, Brand-Miller J. The glycaemic index of potatoes: the effect of variety, cooking method and maturity. *Eur J Clin Nutr.* (1999) 53:249–54. doi: 10.1038/sj.ejcn.1600713

18. Leeman M, Ostman E, Björck I. Glycaemic and satiating properties of potato products. *Eur J Clin Nutr.* (2008) 62:87–95. doi: 10.1038/sj.ejcn.1602677
19. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA.* (2002) 287:2414–23. doi: 10.1001/jama.287.18.2414
20. Ludwig DS. Dietary glycemic index and obesity. *J Nutr.* (2000) 130(2S Suppl.):280S−3S. doi: 10.1093/jn/130.2.280S
21. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care.* (1999) 22:233–40. doi: 10.2337/diacare.22.2.233
22. Kim JS, Nam K, Chung SJ. Effect of nutrient composition in a mixed meal on the postprandial glycemic response in healthy people: a preliminary study. *Nutr Res Pract.* (2019) 13:126–33. doi: 10.4162/nrp.2019.13.2.126

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Relationships Between Food Groups and Eating Time Slots According to Diabetes Status in Adults From the UK National Diet and Nutrition Survey (2008–2017)

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Time of eating is associated with diabetes and obesity but little is known about less healthy foods and specific time of their intake over the 24 h of the day. In this study, we aimed to identify potential relationships between foods and their eating time and to see whether these associations may vary by diabetes status. The National Diet and Nutrition Survey (NDNS) including 6,802 adults (age $\geq$ 19 years old) collected 749,026 food recordings by a 4-day-diary. The contingency table cross-classifying 60 food groups with 7 pre-defined eating time slots (6–9 a.m., 9 a.m.–12 p.m., 12–2 p.m., 2–5 p.m., 8–10 p.m., 10 p.m.–6 a.m.) was analyzed by Correspondence Analysis (CA). CA biplots were generated for all adults and separately by diabetes status (self-reported, pre-diabetes, undiagnosed-diabetes, and non-diabetics) to visually explore the associations between food groups and time of eating across diabetes strata. For selected food groups, odds ratios (OR, 99% CI) were derived of consuming unhealthy foods at evening/night (8 p.m.–6 a.m.) vs. earlier time in the day, by logistic regression models with generalized estimating equations. The biplots suggested positive associations between evening/night and consumption of puddings, regular soft drinks, sugar confectioneries, chocolates, beers, ice cream, biscuits, and crisps for all adults in the UK. The OR (99% CIs) of consuming these foods at evening/night were, respectively, 1.43 (1.06, 1.94), 1.72 (1.44, 2.05), 1.84 (1.31, 2.59), 3.08 (2.62, 3.62), 7.26 (5.91, 8.92), 2.45 (1.84, 3.25), 1.90 (1.68, 2.16), and 1.49 (1.22, 1.82) vs. earlier time in the day adjusted for age, sex, body mass index (BMI), and social-economic levels. Stratified biplots found that sweetened beverages, sugar-confectioneries appeared more strongly associated with evening/night among undiagnosed diabetics. Foods consumed in the evening/night time tend to be highly processed, easily accessible, and rich in added sugar or saturated fat. Individuals with undiagnosed diabetes are more likely to consume unhealthy foods at night. Further longitudinal studies are required to ascertain the causal direction of the association between late-eating and diabetes status.

Keywords: chrononutrition, time of eating, the UK national diet and nutrition survey, nutrition epidemiology, correspondence analysis, diabetes

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INTRODUCTION

The timing of energy intake is associated with obesity and diabetes (1). Specifically, eating late at night or having a late dinner was found to be related to a higher risk of obesity (2, 3), hyperglycemia (4), metabolic syndrome (5), diabetes (6), and poorer glycemic control among diabetics (7). However, the relationship between food choice and the time of food consumption during the day is left largely unknown. Shift workers have an increased risk of obesity (8, 9) and diabetes (10), possibly due to the limited availability of healthy food choices during their night shifts (8, 11). Previous survey data from the UK National Diet and Nutrition Survey Rolling Programme (NDNS RP) found that overall, 3.4% of men and 2.3% of women aged 19–64 had fasting glucose concentrations above the clinical cut-off for diabetes ($\geqslant$ 7 mmol/L). In addition, the proportion of men with undiagnosed diabetes increased with age to over 20% in the UK population (12). Identifying those unhealthy foods that might be chosen during late-night time would be helpful when guiding people to change their eating habits for either weight loss or glycemic control. Dietary diary recordings from NDNS RP surveys can provide detailed food choice data for exploration of the relationships between food groups and their time of consumption in the general population.

In this study, we aimed to describe the relationship between food groups and the time of day when they were consumed, and how such relationships may vary by the status of type 2 diabetes using the data published by the NDNS RP from 2008 to 2017 as this survey includes diet diaries providing detailed information on the time of day of food intake.

METHODS

6,802 adults (2,810 men and 3,992 women) and 749,026 food recordings collected by the NDNS RP 2008-17 were analyzed in the current study (13). The survey comprised a cross-section representative sample of the UK adult population taken over the period 2008-2017. The sample was randomly drawn from a list of all addresses in the UK, clustered into postcode sectors. Details of the rationale, designs, and methods of the survey can be found in the previously published official study reports (14, 15). The NDNS-RP, funded by Public Health England and the UK Food Standards Agency, is registered with the ISRTCN registry in study ID ISRCTN17261407 and received ethical approval from the Oxfordshire Research Ethics Committee.

A 4-day food diary method was used in the NDNS RP to collect the detailed food items and their time of consumption from participants. Comparison between the food diary method and a repeated 24-h recall questionnaire was performed in a subset of the study sample prior to the launch of the NDNS RP in 2008 and found that they were similar in terms of response rate as well as the ability to collect correct nutrition intake data. The 4-day food diary method was adopted because it is considered to be more flexible and adaptable to cover a wide population age range in the survey. More details can be found in the Appendix A of the official NDNS RP study report (14, 15). Furthermore, the same food diary methods are actually used in large studies conducted in the UK, such as the Medical Research Council (MRC) National Survey of Health and Development (NSHD) (1946 British Birth Cohort) (16), the EPIC Norfolk Study (17), the UK Women's Cohort Study in Leeds (18), and the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (19). Another validation study of the food records against double-labeled water had also been undertaken among a subset of NDNS participants. Full results of the analysis have been reported in Appendix X of the official survey report (20).

In the food diary recordings, time of the day was categorized into 7 slots: 6–9 a.m., 9–12 noon, 12–2 p.m., 2–5 p.m., 5–8 p.m., 8–10 p.m., and 10 p.m.–6 a.m. Foods recorded were classified into 60 standard food groups with 1 to 10 subgroups each: the details are given in Appendix R of the NDNS official report (21). We focused on the 60 standard food groups in the current analysis. Diabetes status was defined as: (1) healthy if fasting glucose was lower than 6.10 (mmol/L), hemoglobin A1c (HbA1c) was less than 6.5 (%), and without self-reported diabetes or treatment for diabetes (n = 2,626); (2) pre-diabetic if fasting glucose was between 6.10 and 6.99 (mmol/L, inclusive) but without self-reported diabetes and without treatment for diabetes (n = 133); (3) undiagnosed diabetic if either fasting glucose was higher or equal to 7.00 (mmol/L) or HbA1c higher or equal to 6.5 (%) but without self-reported diabetes and treatment for diabetes (n = 99); (4) diabetic if the participant had self-reported diabetes or was under treatment for diabetes (n = 227). There was also a large number of adults (3,717 adults of whom 1,519 men and 2,198 women) whose diabetes status could not be confirmed due incomplete variable information; these were retained in the whole sample (unstratified) analyses. In addition, the National Statistics Socio-economic Classification (22) was applied in the survey and, accordingly, the socio-economic status of participants was classified in one of 8 categories.

Correspondence analysis (CA) (23–25) was used as a tool for data mining, visualization, and hypotheses generation using half of the randomly selected NDNS diary entries data. Specifically, the contingency table was generated by cross-tabulating 60 food groups and 7 time slots. Through CA, the 60 categories of standard foods and the 7-time slots were projected on biplots, i.e., onto two-dimensional plots that could jointly display large percentage of the Chi-Square deviation (or inertia) of the contingency table. Biplots that graphically show the association between time of day and food groups were derived for all adults and separately according to their diabetes status.

CA is a statistical technique to explore relationships between categorical variables in a two-dimensional contingency table. In the current analysis context, CA was used as a tool to visually depict the relationship between food groups and time of consumption. CA allowed us to identify whether food groups have a similar or different "profile" across time categories or, symmetrically, whether times of day have a similar or different "profile" across food groups. In particular, "profile" indicates the relative frequency of the consumption of one food across different times in the day (or, symmetrically, the relative frequency of consumption of different foods at one specific time slot) and what CA measures is its departure from the average food (or time of day) profile. One simple example is that if

TABLE 1 | The top 37 food groups which contributed up to 90% of the total calories by UK adults (NDNS RP 2008–2017) were sorted by decreasing cumulative percentage of calories.

Food group names	n	Calories	Relative prop (%)	Cal prop (%)	Cal cum prop (%)
Pasta & rice and other cereals	18,353	3512069.99	2.45	7.36	7.36
White bread	18,434	3245641.19	2.46	6.80	14.17
Chips, fried and roast potatoes and potato products	6,749	1884058.68	0.90	3.95	18.12
Cakes, buns, sweet pastries, fruit pies	7,806	1710594.27	1.04	3.59	21.70
Vegetable (not raw)	51,317	1665474.02	6.85	3.49	25.19
Biscuits	13,200	1662598.06	1.76	3.49	28.68
Fruit	33,903	1641675.02	4.53	3.44	32.12
Miscellaneous unclassified foods	48,597	1639024.81	6.49	3.44	35.56
Chicken/turkey	8,863	1617820.30	1.18	3.39	38.95
Cheese	10,983	1492015.32	1.47	3.13	42.07
Beer lager	8,199	1484001.20	1.09	3.11	45.19
Semi-skimmed milk	57,611	1302649.72	7.69	2.73	47.92
Potatos other (in salads and dishes)	10,113	1291447.61	1.35	2.71	50.62
Fat spreads	37,960	1215278.60	5.07	2.55	53.17
Beef	4,987	1124560.42	0.67	2.36	55.53
High fiber breakfast cereals	8,215	1072813.73	1.10	2.25	57.78
Whole meal bread	7,193	1070695.89	0.96	2.24	60.02
Chocolate	6,495	1046112.65	0.87	2.19	62.22
Wine	6,967	1027792.96	0.93	2.15	64.37
Brown, granary and wheatgerm bread	6,183	1009074.95	0.83	2.12	66.48
Butter	10,203	965901.11	1.36	2.02	68.51
Eggs	7,554	964769.19	1.01	2.02	70.53
Soft drinks not diet	11,387	940516.516	1.52	1.97	72.50
Reduced fat spreads	12,620	848834.89	1.68	1.78	74.28
Crisps and savory snacks	5,664	835671.58	0.76	1.75	76.04
Sausages	3,025	775004.13	0.40	1.62	77.66
Meat pastries	1,979	744639.89	0.26	1.56	79.22
Bacon and ham	8,467	738727.49	1.13	1.55	80.77
Yogurt	6,776	665484.55	0.90	1.40	82.16
Low-fiber breakfast cereals	4,303	560296.32	0.57	1.17	83.34
Nuts and seeds	6,259	559873.88	0.84	1.17	84.51
Oily fish	2,610	550425.36	0.35	1.15	85.67
Whole milk	13,628	530449.07	1.82	1.11	86.78
White fish, shellfish	1,597	498928.82	0.21	1.05	87.82
Puddings	2,291	459784.62	0.31	0.96	88.79
Other milk cream	6,605	434239.37	0.88	0.91	89.70
Pork	1,832	420503.76	0.24	0.88	90.58

NDNS RP, National Diet and Nutrition Survey Rolling Programme.
Prop: proportion; Cal Prop: calorie proportion; Cal Cum Prop: Calorie cumulative proportion.

about 77.8% of all foods were consumed during the daytime (earlier than 8 pm), but only 23.5% of beer consumption were recorded during the daytime, then we say beer has a "profile" different from the average food profile with respect to time of day of consumption and, in particular, beer is associated to evening/night consumption. CA can produce biplots to visually show the χ^2 deviation of food (and time) profiles from the average profile which is called "inertia." These biplots use the first two most informative dimensions to display the inertia of the contingency table. The horizontal axis of the biplot represents the direction along which the contingency table rows and columns show their greatest deviations from the average row or column profile. The vertical axis represents the direction, perpendicular to the first, having the second-largest deviations. There are two percentage labels for each axis, indicating how much of the total inertia were explained along that axis. The sum of the two percentages is lower than 100%, the remaining inertia cannot be shown when reducing to two-dimensions if there are more than three foods or time-slots. The origin in each biplot is the average profile of all points in the plot, while the length of the vector from the origin to each profile point represents its deviation from the average profile. The distance between row (food) and column (time slots) profile points and the direction in which they lie away from the origin is indicating how they are associated with each other. The potential association is greater if (1) points are located in similar directions away from the origin and (2) the farther they are from the origin.

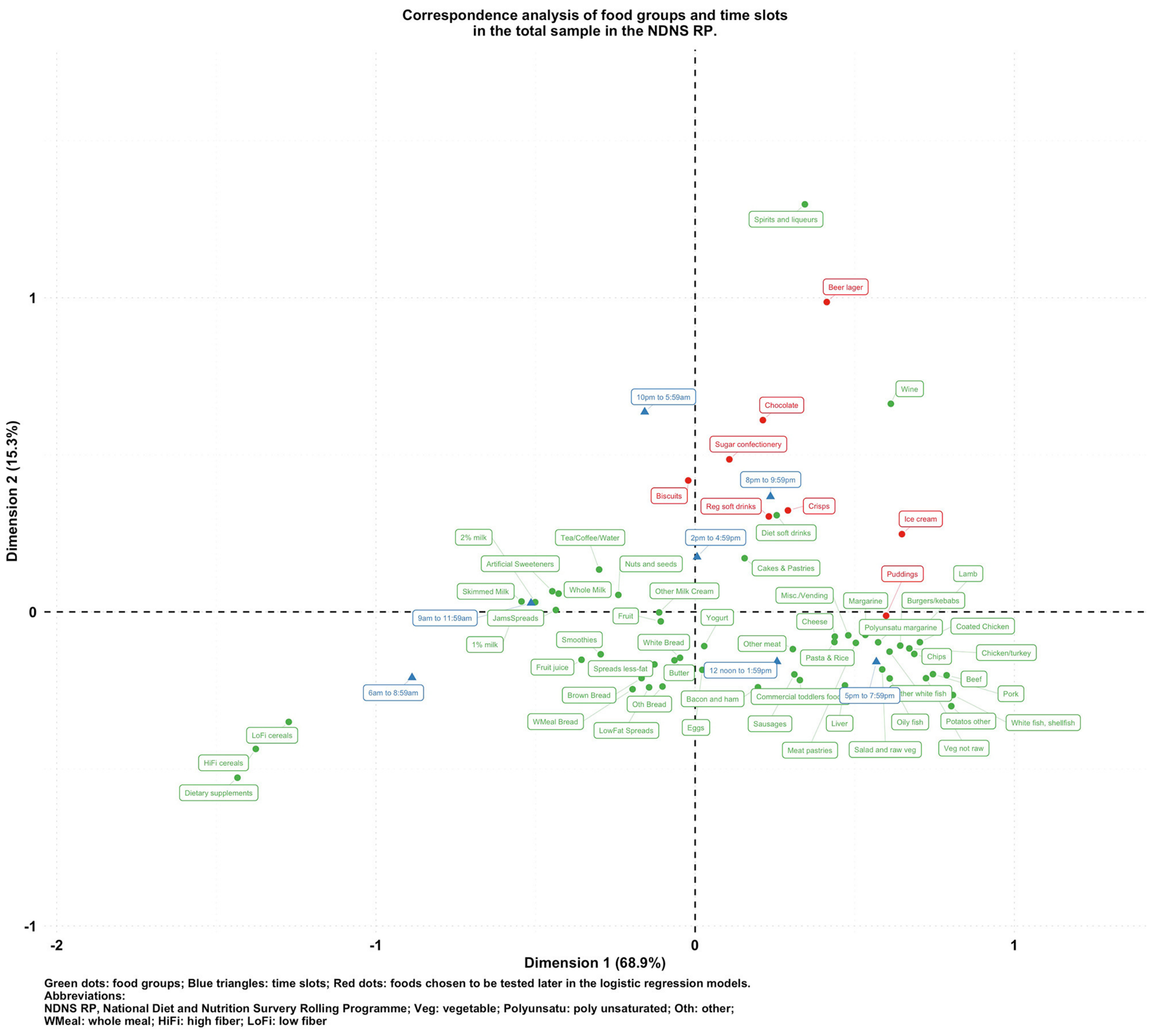

FIGURE 1 | Biplot of food groups and eating time slots in the total sample in the NDNS RP.

To account for the hierarchical structure of the data (food recorded by the same individuals who lived within the same area/sampling units) and to calculate population average odds ratios (OR), logistic regression models with generalized estimating equations (GEE) were subsequently used to test the associations that were first suggested by visual inspection of biplots generated by CA, using the remaining half of the diary entries data. The marginal ORs and their 99% CI were derived of consuming unhealthy food groups (selected by CA) later in the day (8 p.m.–6 a.m., i.e., in the evening and night) compared with earlier in the day (in the morning or afternoon). In the fixed effect of the logistic regression models, 2-time slots and 4 diabetes statuses were entered with interaction terms. This was done to assist performing post fitting estimations of OR for each diabetes status using the same model and avoid running more models on smaller datasets with less statistical power as well as the risk of multiple testing. CA and biplots were conducted and generated by the following packages under R environment (26): `FactoMineR`, `factoextra`, `ggplot2`, and `ggrepel` (27–30). Logistic regression models with GEE were performed with SAS procedure `GENMOD` (31) adjusted for age, sex, body mass index (BMI) and socio-economic levels, which were deemed the main potential confounders of the associations.

RESULTS

The dataset consisted of 2,810 (41.3%) men and 3,992 (58.7%) women aged older than or equal to 19-year-old with a mean age of 49.9 years ($SD = 17.6$). Of these individuals, 22.6% were current smokers, and 24.3% were past smokers. The average BMI was 27.7 kg/m^2 ($SD = 5.41$). Among the food recordings

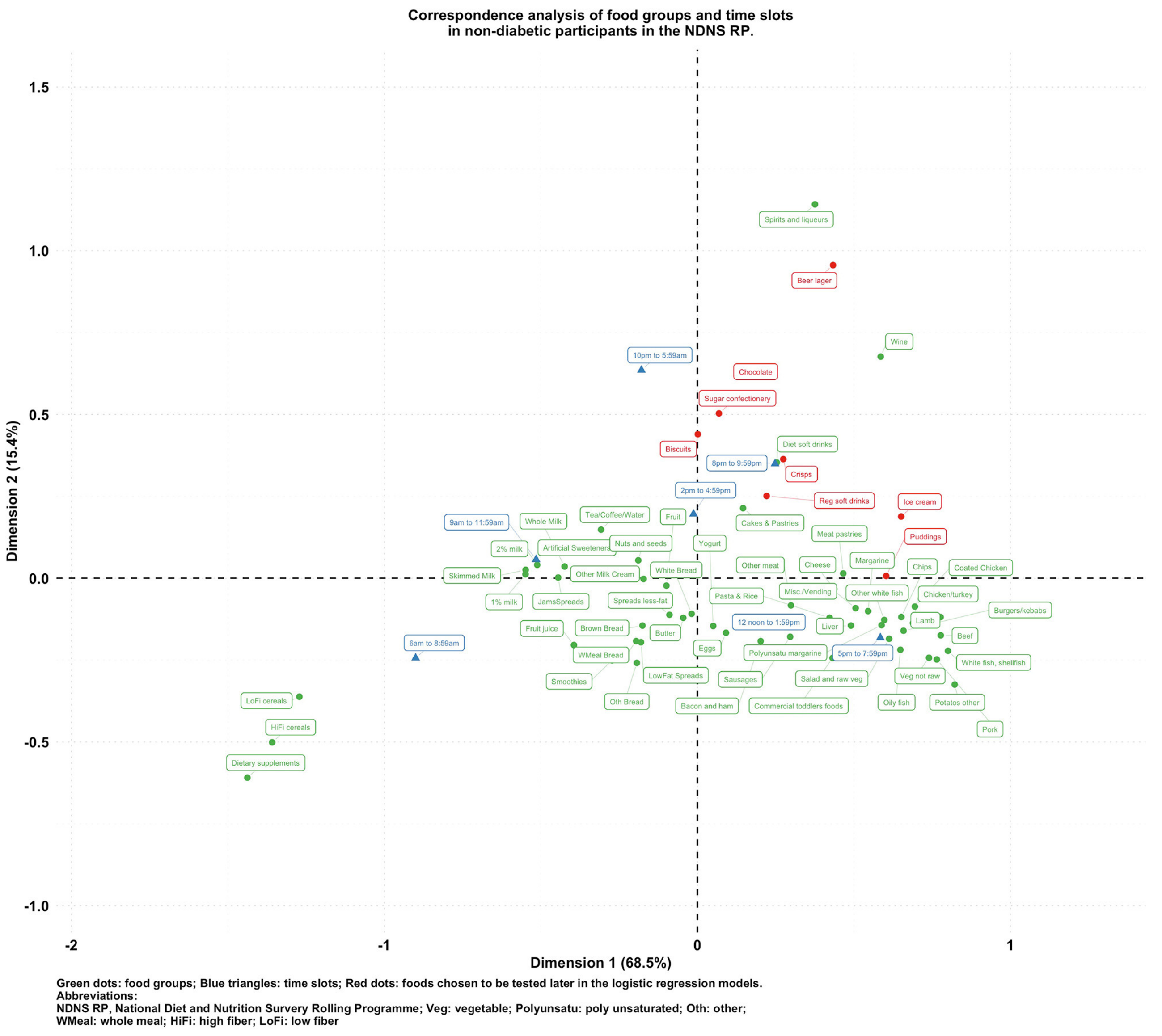

FIGURE 2 | Biplot of food groups and eating time slots in non-diabetic participants in the NDNS RP.

collected (n = 749,026), 56.9% were recorded during traditional breakfast (6 a.m.–9 a.m.: 14.3%), lunch (12 noon–2 p.m.: 18.5%), or dinner (5 p.m.–8 p.m.: 24.1%) time slots, more details can be found in **Supplementary Table 1**. **Table 1** shows the top 37 food groups that contributed to 90% of the total calories consumed by adults in NDNS RP. These food groups accounted for 478,028 of the total diary entries (63.8 %). The random process split the whole set of food recordings into a hypotheses generating dataset of 374,682 and a testing dataset of 374,344 entries.

Figures 1–5 present the CA biplots that visually summarize the associations between 60 food groups and the time of their consumption in the entire sample and then stratifying by their diabetes status. In **Figure 1**, the horizontal axis explains 68.9% of the association structure (inertia) between foods and time slots while the vertical axis reflects 15.3% of the same relationship. Therefore, a total of 84.2% of the inertia between foods and time slots was captured in this figure which shows a visual summary of how those two categorical variables are related. Specifically, time slots later than 8 p.m. are shown in the upper side of the plot closer to alcoholic products or highly processed/energy-dense foods (sugar confectioneries, chocolates, biscuits, regular soft drinks, ice cream, crisps); times earlier than noon appear in the left-hand side together with typical breakfast foods (cereals, milk, bread, etc.).

To visualize the potentially different associational patterns between food groups and time slots according to diabetes status, **Figures 2–5** display the CA biplots in subsets of the data. Depending on diabetes status, these biplots explained between

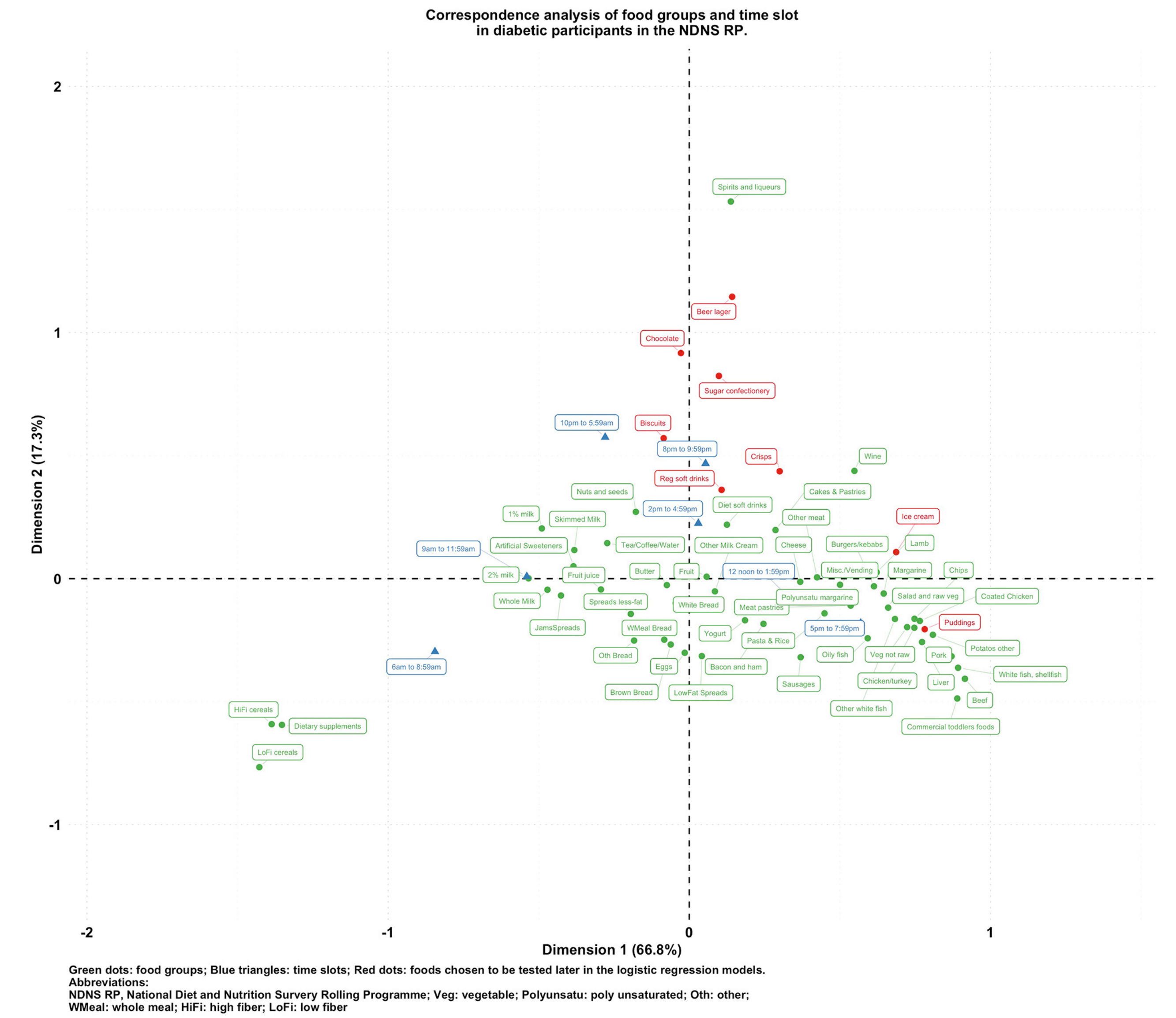

FIGURE 3 | Biplot of food groups and eating time slots in diabetic participants in the NDNS RP.

76.3 and 84.1% of the inertia in the data. Similar to the biplot created from the total sample (**Figure 1**), later times in the day (8 p.m. and later) are shown in the upper side of each figure and suggested an association with alcoholic beverages and highly processed or energy-dense food groups. Additionally, some food group/time slot associations appeared to vary according to diabetes status. For example, puddings seemed to be closer to a later time in the day among undiagnosed diabetics (**Figure 4**), while for diagnosed diabetic patients (**Figure 3**), they were closer to traditional dinner time (5 p.m.–8 p.m.) or earlier in the day. Furthermore, sugar confectioneries/chocolates/biscuits/regular soft drinks appeared to be associated with later times in the day (8 p.m. or later) more strongly among undiagnosed diabetics (**Figure 4**) than in other subgroups.

Based on the findings suggested from **Figures 1–5**, we decided to focus on puddings, regular soft drinks, confectioneries, chocolates, beers, ice cream, biscuits, and crisps as these foods either showed a particularly strong association with time of the day or a different pattern of association across different strata of the survey sample; hence, we tested the following null hypotheses using logistic regression models (adjusted for age, sex, BMI, and socio-economic levels) with GEE: that the odds of consuming each selected food at a later time of the day (8 p.m.–6 a.m.) is the same compared to an earlier time in the day; and the associations of the above-mentioned food groups and time slots are the same among participants with different diabetes status (i.e., no interaction between the time of food intake and diabetes status). The results are summarized in **Table 2**.

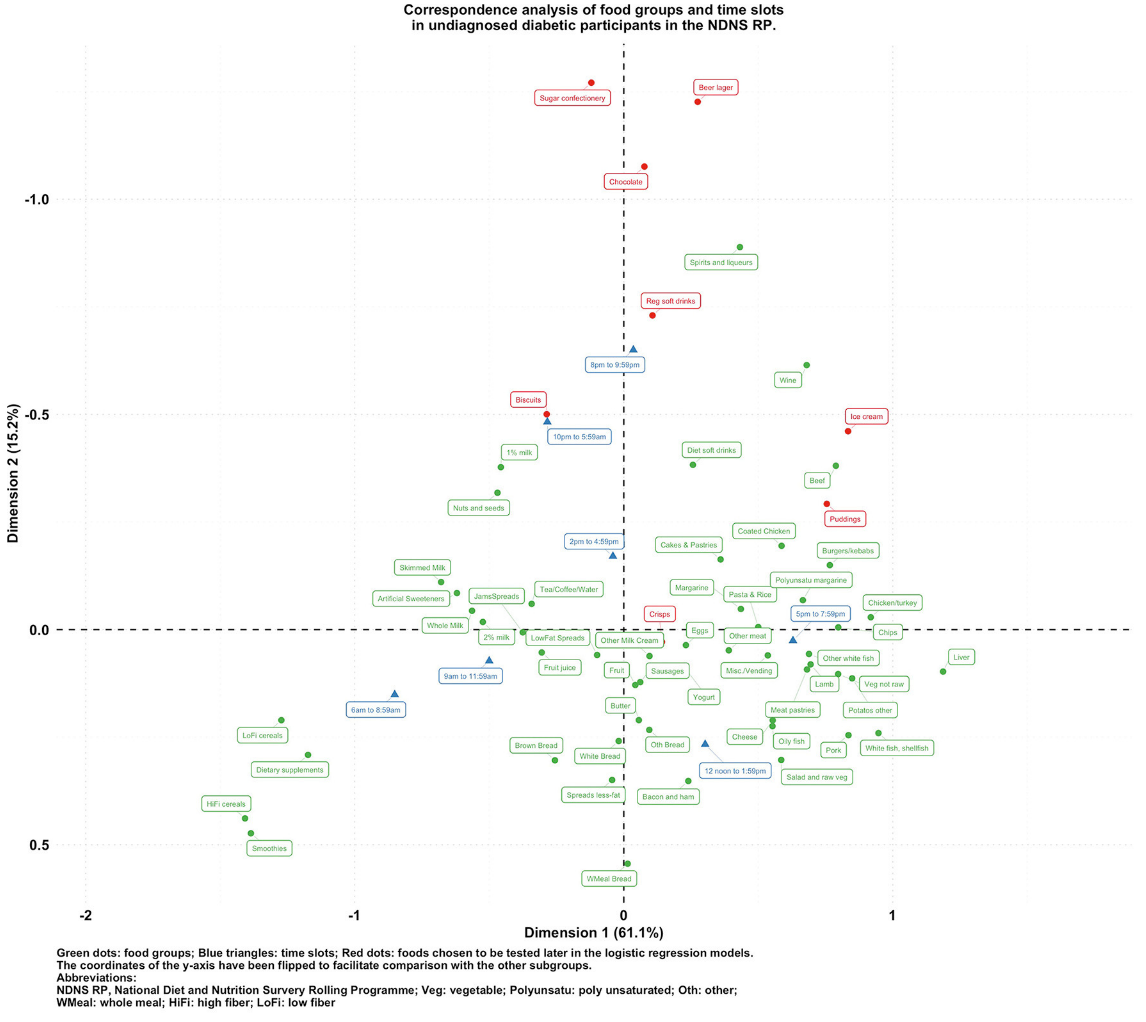

FIGURE 4 | Biplot of food groups and eating time slots in undiagnosed diabetic participants in the NDNS RP.

The listed food groups were found to have higher odds to be consumed between 8 p.m. and 6 a.m. than earlier in the day. The main effect ORs (99% CIs) of consuming these foods in the evening/night were the following: for puddings 1.43 (1.06, 1.94), for regular soft drinks 1.72 (1.44, 2.05), for sugar confectioneries 1.84 (1.38, 2.69), for chocolates 3.08 (2.62, 3.62), for beers 7.26 (5.91, 8.92), for ice cream 2.45 (1.84, 3.25), for biscuits 1.90 (1.68, 2.16), for crisps 1.49 (1.22, 1.82) vs. earlier time. Opposite directions of the association for puddings were detected across diabetes status: the ORs (99% CIs) of consuming puddings at night time (8 p.m. or later) compared with earlier time were 1.55 (1.13, 2.15), 0.95 (0.17, 5.20), 1.82 (0.41, 8.03), and 0.63 (0.15, 2.66) for healthy, prediabetic, undiagnosed diabetic, and diabetic participants, respectively. Furthermore, undiagnosed diabetic patients were found to have particularly high odds of consuming regular soft drinks (OR: 2.82; 99% CI: 1.24, 6.43), and sugar confectioneries (OR: 10.61; 99%CI: 2.35, 47.04) during night-time in comparison with participants with other diabetes status. The same models were also used to estimate the ORs of consuming the selected food groups comparing participants with different diabetes status during either daytime (earlier than 8 p.m.) or nighttime (between 8 p.m. and 6 a.m.). Results are given in **Supplementary Table 2**.

DISCUSSION

The present study described the potential relationships between food groups and time of their consumption in a representative sample from the NDNS RP. Many unhealthy foods that emerged from CA were found to be more likely to be consumed after 8 p.m. These included alcoholic/sweetened beverages, chocolates, and other foods rich in added sugars and saturated fats, such as biscuits and ice cream. Foods chosen in the evening/night time slots tend to be highly processed and easily accessible. Specifically, undiagnosed patients might be at a higher risk of worsening their condition as they were found to have higher odds of consuming less healthy foods after 8 p.m. (sugar confectioneries, regular soft drinks) in comparison with diabetics

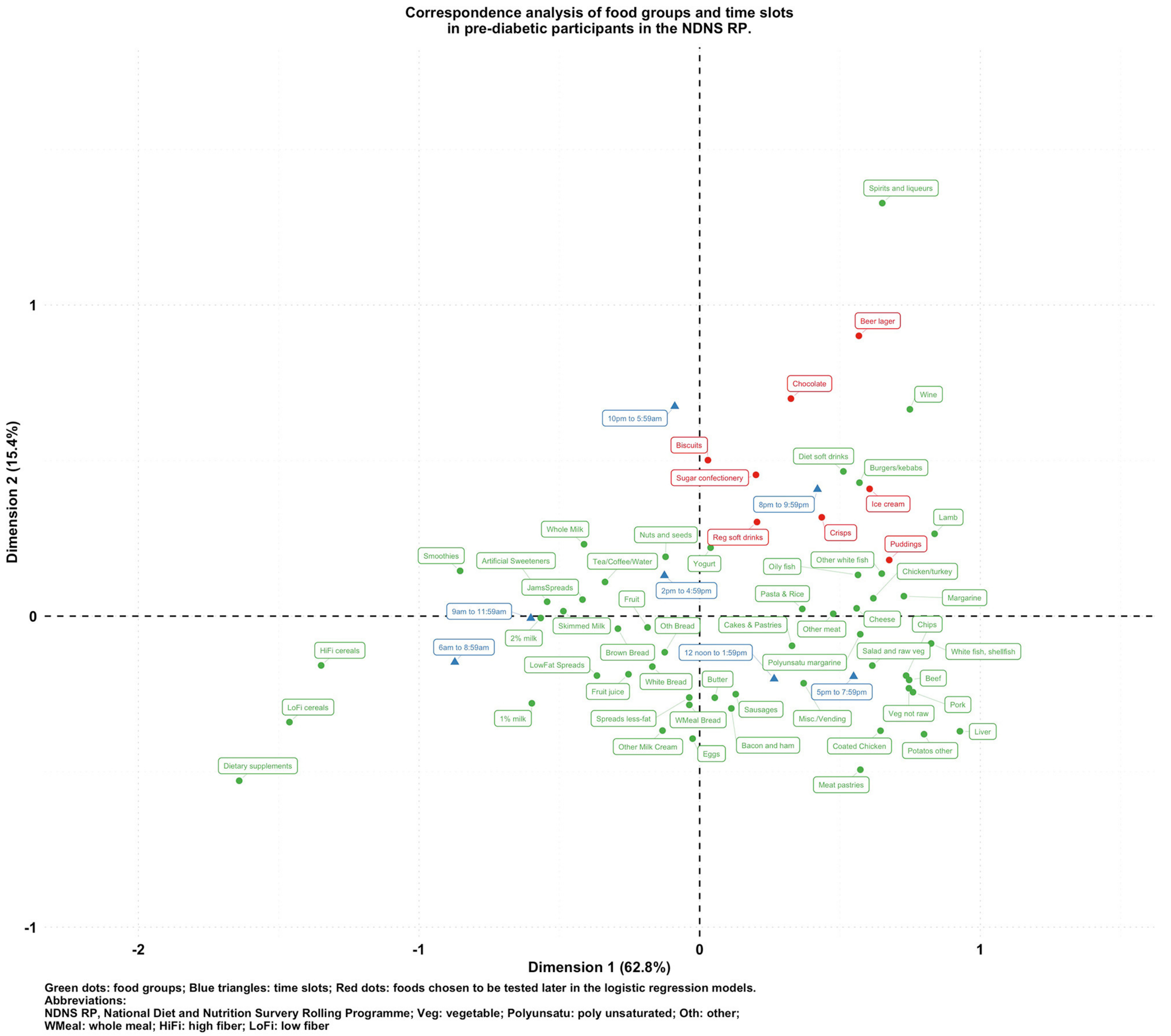

FIGURE 5 | Biplot of food groups and eating time slots in pre-diabetic participants in the NDNS RP.

and non-diabetics. Those foods might need to be targeted when designing an intervention for those who might be at risk of being diabetics.

These findings are concerning considering previous research has indicated that the quality of macronutrient intake in the evening is likely to influence fasting glucose levels and glycemic response to subsequent meals in the morning (32). One prospective study reported women who ate later than 9 p.m. had 1.51 times (95% CI 1.16 to 1.93) higher 5-year risk of developing prediabetes/diabetes than those having their last eating episode between 4 and 9 p.m. (33). More recently, a randomized controlled trial indicated that consuming carbohydrates at dinner irrespective of glycemic index raised postprandial glucose response to breakfast producing what is known as a second meal effect (34). Similar observations have been made by Nitta et al. who observed that eating sweets or snacks post-dinner worsened glycemic excursions in the evening and at subsequent breakfast (35). Added to this is evidence that suggests that the late-night dinners induce post prandial hyperglycemia in patients with type 2 diabetes and that interventions at these eating occasions can result in a profound impact on post-prandial glycemia. On the balance of this evidence, targeting and improving the timing and quality of foods in evening eating occasions provides a unique opportunity to design intervention for those who might be at risk of being diabetics.

A compelling finding of our study is the observation that diabetes patients were found to be potentially controlling their choice of food groups such as avoiding puddings at

TABLE 2 | Odds ratio (99% CI) for food groups eaten at night (8 p.m. - 6 a.m.) vs. earlier time in the day, in the overall sample and according to different diabetes status, NDNS RP 2008-2017.

Selected food groups	Overall	Healthy	Pre-diabetics	Undiagnosed diabetics	Diabetics
Pudding	1.43 (1.06, 1.94)	1.55 (1.13, 2.15)	0.95 (0.17, 5.20)	1.82 (0.41, 8.03)	0.63 (0.15, 2.66)
Regular soft drink	1.72 (1.44, 2.05)	1.70 (1.41, 2.05)	1.78 (0.90, 3.48)	2.82 (1.24, 6.43)	1.36 (0.59, 3.10)
Sugar confectionery	1.84 (1.31, 2.59)	1.55 (1.08, 2.23)	2.13 (0.34, 13.24)	10.51 (2.35, 47.04)	5.94 (1.86, 19.00)
Chocolate	3.08 (2.62, 3.62)	2.98 (2.51, 3.54)	4.06 (1.98, 8.31)	2.41 (0.88, 6.60)	4.92 (2.38, 10.20)
Beer	7.26 (5.91, 8.92)	7.55 (6.04, 9.43)	4.42 (2.19, 8.95)	8.29 (3.70, 18.56)	5.82 (2.03, 16.68)
Ice cream	2.45 (1.84, 3.25)	2.52 (1.86, 3.41)	3.39 (0.77, 14.89)	1.07 (0.15, 7.77)	1.74 (0.57, 5.32)
Biscuit	1.90 (1.68, 2.16)	1.78 (1.55, 2.05)	3.25 (1.99, 5.28)	2.96 (1.43, 6.10)	2.33 (1.45, 3.77)
Crisp	1.49 (1.22, 1.82)	1.49 (1.21, 1.85)	2.21 (0.90. 5.41)	1.59 (0.43, 5.95)	0.89 (0.34, 2.33)

Logistic regression models with GEE were adjusted for age, sex, body mass index, and social-economic levels.
NDNS RP: National Diet and Nutrition Survey Rolling Programme.

night. However, higher odds of consuming alcoholic beverages and energy condensed foods, such as chocolates and sugar confectioneries, at night among individuals with diabetes suggest that their food choice might need further modifications. Food intake late in the night is in misalignment with the circadian rhythm of the insulin response, which may cause greater glycemic exposure and elevated HbA1c levels even for healthy individuals (33). Disrupted timing of food intake, overeating in the evening, unhealthy food chosen at a later time in the day can result in poor glucose control and increase the likelihood of diabetic complications (4, 36–38). Assessing the relationships between food groups and timing of eating by diabetes status can be considered as a first step toward identifying specific public health targets for behavior change/intervention. This is important as most current public health strategies and dietary recommendations do not provide targeted advice that takes into consideration specific eating occasions while targeted advice is more likely to result in sustainable behavioral change. Our findings are consistent with previous evidence that has found that both sweetened and alcoholic beverages are responsible for a large portion of energy consumption at night in other populations (39).

However, an important limitation in this study is the cross-sectional study design. Our findings do not indicate whether it would be better for individual health to consume unhealthy foods later or earlier in the day, which should be clarified through purposedly designed intervention studies in the future. Some of the findings, such as higher consumption of alcoholic beverages at night are already known. However, the facts that certain snacks were more likely to be consumed at night and even more frequently among undiagnosed diabetics are an important piece of public health evidence as these data are representative of national behavior across the UK. Furthermore, the inability to assess the temporal relationship between timing of food intake and diabetes status means that a cause-effect relationship between the time of unhealthy food intake and diabetes status cannot be established. Hence, further prospective studies are warranted to investigate the causal relationship between diabetes and both quality and timing of eating. In addition, the current study assumes that mis-reporting occurred equally amongst all eating occasions. This limitation has been reported by previous literature as an important methodological limitation of chrononutrition (40); indeed, further investigation would be warranted to assess the effect of differential misreporting on epidemiological studies in chrononutrition to suggest possible corrections, e.g., for differential under-reporting at different times of the day (e.g., main meals vs. snack times). Finally, we did not include variables indicating abdominal obesity and sedentary lifestyle, such as physical activity or waist circumference in the second step of the current analysis mainly due to missingness of the variables. The associations comparing food consumed later vs. earlier in the day presented in this study may be partly explained or mediated through a low level of physical activity and/or abdominal obesity especially among those who were unaware that they have diabetes: further investigations to assess the role of these variables in chrononutrition are also warranted.

CONCLUSION

In summary, our study indicates that foods consumed in the evening/night time tend to be highly processed, easily accessible, and rich in added sugar or saturated fat, whatever the diabetic status is. Individuals with undiagnosed diabetes are more likely to consume specific unhealthy foods at night. The survey cross-sectional nature warrants further investigations by longitudinal cohort studies to establish the causal relationship between the time of eating unhealthy foods and diabetes.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. Original data used in this study can be accessed upon request to the UK Data Service (https://www.ukdataservice.ac.uk) for academic usage (Study Number: 6533).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the NDNS RP, funded by Public Health England and the UK Food Standards Agency, is registered with the ISRTCN registry under study ID ISRCTN17261407 and received ethical approval from the Oxfordshire Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CW, SA, and LP designed research and had primary responsibility for final content. CW and LP performed statistical analysis. All authors wrote the manuscript, read, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Almoosawi S, Vingeliene S, Karagounis L, Pot G. Chrono-nutrition: a review of current evidence from observational studies on global trends in time-of-day of energy intake and its association with obesity. *Proc Nutr Soc.* (2016) 75:487–500. doi: 10.1017/S0029665116000306
2. Xiao Q, Garaulet M, Scheer FA. Meal timing and obesity: interactions with macronutrient intake and chronotype. *Int J Obesity.* (2019) 43:1701–11. doi: 10.1038/s41366-018-0284-x
3. Yoshida J, Eguchi E, Nagaoka K, Ito T, Ogino K. Association of night eating habits with metabolic syndrome and its components: a longitudinal study. *BMC Public Health.* (2018) 18:1366. doi: 10.1186/s12889-018-6262-3
4. Nakajima K, Suwa K. Association of hyperglycemia in a general Japanese population with late-night-dinner eating alone, but not breakfast skipping alone. *J Diabet Metab Disord.* (2015) 14:16. doi: 10.1186/s40200-015-0147-0
5. Kutsuma A, Nakajima K, Suwa K. Potential association between breakfast skipping and concomitant late-night-dinner eating with metabolic syndrome and proteinuria in the japanese population. *Scientifica.* (2014) 2014:253581. doi: 10.1155/2014/253581
6. Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, Malaisse WJ, et al. Meal frequency and timing in health and disease. *Proc. Natl. Acad. Sci. U.S.A.* (2014) 111:16647–53. doi: 10.1073/pnas.1413965111
7. Sakai R, Hashimoto Y, Ushigome E, Miki A, Okamura T, Matsugasumi M, et al. Late-night-dinner is associated with poor glycemic control in people with type 2 diabetes: the KAMOGAWA-DM cohort study. *Endocrine J.* (2018) 65:395–402. doi: 10.1507/endocrj.EJ17-0414
8. Balieiro LCT, Rossato LT, Waterhouse J, Paim SL, Mota MC, Crispim CA. Nutritional status and eating habits of bus drivers during the day and night. *Chronobiol int.* (2014) 31:1123–9. doi: 10.3109/07420528.2014.957299
9. Barbadoro P, Santarelli L, Croce N, Bracci M, Vincitorio D, Prospero E, et al. Rotating shift-work as an independent risk factor for overweight italian workers: a cross-sectional study. *PLoS ONE.* (2013) 8:e63289. doi: 10.1371/journal.pone.0063289
10. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med.* (2011) 8:e1001141. doi: 10.1371/journal.pmed.1001141
11. Bonnell EK, Huggins CE, Huggins CT, McCaffrey TA, Palermo C, Bonham MP. Influences on dietary choices during day versus night shift in shift workers: a mixed methods study. *Nutrients.* (2017) 9:193. doi: 10.3390/nu9030193
12. Almoosawi S, Cole D, Nicholson S, Bayes I, Teucher B, Bates B, et al. Biomarkers of diabetes risk in the national diet and nutrition survey rolling programme (2008–2011). *J Epidemiol Commun Health* (2014) 68:51–6. doi: 10.1136/jech-2013-202885
13. MRC Elsie Widdowson Laboratory, NatCen Social Research. *National Diet and Nutrition Survey Years 1-9, 2008/09-2016/17. [data collection]. 13th Edition*. UK Data Service. SN: 6533 (2019). doi: 10.5255/UKDA-SN-6533-18
14. Beverley B, Lennox A, Prentice A, Bates CJ, Page P, Nicholson S, et al. (editors). *National Diet and Nutrition Survey: Results from Years 1, 2, 3 and 4 (Combined) of the Rolling Programme (2008/2009-2011/2012): A Survey Carried out on Behalf of Public Health England and the Food Standards Agency*. Public Health England (PHE) (2014).
15. Roberts C, Steer T, Maplethorpe N, Cox L, Meadows S, Nicholson S, et al. (editors). *National Diet and Nutrition Survey: Results from Years 7 and 8 (Combined) of the Rolling Programme (2014/2015–2015/2016)*. Public Health England (PHE), Food Standards Agency (FSA) (2018).
16. Price G, Paul A, Cole T, Wadsworth MJ. Characteristics of the low-energy reporters in a longitudinal national dietary survey. *Br J Nutr.* (1997) 77:833–51. doi: 10.1079/bjn19970083
17. Bingham SA, Welch AA, McTaggart A, Mulligan AA, Runswick SA, Luben R, et al. Nutritional methods in the European prospective investigation of cancer in norfolk. *Public Health Nutr.* (2001) 4:847–58. doi: 10.1079/phn2000102
18. Cade JE, Burley VJ, Greenwood DC, Group UWCSS. The UK women's cohort study: comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr.* (2004) 7:871–8. doi: 10.1079/phn2004620
19. Glynn L, Emmett P, Rogers I, Team AS. Food and nutrient intakes of a population sample of 7-year-old children in the south-west of england in 1999/2000–what difference does gender make? *J. Hum. Nutr. Dietet.* (2005) 18:7–19. doi: 10.1111/j.1365-277X.2004.00582.x
20. Lennox A, Bluck L, Page P, Pell D, Cole D, Ziauddeen N, et al. Appendix X: *Misreporting in the National Diet and Nutrition Survey Rolling Programme (NDNS RP): Summary of Results and Their Interpretation*. (2014). Available online at: https://fsa-catalogue2.s3.eu-west-2.amazonaws.com/ndns-appendix-x.pdf
21. NatCen Social Research, MRC Elsie Widdowson Laboratory, University College London. *Medical School. National Diet and Nutrition Survey Years 1-8, 2008/09-2015/16. [data collection]. 9th Edition*. UK Data Service. SN: 6533 (2018). doi: 10.5255/UKDA-SN-6533-8
22. Rose D, Pevalin DJ. *The National Statistics Socio-economic Classification: Unifying Official and Sociological Approaches to the Conceptualisation and Measurement of Social Class*. Institute for Social and Economic Research (ISER) Working Papers. Paper No. 2001-4 Colchester: University of Essex (2001). Available online at: https://www.iser.essex.ac.uk/files/iser_working_papers/2001-04.pdf
23. Greenacre M. *Correspondence Analysis in Practice*. New York, NY: Chapman; Hall (2017).
24. Chapman AN, Beh EJ, Palla L. Application of correspondence analysis to graphically investigate associations between foods and eating locations. *Stud Health Technol Inform.* (2017) 235:166–70.
25. Palla L, Chapman A, Beh E, Pot G, Almiron-Roig E. Where do adolescents eat less-healthy foods? Correspondence analysis and logistic regression results from the UK national diet and nutrition survey. *Nutrients.* (2020) 12:2235. doi: 10.3390/nu12082235
26. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2019).
27. LS, Josse J, Husson F. FactoMineR: a package for multivariate analysis. *J Stat Softw.* (2008) 25:1–18. doi: 10.18637/jss.v025.i01
28. Kassambara A, Mundt F. *Factoextra: Extract and Visualize the Results of Multivariate Data Analyses* (2019). Available online at: https://CRAN.R-project.org/package=factoextra
29. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer-Verlag (2016).
30. Slowikowski K. *Ggrepel: Automatically Position Non-overlapping Text Labels With 'Ggplot2'* (2019). Available online at: https://CRAN.R-project.org/package=ggrepel

31. SAS Institute. *SAS 9.4 Language Reference: Concepts*. Cary, NC: SAS Institute Inc. (2013).
32. Wolever TM, Jenkins DJ, Ocana AM, Rao VA, Collier GR. Second-meal effect: low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. *Am J Clin Nutr*. (1988) 48:1041–7. doi: 10.1093/ajcn/48.4.1041
33. Faerch K, Quist JS, Hulman A, Witte D, Tabak A, Brunner E, et al. Prospective association between late evening food consumption and risk of prediabetes and diabetes: the whitehall II cohort study. *Diabet. Med.* (2019) 36:1256–60. doi: 10.1111/dme.13951
34. Haldar S, Egli L, De Castro CA, Tay SL, Koh MXN, Darimont C, et al. High or low glycemic index (GI) meals at dinner results in greater postprandial glycemia compared with breakfast: a randomized controlled trial. *BMJ Open Diabetes Res. care* (2020) 8:e001099. doi: 10.1136/bmjdrc-2019-001099
35. Nitta A, Imai S, Kajiyama S, Miyawaki T, Matsumoto S, Ozasa N, et al. Impact of different timing of consuming sweet snack on postprandial glucose excursions in healthy women. *Diabet Metab.* (2019) 45:369–74. doi: 10.1016/j.diabet.2018.10.004
36. Sato M, Nakamura K, Ogata H, Miyashita A, Nagasaka S, Omi N, et al. Acute effect of late evening meal on diurnal variation of blood glucose and energy metabolism. *Obesity Res Clin Pract.* (2011) 5:e220–8. doi: 10.1016/j.orcp.2011.02.001
37. Kadowaki T, Haneda M, Ito H, Sasaki K, Hiraide S, Matsukawa M, et al. Relationship of eating patterns and metabolic parameters, and teneligliptin treatment: interim results from post-marketing surveillance in Japanese type 2 diabetes patients. *Adv. Therapy*. (2018) 35:817–31. doi: 10.1007/s12325-018-0704-2
38. Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL. The relationship between breakfast skipping, chronotype, and glycemic control in type 2 diabetes. *Chronobiol Int.* (2014) 31:64–71. doi: 10.3109/07420528.2013.821614
39. Hassen WS, Castetbon K, Tichit C, Pneau S, Nechba A, Ducrot P, et al. Energy, nutrient and food content of snacks in French adults. *Nutr J*. (2018) 17:33. doi: 10.1186/s12937-018-0336-z
40. Fayet-Moore F, McConnell A, Kim J, Mathias KC. Identifying eating occasion-based opportunities to improve the overall diets of Australian adolescents. *Nutrients.* (2017) 9:608. doi: 10.3390/nu9060608

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Sex Difference in the Association Between Eating Away From Home and the Risk of High Serum Uric Acid in South China

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Background: The prevalence of high serum uric acid is increasingly rising in recent years, and diet behavior is perceived to be associated with it. This study aimed to explore the relationship between eating away from home (EAFH) and the risk of high serum uric acid in adults in South China.

Methods: The data utilized in this study were from Guangdong Nutrition and Health Survey (NHS) 2015. Serum uric acid concentration was detected. EAFH in the past week was investigated. We defined EAFH as food consumption away from home. Dietary data were collected by 24-h recalls on 3 consecutive days. A generalized linear mixed-effects model was applied to compute the odds ratio (OR) and its corresponding 95% CI.

Results: A total of 3,489 individuals were included in this study. A 1.27-fold OR (95% CI: 1.05–1.52, $P = 0.012$) of high serum uric acid was identified in adults with EAFH in comparison with those without EAFH. With respect to men, a 1.66-fold OR (95% CI: 1.3–2.1, $P < 0.001$) of high serum uric acid was observed. We also observed that men with EAFH had higher intakes of red meat, poultry, vegetable, carbohydrate, protein, fat, and total energy, while a lower grain intake than those without EAFH. However, there was a lack of significant association between EAFH and the odds ratio of high serum uric acid in women. Women with EAFH did not have higher consumptions of red meat, vegetable, fish, fat, and water than those without EAFH.

Conclusions: This study found that EAFH was associated with an increased odds ratio of high serum uric acid in men, but not in women.

Keywords: hyperuricemia, eating away from home, nutrition and health survey, dietary assessment, adult

INTRODUCTION

Hyperuricemia is perceived as a diet-related disease, which is characterized as the abnormal metabolism of purine (1). According to incomplete statistics, the global prevalence of hyperuricemia ranges from 6.7 to 17.1% (2). The prevalence of the disease in China was reported to be 13.3% (95% CI: 11.9–14.6%) (3), while it could be up to 25%

in some coastal areas of the same country (3, 4), where citizens may have a high consumption of purine-rich foods such as seafood. Hyperuricemia could further develop to gout without implementation of any preventions and treatments. In addition, there is growing evidence that hyperuricemia is associated with an elevated risk of other diseases, such as hypertension, diabetes mellitus, and cardiovascular diseases (5–8).

Risk factors for hyperuricemia include age, sex, genetics, lifestyle, and environmental quality (9, 10). Previous publications have shown that diet patterns and behaviors exert an important role in the occurrence and development of hyperuricemia (11–13). Dietary sources are also considered as vital factors for diet health. Eating away from home (EAFH) was found to be associated with diet-related non-communicable diseases, such as obesity and diabetes (14–16). The plausible explanations could be a higher consumption of energy, fat, and meat, but lower consumption of minerals and vitamins such as calcium and vitamin A in individuals with EAFH (17, 18). However, some contrary views issued that eating at home may also adversely affect those who are responsible for preparing meals as they are more exposed to cooking fumes and other hazardous substances (19, 20). Therefore, the effect of EAFH on non-communicable diseases should be verified.

Guangdong province is located in South China and its economy has a rapid development since the reform and opening-up. Diet patterns and food sources in local citizens have dramatically changed in the last few decades. According to some recent studies, animal-derived foods account for an increasing proportion of the total caloric intake in this population (3, 21). Along with the improvement of living standards, the EAFH rate has been increased rapidly in Guangdong province in the past few years. However, whether NAFH has an impact on the occurrence and development of abnormally high serum uric acid has not been fully understood. Therefore, we conducted a cross-sectional study involving 3489 adult participants to explore it.

MATERIALS AND METHODS

Study Design

Data utilized in this study were derived from Guangdong Nutrition and Health Survey (NHS) 2015, which was cross-sectional designed and a part of Chinese NHS 2015 (22). NHS was employed to evaluate food consumption, nutritional status, and their related factors. The study design was described in our previously published paper (23). Briefly, we applied a probability sampling method to select representative samples. There were 125 counties in Guangdong province, which were stratified into urban or rural layers and 14 counties were randomly selected (**Figure 1**). Afterward, three communities in the urban layer and three townships in the rural layer were further randomly selected. Finally, we randomly selected 45 households in each county, and individuals aged ≥18 years old in the households were recruited. Among the selected households, 20 households attended food consumption surveys and 25 households attended other health-related surveys. Participant selection is shown in **Figure 2**.

To obtain a minimum sample size in each county, the following formula was applied:

$$N = deff \times \frac{u^2 \times p(1-p)}{d^2}$$

where N is the sample size, deff is design efficiency and set to be 3, u is the dividing value of normal distribution and set to be 1.96, p is probability and set to be 9.7% (the prevalence rate of diabetes mellitus in China in 2010), and d is deviation and set to be 0.0196 (20% × 9.7%). Thus, at least 612 adults were needed in each county.

A total of 8,991 adults were recruited in Guangdong NHS and 3,643 adults finished the food consumption survey. Since 157 participants lacked complete information, a total of 3,489 adults were included in this study.

Dietary Data

Individual dietary data were collected by three consecutive 24-h recalls, 2 weekdays, and 1 weekend. Dietary assessment was performed by well-trained staff through face-to-face interviews and household surveys. All kinds of food and taking amount by participants in the 3 days were recorded. Food weight was evaluated by the investigator according to the recall of participants and with the help of a food map, comparison with the container, etc. Since cooking oil and condiments were consumed by family members at the household, we recorded their consumption amount at the household level. And then individual consumption of cooking oil and condiments was calculated based on the individual ratio of energy intake among family members and the times of taking meals at home. Major nutrients intake, including carbohydrate, protein, and fat, as well as total energy intake, were calculated according to the Chinese Food Composition Tables (2004 and 2009) (24, 25).

The dining places of participants in the past week were investigated. We defined EAFH as food consumption away from home in this study. In order to explore the combined effect of EAFH on high serum uric acid, adults who had more than one meal (breakfast, lunch, and dinner) EAFH (restaurant and/or company/school canteen) in the past week were perceived as having a habit of eating outside.

Anthropometric and Biomarker Measurements

Anthropometric measurements were performed by well-trained investigators. Weight (kg), height (m), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg) were measured, and their procedures were described elsewhere (23). Electronic bodyweight meter (HD-390, Tanita CO., LTD, China), electronic height meter (TZG, Wuxi Weighing Instrument CO., LTD, China), and electronic sphygmomanometer (HBP-1300, Omron CO., LTD, Japan) were used in measurements. Body mass index (BMI) was computed as weight (kg)/height (m^2). Definition of hypertension was based on guidelines of the World Health Organization (WHO) (26).

The blood sample was collected from each participant in the morning after fasting for at least 8 h. The serum sample was

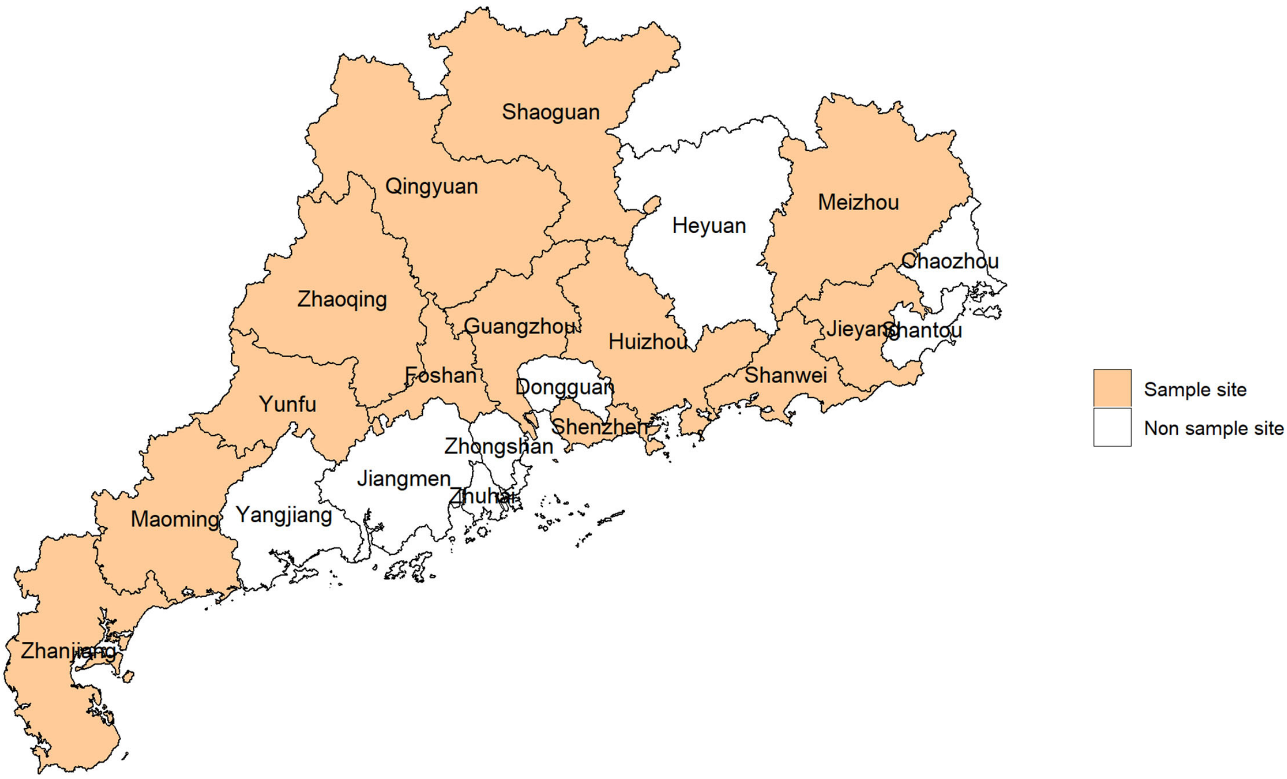

FIGURE 1 | Sample sites in this study.

separated after centrifugation. Serum uric acid concentration was determined by the oxidase method on an automated analyzer (Hitachi 7600, Hitachi Inc., Tokyo, Japan). Since serum uric acid was measured only once and serum sample from another day was no longer available, adults with hyperuricemia cannot be confirmed. Thus, we applied high serum uric acid to describe the abnormally high level of serum uric acid and it was defined as serum uric acid >420 μmol/L in men, while >360 μmol/L in women according to the definition of hyperuricemia in a previous study (27). Additionally, the participant with gout or with hyperuricemia treatment was also considered to be high serum uric acid.

Statistical Analysis

Continuous variables were exhibited as mean and standard deviation if they were normal distribution, or exhibited as median and quartile if they were skewed distribution. Discrete variables were exhibited as number and proportion. To compare the differences of continuous variables (grain, vegetable, red meat, fish, poultry, water, carbohydrate, protein, fat, and total energy intake) between two groups (EAFH and non-EAFH), Student's *t*-test or Kruskal Wallis test was employed.

To explore the association between EAFH and the odds ratio of high serum uric acid, a generalized linear mixed-effects model was used and crude odds ratio (OR) and its corresponding 95% confidence interval (CI) were computed, as described in a previous study (23). We put possible confounding factors into the model to adjust the potential confounding effects and adjusted OR and its corresponding 95% CI were computed. Firstly, the effect of sex was adjusted. Secondly, the effect of age was adjusted. Thirdly, the effect of both sex and age was adjusted. Finally, the effect of multifactor, including sex, age, smoking, drinking, body mass index, sedentary leisure time, physical activity time, education, and marital status, was adjusted.

To obtain a robust association between EAFH and the odds ratio of high serum uric acid, subgroup analysis stratified by different sexes (men and women), meals (breakfast, lunch, and dinner), and dining out places (restaurant and canteen) were performed. Possible confounding effects mentioned previously were also adjusted applying different models.

Statistical analysis in the present study was performed in SAS Enterprise Guide (SAS Institute Inc., Cary, NC, USA) and R version 3.5.1 (R Core Development Team, Vienna, Austria). A p-value < 0.05 was characterized as statistically significant.

RESULTS

Characteristics of Included Participants

A total of 3,489 adults with an average age of 52.0 ± 14.9 years were included in this study. Men accounted for 45.9% (1,603/3,489). The mean of serum uric acid was 342.4 ± 94.9 umol/L in the total sample, 385.9 ± 91.9 umol/L in men, and

FIGURE 2 | Flow chart of selecting participants.

305.3 ± 80.7 umol/L in women. The frequency of EAFH was 19.9% (696/3,489) in the total sample, 23.6% (378/1,603) in men, and 16.9 % (318/1,886) in women. The proportion of high serum uric acid was 26.4% (919/3,489) in the total sample, 32.5% (520/1,603) in men, and 21.2% (399/1,886) in women. Additional information about included participants is exhibited in **Table 1**.

Association Between EAFH and the Odds Ratio of High Serum Uric Acid

A 1.27-fold OR (95%CI: 1.05–1.52, $P = 0.012$) of high serum uric acid was found in participants who had a habit of EAFH. The positive association remains after adjusting for age (OR: 1.34, 95% CI: 1.11–1.61, $P = 0.002$) or age and sex (OR: 1.25, 95% CI: 1.04–1.52, $P = 0.019$), while the association was not statistically significant after adjusting for sex (OR: 1.2, 95% CI: 0.99–1.44, $P = 0.058$) or multifactor (OR: 1.15, 95% CI: 0.93–1.41, $P = 0.195$). Detail results are shown in **Table 2**.

Subgroup Analysis

Different Sexes

With respect to men, EAFH was found to be associated with an elevated OR of high serum uric acid applying a crude effect model

TABLE 1 | Characteristic of eligible participants.

Variables	Male (n = 1,603)	Female (n = 1,886)	Overall (n = 3,489)
Age (years)	52.9 ± 15.2	51.2 ± 14.7	52.0 ± 14.9
Ethnicity (N, %)			
Han	1,589 (99.4)	1,863 (99.0)	3,452 (99.2)
Other	9 (0.6)	18 (1.0)	27 (0.8)
BMI (Kg/m^2)	23.3 ± 3.4	23.4 ± 3.6	23.4 ± 3.5
Food intake (g/d)			
Grain	237.7 (174.5, 313.5)	194.1 (146.2, 260.6)	215 (156.2, 283.9)
Vegetable	260.0 (190.0, 348.3)	258.3 (183.3, 343.3)	258.7 (186.7, 346.7)
Red meat	115.0 (66.7, 170)	90.0 (51.7, 137.3)	100.0 (60.0, 152.7)
Fish	40.0 (0, 91.8)	33.3 (0, 75)	35.1 (0, 82.9)
Poultry	19.7 (0, 53.3)	16.7 (0, 44)	17.6 (0, 48.7)
Water	751.2 (578.6, 958.5)	682.9 (528.6, 866.6)	713.8 (550.2, 913.1)
Nutrient intake (g/d)			
Carbohydrate	209.4 (162.8, 265.7)	182.7 (145.4, 230.5)	193.3 (152.2, 247.5)
Protein	67.4 (53.5, 83.3)	57.7 (46, 71.4)	61.7 (48.7, 77.5)
Fat	82.0 (61.1, 109.6)	69.2 (51.5, 91.9)	74.9 (54.9, 99.9)
Total energy intake (Kcal/d)	1899.0 (1538.5, 2316.2)	1614.2 (1323.4, 1941.4)	1739.3 (1398.7, 2130.5)
Sedentary leisure time (h/d)	5.1 ± 2.8	4.8 ± 2.8	4.9 ± 2.8
Physical activity time (h/d)	0.14 ± 0.47	0.05 ± 0.28	0.09 ± 0.38
Serum uric acid (umol/L)	385.9 ± 91.9	305.3 ± 80.7	342.4 ± 94.9
Eating away from home (N, %)			
Total	378 (23.6)	318 (16.9)	696 (19.9)
Breakfast	206 (12.9)	171 (9.1)	377 (10.8)
Lunch	260 (16.2)	229 (12.1)	489 (14.0)
Dinner	11.9 (7.4)	89 (4.7)	208 (6.0)
Restaurant	276 (17.2)	183 (9.7)	459 (13.2)
Canteen	147 (9.2)	166 (8.8)	313 (9.0)
High serum uric acid (N, %)	520 (32.5)	399 (21.2)	919 (26.4)
Hypertension (N, %)	522 (32.7)	545 (29.0)	1,067 (30.7)
Smoking (N, %)	896 (56.1)	46 (2.5)	942 (27.1)
Drinking (N, %)	852 (53.3)	470 (25.0)	1,322 (38.0)
Education (N, %)			
≤6 years	823 (51.5)	647 (34.4)	1,470 (42.3)
7–12 years	609 (38.1)	1,055 (56.1)	1,664 (47.8)
≥13 years	166 (10.4)	179 (9.5)	345 (9.9)
Marital status (N, %)			
Married	1,452 (90.9)	1,705 (90.6)	3,157 (90.7)
Other	146 (9.1)	176 (9.4)	322 (9.3)

BMI, body mass index.

(OR: 1.66, 95% CI: 1.3–2.1, $P < 0.001$), adjusting for age (OR: 1.63, 95% CI: 1.28–2.08, $P < 0.001$), or adjusting for multifactor (OR: 1.38, 95% CI: 1.06–1.81, $P = 0.017$). However, as for women, the associations were not statistically significant (**Table 2**).

Different Meals

Eating away from home during breakfast was found to be associated with an elevated OR of high serum uric acid whether applying a crude effect model or applying adjusted effect models. However, EAFH during lunch and dinner was not associated with the OR of high serum uric acid (**Table 3**). The disparity of the association between the two sexes was also observed regarding various meals.

Different Dining Out Places

An increased OR of high serum uric acid was observed in EAFH at a restaurant, while EAFH in a canteen was not associated with the OR of high serum uric acid. Similar results about sex differences were also identified. Detailed results are summarized in **Table 4**.

TABLE 2 | Association between eating away from home and risk of high serum uric acid.

Groups	Models	OR	95%CI	*P*-value
Total	Crude effect	1.27	1.05–1.52	0.012
	Adjusted for sex	1.20	0.99–1.44	0.058
	Adjusted for age	1.34	1.11–1.61	0.002
	Adjusted for sex and age	1.25	1.04–1.52	0.019
	Adjusted for multifactor[a]	1.15	0.93–1.41	0.195
Male	Crude effect	1.66	1.30–2.10	<0.001
	Adjusted for age	1.63	1.28–2.08	<0.001
	Adjusted for multifactor[b]	1.38	1.06–1.81	0.017
Female	Crude effect	0.72	0.53–0.99	0.044
	Adjusted for age	0.83	0.60–1.15	0.259
	Adjusted for multifactor[b]	0.89	0.63–1.26	0.514

[a]*Generalized linear mixed-effects model adjusted for sex, age, smoking, drinking, body mass index, sedentary leisure time, physical activity time, education, and marital status;* [b]*Generalized linear mixed-effects model adjusted for age, smoking, drinking, body mass index, sedentary leisure time, physical activity time, education, and marital status.*

TABLE 3 | Association between eating away from home and risk of high serum uric acid regarding breakfast, lunch, and dinner.

Groups	Models	Breakfast			Lunch			Dinner		
		OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Total	Crude effect	1.50	1.20–1.89	0.001	1.07	0.87–1.33	0.513	1.20	0.88–1.63	0.251
	Adjusted for sex	1.43	1.14–1.80	0.002	1.02	0.82–1.27	0.831	1.12	0.82–1.53	0.473
	Adjusted for age	1.56	1.24–1.97	<0.001	1.13	0.81–1.41	0.262	1.25	0.92–1.70	0.161
	Adjusted for sex and age	1.48	1.17–1.87	0.001	1.07	0.86–1.34	0.535	1.16	0.85–1.59	0.348
	Adjusted for multifactor[a]	1.37	1.07–1.75	0.012	0.94	0.74–1.19	0.593	1.04	0.75–1.45	0.805
Male	Crude effect	1.78	1.32–2.40	<0.001	1.54	1.17–2.02	0.002	1.56	1.07–2.28	0.022
	Adjusted for age	1.75	1.30–2.36	<0.001	1.50	1.14–1.99	0.004	1.52	1.04–2.23	0.031
	Adjusted for multifactor[b]	1.52	1.10–2.08	0.010	1.22	0.90–1.65	0.197	1.22	0.81–1.84	0.332
Female	Crude effect	1.03	0.70–1.51	0.886	0.50	0.33–0.75	0.001	0.57	0.30–1.05	0.071
	Adjusted for age	1.17	0.79–1.72	0.435	0.58	0.38–0.88	0.010	0.65	0.35–1.21	0.173
	Adjusted for multifactor[b]	1.23	0.82–1.85	0.321	0.61	0.39–0.94	0.027	0.72	0.38–1.37	0.317

[a]*Generalized linear mixed–effects model adjusted for sex, age, smoking, drinking, body mass index, sedentary leisure time, physical activity time, education, and marital status;* [b]*Generalized linear mixed-effects model adjusted for age, smoking, drinking, body mass index, sedentary leisure time, physical activity time, education, and marital status.*

Food, Nutrients, and Energy Intake

Participants with EAFH consumed more red meat, poultry, fish, and vegetable than those with non-EAFH, while grain intake was the opposite. Men participants with EAFH had a higher intake of red meat, poultry, and vegetable, but a lower intake of grain than those with non-EAFH.

However, with respect to the women, there was a lack of significant difference in red meat, vegetable, fish, and water intake between participants with EAFH and non-EAFH (**Figure 3**).

In addition, participants with EAFH had more intake of three major nutrients and energy than those with non-EAFH (**Figure 4**), and men participants had similar results. However, there was a lack of statistical significance in fat intake between women with EAFH and non-EAFH.

We also compared intake of food, nutrients, and energy between EAFH and non-EAFH regarding different subgroups, and similar results remained (see the **Supplementary Tables 1**, **2**).

DISCUSSION

The current study was based on a sample size of 3,489 individuals in South China and suggested a 1.27-fold OR of high serum uric acid in adults who had a habit of EAFH, compared with those without EAFH. We also found sex differences regarding the association. A positive association was found in men, but not in women. Adults eating out during breakfast or at a restaurant were inclined to be associated with an increased OR of high serum uric acid. Our findings were robust since the results from subgroup analysis did not have large fluctuations even after adjusting for a broad of potential confounders.

The rate of EAFH has been rising in China in recent years. A previous study demonstrated that the EAFH rate rose from 9.4 to 13.95% between 2004 and 2011 (28). Our study identified an EAFH frequency of 19.9% in 2015, indicative of an upward trend. However, some other places in China, such as Shanghai, reported a higher rate of 55.05% (17).

TABLE 4 | Association between eating away from home and risk of high serum uric acid regarding restaurant and canteen.

Groups	Models	Restaurant			Canteen		
		OR	95% CI	*P*-value	OR	95% CI	*P*-value
Total	Crude effect	1.51	1.22–1.83	<0.001	1.03	0.79–1.33	0.853
	Adjusted for sex	1.38	1.12–1.71	0.003	1.02	0.78–1.33	0.891
	Adjusted for age	1.57	1.28–1.95	<0.001	1.08	0.83–1.41	0.572
	Adjusted for sex and age	1.44	1.16–1.79	0.001	1.07	0.82–1.40	0.639
	Adjusted for multifactor[a]	1.33	1.06–1.68	0.013	0.95	0.71–1.26	0.706
Male	Crude effect	1.78	1.36–2.32	<0.001	1.49	1.05–2.11	0.025
	Adjusted for age	1.75	1.36–2.28	<0.001	1.45	1.02–2.05	0.040
	Adjusted for multifactor[b]	1.53	1.15–2.03	0.004	1.14	0.78–1.66	0.485
Female	Crude effect	0.87	0.59–1.28	0.469	0.60	0.39–0.95	0.027
	Adjusted for age	0.98	0.66–1.45	0.929	0.71	0.45–1.12	0.141
	Adjusted for multifactor[b]	1.08	0.71–1.63	0.733	0.76	0.47–1.22	0.250

[a]*Generalized linear mixed-effects model adjusted for sex, age, smoking, drinking, body mass index, sedentary leisure time, physical activity time, education, and marital status;* [b]*Generalized linear mixed-effects model adjusted for age, smoking, drinking, body mass index, sedentary leisure time, physical activity time, education, and marital status.*

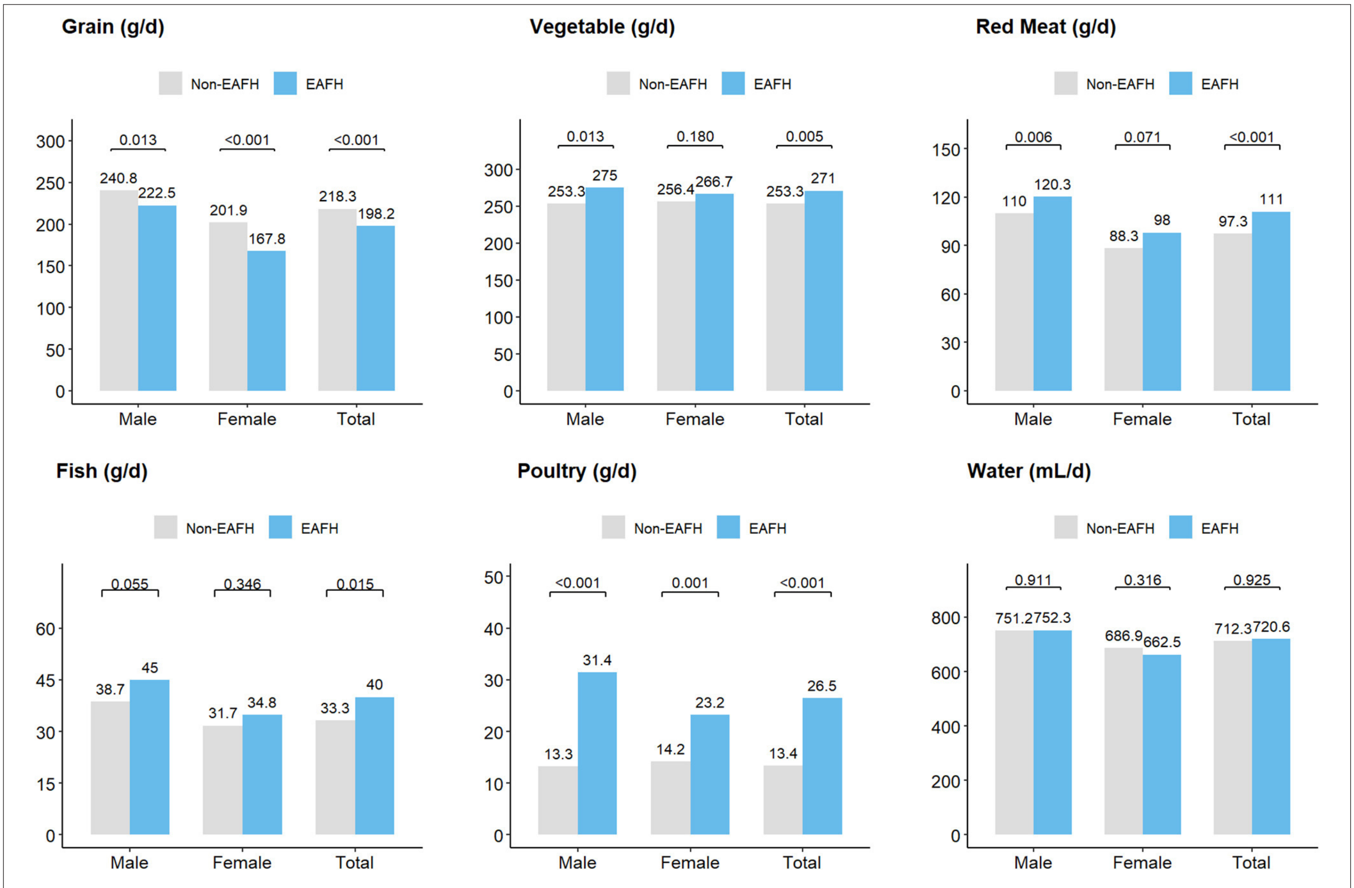

FIGURE 3 | Food intake (g/d) among different populations. EAFH, Eating away from home.

It should be noted that the definition of EAFH varies in these studies. The study by Zeng et al. (28) focused on the place where people take food but did not decompose consumption behaviors by cooking place further, while a study from Shanghai included meals prepared away from home, such as takeaway food but eating at home (17). We restricted EAFH to eating at restaurants or company/school canteen but not takeaway food eating at home. The definitions with some minor differences would be affected the frequencies of eating away from different studies. The inconsistent definitions of EAFH

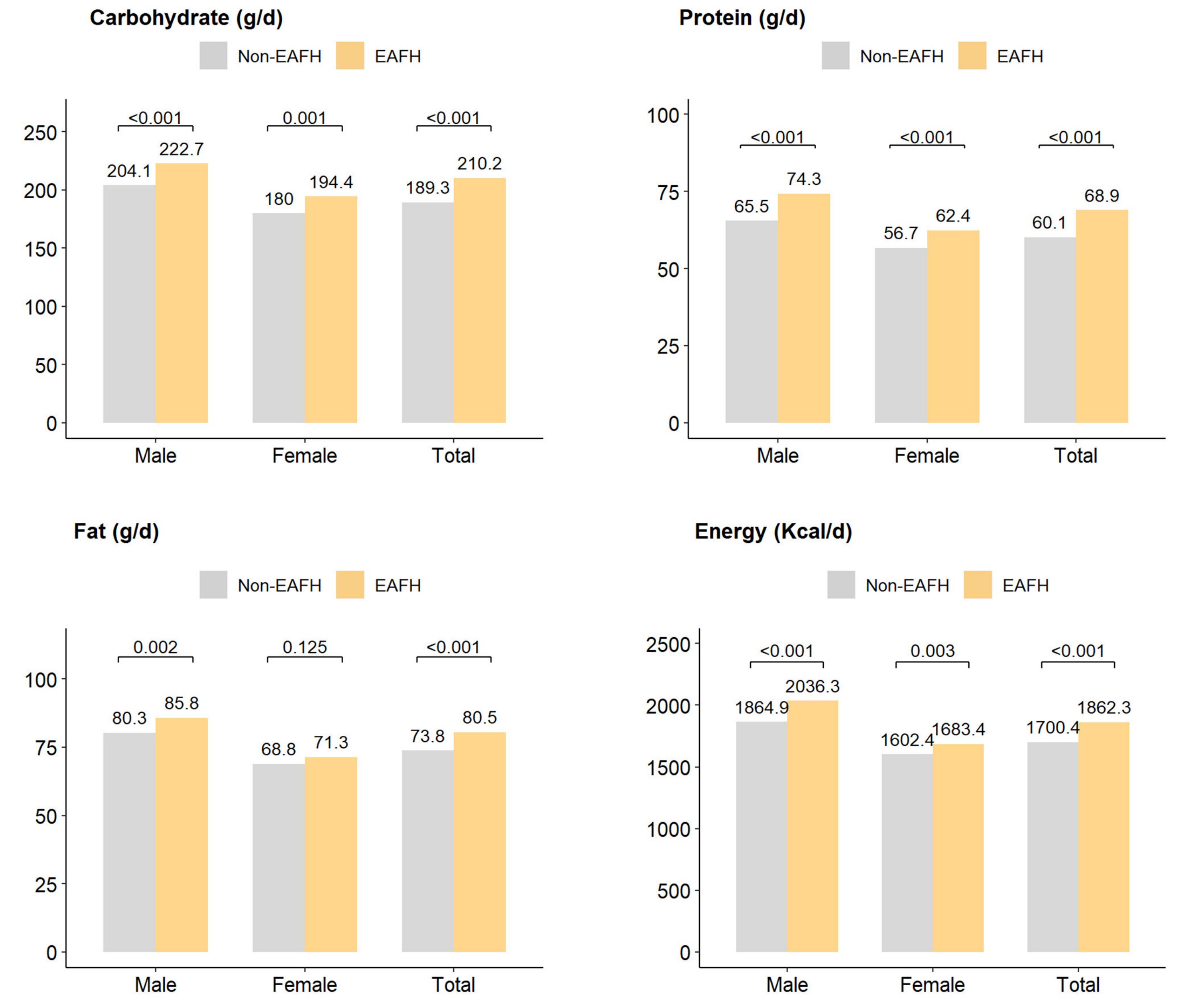

FIGURE 4 | Three major nutrients intake (g/d) and energy intake (Kcal/d) among different populations. EAFH, Eating away from home.

existing in different studies indicated that an accordant one should be proposed.

Previous studies have shown an elevated risk of diet-related diseases and EAFH (14–16). The positive association between EAFH and obesity or an increased BMI has been confirmed by large sample studies (16, 28, 29). Our study discovered an elevated risk of high serum uric acid in adults with EAFH. EAFH has been linked to the consumption of low-quality, high-calorie foods as well as some unhealthy food, such as snacks, beverages, foods in fat and sugar (14, 30, 31). Poor food quality may explain the association between EAFH and high serum uric acid. Our study found that people with EAFH had higher red meat, fat, and total energy intake, especially in restaurants. A previous study has also reported that a high level of surplus energy was associated with the risk of diet-related disease (28). However, how the dietary behaviors exert roles on high serum uric acid should be further study.

Sex discrepancies in the association between EAFH and the OR of high serum uric acid were identified. A positive association was found in men but not in women. Possible reasons are listed as follows. To start with, men are more inclined to have EAFH than women. The rate of EAFH in men (23.6%) was higher than in women (16.9%) in our study. This may be explained by sex differences in family responsibilities. In China, most women should take the responsibility of taking care of the family, which would reduce the frequency of EAFH (15, 28). Furthermore, the diet behavior may induce more impacts on the men than women, which were largely attributable to the differences in amphoteric physiological anatomy and hormone (32, 33). Our study also found a higher proportion of high serum uric acid in men (32.5%)

than women (21.2%). In addition, women are more likely to control their body weight by reducing food intake (34, 35), even when eating away from home. Higher food consumption was observed in men with EAFH than those eating at home, while there was a lack of such large differences of food intake (red meat, vegetable, and fish) between women with EAFH and those eating at home in our study.

Several limitations in this study should be discussed. Firstly, although this study was based on a large sample size of 3,489 individuals, the extrapolated conclusion should limit to the adult as only participants over 18 years old were eligible. High serum uric acid is more prevalent in middle-aged adults than young-aged adults or children and adolescents. We did not analyze the different effects regarding various age groups for spatial confined. Secondly, it should be noted that a cross-sectional study cannot draw a causal relationship because of the indeterminately chronological order of the relation and potential confounding factors. We employed a generalized linear mixed-effects model and put possible risk factors into the model as we could to adjust their potential confounding effects. However, effects from other possible risk factors such as family history and co-existing diseases, cannot be eliminated. Thirdly, we did not analyze the effect of consuming takeaway food on high serum uric acid, which might introduce potential misclassification bias. As the rate of consuming takeaway food is increasingly rising, its impact on diet-related disease should be uncovered and further studies are warranted. Fourthly, serum uric acid would be affected by dietary factors with a medium to a long period, while we only applied 3 consecutive 24-h recalls collecting food consumption, which only provided clues to the cause of high serum uric acid. The association between medium or long-term EAHF and the OR of high serum uric acid should be verified.

CONCLUSIONS

This study demonstrated an increased OR of high serum uric acid in adults with EAFH in 3,489 individuals who participated in Guangdong NHS in South China. Sex differences in the association were observed. Compared with those without EAFH, a 1.66-fold OR of high serum uric acid was found in men with EAFH, while the association was not statistically significant in women. We also found sex differences in food intake between EAFH and non-EAFH. Diet behavior has a close link to diet-related diseases and good diet behaviors should be publicly advocated to promote their health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of Chinese Center for Disease Control and Prevention. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-wP and Z-hC conceived and designed the experiments. S-wC and PW performed the analyses. S-wC wrote the first draft of the manuscript. PW, G-yJ, QJ, X-mH, W-jM, and RH significantly contributed to the development of the final draft of the manuscript. All authors approve of the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Trifiro G, Morabito P, Cavagna L, Ferrajolo C, Pecchioli S, Simonetti M, et al. Epidemiology of gout and hyperuricaemia in Italy during the years 2005-2009: a nationwide population-based study. *Ann Rheum Dis.* (2013) 72:694–700. doi: 10.1136/annrheumdis-2011-201254
2. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. *Nat Rev Rheumatol.* (2020) 16:380–90. doi: 10.1038/s41584-020-0441-1
3. Liu R, Han C, Wu D, Xia X, Gu J, Guan H, et al. Prevalence of hyperuricemia and gout in mainland China from 2000 to 2014: a systematic review and meta-analysis. *Biomed Res Int.* (2015) 2015:762820. doi: 10.1155/2015/762820
4. Nan H, Qiao Q, Dong Y, Gao W, Tang B, Qian R, et al. The prevalence of hyperuricemia in a population of the coastal city of Qingdao, China. *J rheumatol.* (2006) 33:1346–50.
5. Virdis A, Masi S, Casiglia E, Tikhonoff V, Cicero A, Ungar A, et al. Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality over 20 years. *Hypertension.* (2020) 75:302–8. doi: 10.1161/HYPERTENSIONAHA.119.13643
6. Filippatos GS, Ahmed MI, Gladden JD, Mujib M, Aban IB, Love TE, et al. Hyperuricaemia, chronic kidney disease, and outcomes in heart failure: potential mechanistic insights from epidemiological data. *Eur Heart J.* (2011) 32:712–20. doi: 10.1093/eurheartj/ehq473
7. Pascual-Figal DA, Hurtado-Martinez JA, Redondo B, Antolinos MJ, Ruiperez JA, Valdes M. Hyperuricaemia and long-term outcome after hospital discharge in acute heart failure patients. *Eur J Heart Fail.* (2007) 9:518–24. doi: 10.1016/j.ejheart.2006.09.001
8. Zoppini G, Targher G, Chonchol M, Ortalda V, Abaterusso C, Pichiri I, et al. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. *Diabetes Care.* (2012) 35:99–104. doi: 10.2337/dc11-1346

9. Kawamura Y, Nakaoka H, Nakayama A, Okada Y, Yamamoto K, Higashino T, et al. Genome-wide association study revealed novel loci which aggravate asymptomatic hyperuricaemia into gout. *Ann Rheum Dis.* (2019) 78:1430–7. doi: 10.1136/annrheumdis-2019-215521
10. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. *Sci Rep.* (2018) 8:4314. doi: 10.1038/s41598-018-22570-9
11. Kim HS, Kwon M, Lee HY, Shivappa N, Hebert JR, Sohn C, et al. Higher pro-inflammatory dietary score is associated with higher hyperuricemia risk: results from the case-controlled Korean genome and epidemiology study cardiovascular disease association study. *Nutrients.* (2019) 11:1803 doi: 10.3390/nu11081803
12. Xia Y, Xiang Q, Gu Y, Jia S, Zhang Q, Liu L, et al. A dietary pattern rich in animal organ, seafood and processed meat products is associated with newly diagnosed hyperuricaemia in Chinese adults: a propensity score-matched case-control study. *Br J Nutr.* (2018) 119:1177–84. doi: 10.1017/S0007114518000867
13. Tsai YT, Liu JP, Tu YK, Lee MS, Chen PR, Hsu HC, et al. Relationship between dietary patterns and serum uric acid concentrations among ethnic Chinese adults in Taiwan. *Asia Pac J Clin Nutr.* (2012) 21:263–70.
14. Dong F, Howard AG, Herring AH, Thompson AL, Adair LS, Popkin BM, et al. Longitudinal associations of away-from-home eating, snacking, screen time, and physical activity behaviors with cardiometabolic risk factors among Chinese children and their parents. *Am J Clin Nutr.* (2017) 106:168–78. doi: 10.3945/ajcn.116.146217
15. Du WW, Zhang B, Wang HJ, Wang ZH, Su C, Zhang JG, et al. Gender difference in the association between food away-from-home consumption and body weight outcomes among Chinese adults. *Public Health Nutr.* (2016) 19:2984–90. doi: 10.1017/S1368980016001257
16. Kant AK, Whitley MI, Graubard BI. Away from home meals: associations with biomarkers of chronic disease and dietary intake in American adults, NHANES 2005-2010. *Int J Obes.* (2015) 39:820–7. doi: 10.1038/ijo.2014.183
17. Zang J, Luo B, Wang Y, Zhu Z, Wang Z, He X, et al. Eating out-of-home in adult residents in shanghai and the nutritional differences among dining places. *Nutrients.* (2018) 10:951. doi: 10.3390/nu10070951
18. Jia X, Liu J, Chen B, Jin D, Fu Z, Liu H, et al. Differences in nutrient and energy contents of commonly consumed dishes prepared in restaurants vs. at home in Hunan Province, China. *Public Health Nutr.* (2018) 21:1307–18. doi: 10.1017/S1368980017003779
19. Chen HC, Wu CF, Chong IW, Wu MT. Exposure to cooking oil fumes and chronic bronchitis in nonsmoking women aged 40 years and over: a health-care based study. *BMC Public Health.* (2018) 18:246. doi: 10.1186/s12889-018-5146-x
20. Wei F, Nie G, Zhou B, Wang L, Ma Y, Peng S, et al. Association between Chinese cooking oil fumes and sleep quality among a middle-aged Chinese population. *Environ Pollut.* (2017) 227:543–51. doi: 10.1016/j.envpol.2017.05.018
21. Li M, Shi Z. Dietary pattern during 1991-2011 and its association with cardio metabolic risks in Chinese adults: the china health and nutrition survey. *Nutrients.* (2017) 9:1218. doi: 10.3390/nu9111218
22. Zhao J, Su C, Wang H, Wang Z, Wang Y, Zhang B. Secular trends in energy and macronutrient intakes and distribution among adult females (1991-2015): results from the China health and nutrition survey. *Nutrients.* (2018) 10:115. doi: 10.3390/nu10020115
23. Chen SW, Ji GY, Jiang Q, Wang P, Huang R, Ma WJ, et al. Association between dietary acid load and the risk of hypertension among adults from South China: result from nutrition and health survey (2015-2017). *BMC Public Health.* (2019) 19:1599. doi: 10.1186/s12889-019-7985-5
24. Yang YX, He M, Pan XC. *China Food Composition Table 2004*. Beijing: Peking University Medical Press (2004).
25. Yang YX, Wang GY, Pan XC. *China Food Composition Table 2nd ed.* Beijing: Peking University Medical Press (2009).
26. Organization WH. *A Global Brief on Hypertension Silent Killer Online, Global Public Health Crisis.* Available online at: http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/
27. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. *Curr Opin Rheumatol.* (2014) 26:186–91. doi: 10.1097/BOR.0000000000000028
28. Zeng Q, Zeng Y. Eating out and getting fat? A comparative study between urban and rural China. *Appetite.* (2018) 120:409–15. doi: 10.1016/j.appet.2017.09.027
29. Seguin RA, Aggarwal A, Vermeylen F, Drewnowski A. Consumption frequency of foods away from home linked with higher body mass index and lower fruit and vegetable intake among adults: a cross-sectional study. *J Environ Public Health.* (2016) 2016:3074241. doi: 10.1155/2016/3074241
30. Wellard-Cole L, Jung J, Kay J, Rangan A, Chapman K, Watson WL, et al. Examining the frequency and contribution of foods eaten away from home in the diets of 18- to 30-year-old Australians using smartphone dietary assessment (MYMeals): protocol for a cross-sectional study. *JMIR Res Protoc.* (2018) 7:e24. doi: 10.2196/resprot.9038
31. Bezerra IN, de Moura SA, Pereira RA, Sichieri R. Contribution of foods consumed away from home to energy intake in Brazilian urban areas: the 2008-9 Nationwide Dietary Survey. *Br J Nutr.* (2013) 109:1276–83. doi: 10.1017/S0007114512003169
32. Grzymislawska M, Puch EA, Zawada A, Grzymislawski M. Do nutritional behaviors depend on biological sex and cultural gender? *Adv Clin Exp Med.* (2020) 29:165–72. doi: 10.17219/acem/111817
33. Funabashi T, Hagiwara H, Mogi K, Mitsushima D, Shinohara K, Kimura F. Sex differences in the responses of orexin neurons in the lateral hypothalamic area and feeding behavior to fasting. *Neurosci Lett.* (2009) 463:31–4. doi: 10.1016/j.neulet.2009.07.035
34. Garawi F, Devries K, Thorogood N, Uauy R. Global differences between women and men in the prevalence of obesity: is there an association with gender inequality? *Eur J Clin Nutr.* (2014) 68:1101–6. doi: 10.1038/ejcn.2014.86
35. Wells JC, Marphatia AA, Cole TJ, McCoy D. Associations of economic and gender inequality with global obesity prevalence: understanding the female excess. *Soc Sci Med.* (2012) 75:482–90. doi: 10.1016/j.socscimed.2012.03.029

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Complementary Feeding Habits in Children Under the Age of 2 Years Living in the City of Adama in the Oromia Region in Central Ethiopia: Traditional Ethiopian Food Study

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Updated information on child feeding practices, nutritional status, and trends related to parental sociodemographic variables is required in developing countries. The objective of this study was to describe infant feeding practices and associated sociodemographic factors among Ethiopian children with an emphasis on complementary feeding (CF). Information on infant feeding and anthropometric measures was obtained from 1,054 mother-child pairs participating in a birth cohort study of children born between 2017 and 2020 prospectively followed in the city of Adama located in the Oromia region of central Ethiopia. Logistic regression models were used to identify sociodemographic and food groups associated with the initiation of CF. The introduction of complementary foods at 6 months of age was 84.7% (95% CI, 82.5, 86.8). Vegetables, cereals (teff, wheat, barley), and fruits were most often the earliest types of foods introduced. Wasting, stunting, underweight, and low body mass index (BMI) by age were found in 6.0, 16.9, 2.5, and 6.3%, respectively. Maternal age and occupation were the factors associated with timely initiation of CF [$OR = 2.25$, (95% CI, 1.14, 4.41)] and [$OR = 0.68$, (95% CI, 0.48, 0.97)], respectively. This study demonstrates that the majority of Ethiopian children in the Oromia region follow the recommendations of WHO on CF.

Keywords: children, complementary feeding, Ethiopia, gluten, malnutrition, teff

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INTRODUCTION

The introduction of complementary foods during weaning at the age of 6 months is generally recommended to ensure the growth, health, and development of children to reach their optimal growth potential during the first 2 years of childhood (1). However, several studies have demonstrated that infant feeding practices are not followed worldwide (2, 3). Early or late introduction of adequate complementary foods of suboptimal quality and quantity, as well as poor hygienic conditions, is still common in developing countries.

Early and delayed introduction of complementary feeding (CF) may result in poor nutritional status and increased morbidity in growing children (4, 5). As such, the WHO Infant and Young Child Feeding (IYCF) practices strategy was developed, which includes infant feeding recommendations for breastfeeding children under the age of 2 years, the introduction of solid and semisolid foods at the age of 6 months, and a gradual increase in the amount and frequency of different foods as the child grows older (6). Inappropriate feeding practices attributed to poor nutritional knowledge can, therefore, be a significant contributor to poor nutritional status and growth development, as well as long-term risk of developing chronic diseases in developing countries (7–9).

Several studies from the sub-Saharan regions, which include Ethiopia, Malawi, Benin, and the Democratic Republic of Congo, have identified cereals as the most common source of food in early childhood, but access is highly dependent on sociodemographic factors with significant cultural differences (10–12). However, there is a lack of recent studies exploring the paradigm shift in dietary patterns of infants in African countries with increasing wealth since the millennium.

In Ethiopia, most of the solid foods first introduced to infants between 6 and 23 months of age are homemade, since commercially ready-made foods are often beyond the reach of the low-income population. The most common solid foods are based on three major staples that are locally available, including (1) corn/enset/teff, (2) wheat/barley, and (3) sorghum/maize, all of which meet the nutritional contents recommended by WHO for children between 6 and 23 months of age (**Supplementary Table 1**) (13). Homemade solid foods for infants in Ethiopia are mainly based on cereals or starchy tubers such as corn (*Zea mays*), sorghum (*Sorghum biocolor*), millet (*Panicum miliaceum*), oats (*Avena sativa*), teff (*Eragrostis tef*), rice (*Oryza sativa*), yam (*Dioscorea*), potato (*Solanum tuberosum*), barley (*Hordeum vulgare*), and legumes (*Fabaceae*). These foods are generally served as gruel, porridge, fetfet, kitta, and bread. However, the consumption of meat (beef, lamb, goat, poultry), fruits, and vegetables is very low (13).

Teff (*Eragrostis tef*) is the most common staple food in Ethiopia and is an important part of the cultural heritage and national identity (14). Although teff is considered to be highly nutritious (15, 16), the 2019 Ethiopia Demographic and Health Survey (EDHS) report found that about 37% of children younger than 5 years of age were stunted (of whom 12% were severely stunted), 7% were wasted (of whom 1% were severely wasted), and 21% of the children were underweight (of whom 6% were severely underweight). The EDHS nutritional survey also found that undernutrition differed between regional location, sex, and age groups of children (17).

The aim of this study was to describe recent infant feeding practices and associated sociodemographic factors in children under the age of 2 years who were born between 2017 and 2020 and lived in the city of Adama and the surrounding Oromia region in central Ethiopia.

MATERIALS AND METHODS

Study Population

The main aim of the Traditional Ethiopian Food (TEF) study is to investigate the genetic propensity, feeding practices, nutritional status, and gut microbiome on the risk of celiac disease in children living in the Oromia region in central Ethiopia (18). Between 2017 and 2020, 1,389 newborn children were approached from the general population of the city of Adama and the surrounding Oromia region of central Ethiopia to be enrolled in a 4-year follow-up study. The cohort consisted of women and their offspring participating in parallel research studies at three public health facilities in the city of Adama. Mothers were participating in the pregnancy tuberculosis study investigating the role of tuberculosis infection on pregnancy outcomes, while infants were participating in the TEF birth cohort study examining the prevalence of celiac disease in children (18, 19). A physical examination was performed, and baseline data were collected when the child was 6 weeks of age and then subsequently at 9, 18, 24, 36, and 48 months of age.

Food Questionnaire Data

At the scheduled study visits, a legal guardian filled in structured questionnaires regarding the information on the early infant feeding practices of the participating child. The form was developed in English and translated to the local language used for the data collection. The food questionnaire was developed for this study to gather information on breastfeeding, time for the introduction of complementary foods, and dietary infant feeding habits.

For the present study, information about breastfeeding duration and age at first introduction to complementary foods was examined for 1,054 children whose mothers had completed the questionnaire at the 9 and 18 months of age visits. Baseline maternal sociodemographic data were collected during the antenatal care (ANC) follow-up of the mother and at the 6-week post-delivery visit for the pregnancy tuberculosis cohort (19).

Anthropometrics

Anthropometric measurements were done by trained nurses according to the WHO manual. Children were measured while lying down without wearing shoes using a calibrated length board for height. The weight of the children was measured with lightweight clothing and recorded to the nearest 0.1 kg using an infant weight scale. A Z-score <-2 SD in height-for-age was defined as stunted, <-2 SD in weight-for-height was defined as wasted, <-2SD in weight-for-age was defined as underweight, and <-2 SD in body mass index (BMI) for age was defined as low BMI (20).

Statistical Methods

Frequency distribution and descriptive characteristics were investigated for maternal age, marital status, education, occupation, family size, as well as the birth order, sex, and age of the child at the introduction of selected solid foods. Logistic regression models were used to identify sociodemographic variables associated with the timing of complementary food initiation. After the necessary adjustments, adjusted odds ratios (AOR) with 95% confidence intervals (CI) were used to assess the strength of association. *P*-values <0.05 were considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software for Windows (version 25; SPSS Inc. Chicago, IL). Anthropometric data were analyzed by using WHO Anthro (version 3.2.2) and supported by SPSS.

TABLE 1 | Proportion of initiation of complementary feeding (CF) at 6 months of age by maternal sociodemographic characteristics.

Variable	N (%)	Initiation of CF at 6 months of age	
		Yes (%)	No (%)
Maternal age:			
<20	161 (15.3)	144 (89.4)	17 (10.6)
20–24	259 (24.6)	213 (82.2)	46 (17.8)
25–30	443 (42.0)	374 (84.4)	69 (15.6)
>30	189 (17.9)	152 (80.4)	37 (19.6)
Missing data	2 (0.2)		
Marital status:			
Married	1017 (96.5)	852 (83.8)	165 (16.2)
Single	35 (3.3)	31 (88.6)	4 (11.4)
Missing data	2 (0.2)		
Family size:			
≤ 3	762 (72.6)	641 (84.1)	121 (15.9)
≥ 4	288 (27.3)	241 (83.7)	47 (16.3)
Missing data	11(1.0)		
Maternal education:			
< 6th grade	326 (30.9)	270 (82.8)	56 (17.2)
≥6th grade	726 (68.9)	613 (84.4)	113 (15.6)
Missing data	2 (0.2)		
Maternal working condition:			
Housewife	668 (63.4)	574 (85.9)	94 (14.1)
Employed	382 (36.2)	307 (80.4)	75 (19.6)
Missing data	4 (0.4)		
Mother's religious affiliation:			
Orthodox	631 (59.9)	522 (82.7)	109 (17.3)
Muslim	154 (14.6)	127 (82.5)	27 (17.5)
Protestant Christian	263 (25.0)	230 (87.5)	33 (12.5)
Missing data	6 (0.5)		
Mother's first child:			
Yes	354 (33.6)	300 (84.7)	54 (15.3)
No	700 (66.4)	585 (83.6)	115 (16.4)
Mode of delivery:			
Vaginal	890 (84.4)	747 (83.9)	143 (16.1)
Cesarean section or other	130 (12.3)	114 (87.7)	16 (12.3)
Missing data	34 (3.2)		
Child's sex:			
Male	564 (53.5)	466 (82.6)	98 (17.4)
Female (reference)	490 (46.5)	419 (85.5)	71 (14.5)
Breastfeeding:			
Yes	915 (88.2)	772 (84.4)	143 (15.6)
No	122 (11.8)	98 (80.3)	24 (19.7)

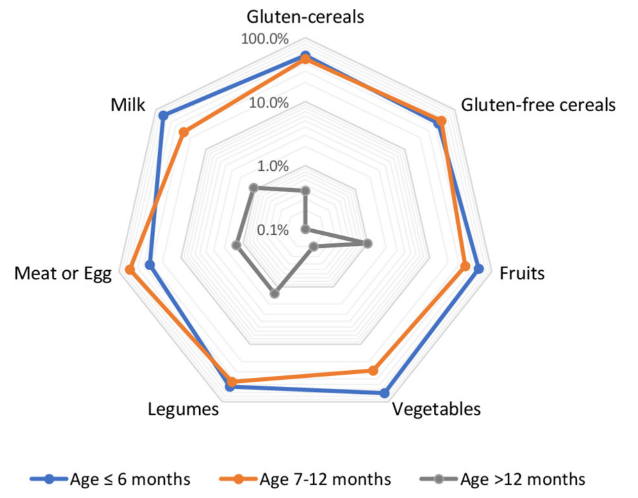

FIGURE 1 | First introduction to complementary foods by age (%).

RESULTS

Sociodemographic Characteristics of the Study Population

A total of 1,054 mother-child (53.5% boys) pairs from the 9- and 18-month visits were included in the study (**Table 1**). The median age of mothers in the study was 25 (range 15–40) years. The distribution of the marital status of mothers showed that the majority of women (96.5%) were married. More than half of the mothers (68.8%) had 6 years of primary school education or longer. Most of the women identified their religious affiliation as Orthodox Christianity (60%), were housewives by occupation (63.8%), and had an average of three family members living in the household (72.6%). Information about the mode of the delivery indicated that most mothers gave birth by vaginal delivery (84.4%). A third of the participating infants (33.6%) was the first-born child, and the median age of the children at the time of data collection was 9 months (range 9–18).

Infant Feeding Practices and Factors Associated With Early CF

At the age of 6 months, 86.1% of the children were still being breastfed and had started CF. The majority (84.0%) of children were introduced to solid, semi-solid, or liquid forms of complementary food, on an average at 6 months of age. Few children (3.5%) were introduced to complementary food before 6 months of age. A cow milk-based infant formula was among the first foods to be introduced, often initiated earlier than 2 months by some families. The most common foods introduced before 6 months were milk, vegetables, fruits, gluten-containing cereals, legumes, gluten-free cereals, while meat or eggs were the most common foods introduced at 6 months of age (**Figure 1**).

Gluten-containing cereals (wheat, barley, and rye) were introduced at a median age of 6.8 months (range 4–18), while a gluten-free cereal such as teff was introduced at a median age of 7.0 (range 5–16) months. The majority of children were fed with both gluten-containing foods (53.0%) and gluten-free cereal-based foods (52.0%) more than two times a day. Vegetables, fruits, gluten-containing grains, legumes, and milk were often introduced simultaneously at 6 months, whereas teff, meat, and eggs were introduced, on average, after 6 months of age.

Young maternal age (< 20 years) was associated with timely initiation of CF (i.e., by age of 6 months) as compared to

TABLE 2 | Multivariable logistic regression analysis of factors associated with the initiation of CF at 6 months of participating children.

Variable	COR (95%CI)	AOR (95%CI)
Maternal age:		
<20	2.06 (1.11–3.82)*	2.66 (1.28–5.53)*
20–24	1.13 (0.70–1.18)	1.18 (0.68–2.03)
25–30	1.32 (0.85–2.05)	1.38 (0.86–2.23)
>30 (reference)	1	1
Marital status:		
Married	1	1
Single	1.50 (0.52–4.31)	1.58 (0.54–4.64)
Family size:		
≤3 (reference)	1	1
≥ 4	0.97 (0.67–1.40)	1.18 (0.76–1.82)
Maternal education:		
<6th grade	0.89 (0.63–1.26)	0.93 (0.64–1.37)
≥6th grade	1	1
Maternal occupation:		
Housewife (reference)	1	1
Employed	1.49 (1.07–2.08)*	0.68 (0.48–0.97)*
Mother's religious affiliation:		
Orthodox (reference)	1	
Muslim	0.08 (0.45–1.04)	-
Protestant Christian	0.68 (0.39–1.17)	-
Mother's first child:		
Yes	1.09 (0.77–1.55)	0.98 (0.65–1.50)
No (reference)	1	1
Mode of delivery:		
Cesarean section	0.73 (0.42–1.28)	0.98 (0.65–1.50)
Vaginal	1	1
Child's sex:		
Male	0.73 (0.42–1.28)	1.24 (0.87–1.76)
Female (reference)	1	1
Breastfeeding:		
Yes	0.76 (0.47–1.22)	0.71 (0.43–1.18)
No	1	1

**P < 0.05; CF, complementary food; CI, confidence interval; AOR, adjusted odds ratio; COR, crude odds ratio.*

older mothers (>20 years) [$COR = 2.06$, (95% CI, 1.11, 3.83) and $AOR = 2.66$, (95% CI, 1.28, 5.53)]. Mothers who were employed outside of the home were also associated with the time of initiation of CF compared with mothers who reported their occupation as a housewife [$COR = 1.49$, (95% CI, 1.07, 2.08) and $AOR = 0.68$, (95% CI, 0.48, 0.97)] (**Table 2**). None of the other sociodemographic factors (maternal education, marital status, religion, the birth order of the child, or gender) were associated with the timing of CF in this study.

Anthropometrics

The child anthropometry revealed that about 16.9% of the children were stunted (**Figure 2**). The corresponding numbers for wasting, underweight, and low BMI by age were 4.5, 2.5, and 6.3%, respectively (**Figure 2**). There was an association between a child's sex with stunting (95% CI, 0.12, 0.63) and underweight (95% CI, 0.08, 0.036), respectively (**Figure 2**).

DISCUSSION

The first 2 years of life are a critical time window for optimal growth, development, and health of a child (21). The introduction of an adequate, appropriate, and safe dietary intake at the age of 6 months following exclusive breastfeeding is recommended by WHO since inadequate nutrient intake during this period increases the risk for underweight or overweight with potentially lifelong health problems.

The present study included children under the age of 2 years living in the city of Adama and the surrounding area in the Oromia region in central Ethiopia. The median age of initiation of CF was 6 months of age and only 3.6% of the parents started CF earlier than the WHO recommendations (22). Results of this study are in line with a study conducted in Addis Ababa, in which 83% followed the WHO infant feeding recommendations (10). On the other hand, the proportion of children following the recommendations is higher than studies conducted in other parts of the country, including Mekele in northern Ethiopia (62%) (23), Arsi Negelle (72%) (24), and in Sodo town in southern Ethiopia (71%) (25). The proportion is also much higher than the finding from the national prevalence in Ethiopia (56%) (26), Tahatay Maichew (53%) (27), Gonder town in northern Ethiopia (47%) (28), Damot Weydie (50.6%) (29), and Kamba in southern Ethiopia (40.6%) (30).

Disparities in the timely initiation of CF between different parts of Ethiopia could be explained by the variation in maternal occupations, awareness of recommended WHO guidelines, urban vs. rural residency of the study participants, data collection approaches, the identified religious affiliation of a population, and/or socioeconomic status. Location can also contribute to varied access to health services and information. All mothers who were enrolled in the present study attended both ANC and postnatal care at health institutes where the study was conducted. The variables are both important indicators of successful infant and young children feeding practices.

The majority of children in the study received foods made from vegetables (96%) and gluten-free cereals (92%) by 18 months of age. In contrast, foods made from legumes and dairy products are received by relatively low numbers of children. These results are in accordance with previous studies in Ethiopia regarding foods made from cereals and dairy products but are higher than other studies, which usually found low consumption of vegetables (31). Discrepancies in types of foods consumed might be explained by a variation in the socioeconomic status of the study participants or differences among parents' awareness of the importance of the variety of food items recommended by WHO.

Being a mother younger than age 20 years was one of the factors associated with following the complementary infant feeding recommendations of WHO, which is in contrast with studies from Southwest of Ethiopia (30). The other associated factor with the time of infant feeding was maternal

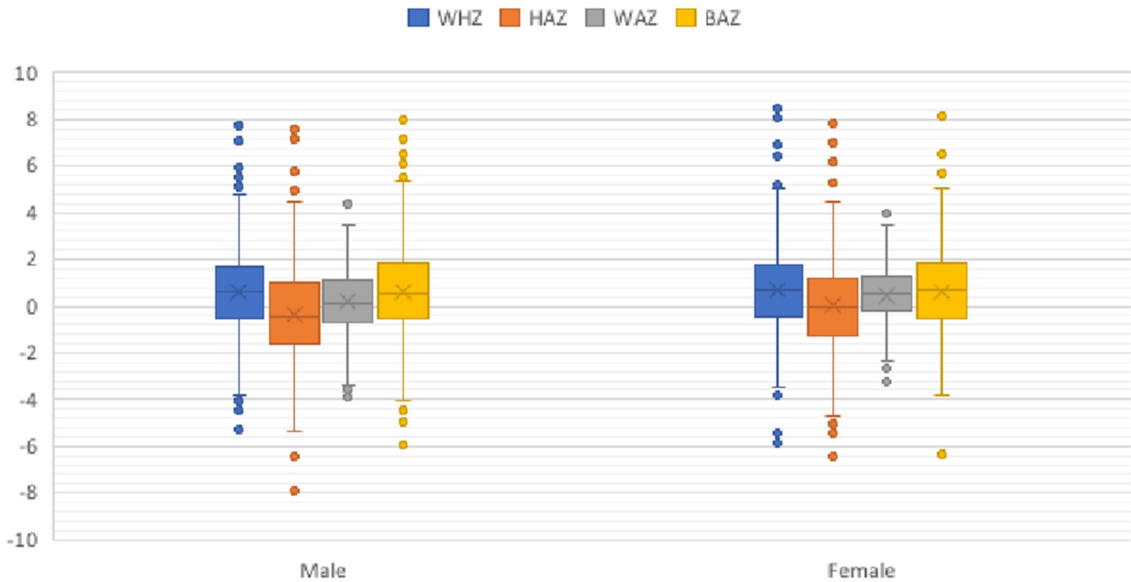

FIGURE 2 | Child anthropometrics by sex. BAZ, body mass index for age z-score (<-2 SD, low BMI); HAZ, height-for-age z-score (<-2 SD, stunted); WAZ, weight-for-age *z*-score (<-2 SD, underweight); WHZ, weight-for-height z-score (<-2 SD, wasted).

occupation (32). These findings are in contrast with those of previous studies that demonstrated an association between time of infant feeding and religious affiliation (33) or mode of delivery (34, 35). The disparities in CF habits in mothers by age compared with previous studies from other regions of Ethiopia may be severalfold; this study indicates the associations with the employment of the mother outside the home and having access to health services during ANC and postnatal care.

In the present study, a lower proportion of the children experienced wasting, stunting, underweight, and low BMI for their age compared with studies from other areas of Ethiopia (26, 36). This discrepancy might be related to the difference in the culture of feeding, parents' awareness of WHO feeding recommendations, or socioeconomic variation, access to information or methods of measures on IYCF practices. Another plausible explanation could be a selection bias in study participants, in which those attending health services are also more likely to participate in a research study. Although these may all confound the findings, stunting and underweight were more common in males compared with females, which confirms previous reports (37, 38).

A strength of the present study is the study design in which data were continuously and prospectively collected close to birth with information about the health status of both the mother and the child. A limitation is that data were collected in only one city with close surroundings, which may not be representative for all surrounding rural areas or other urban cities of Ethiopia and, therefore, may not fully represent the community in the Oromia region. Moreover, information on CF habits was only presented at the 9- and 18-month visits, which may not be represented as the children grow older. Other potential limitations include missing data on the socioeconomic status of the mother and only including one child per family to participate in the study. It cannot be ignored that CF habits differ in families with more than one child in the household and families with different socioeconomic backgrounds. Also, the study focuses on the age of initiation of CF practices and does not investigate CF indicators, such as minimum dietary diversity, meal frequency, and recommended diets. Finally, the quality and quantity of the food types were not investigated.

CONCLUSION

In conclusion, the present study from the city of Adama in the Oromia region in central Ethiopia demonstrates that a majority of mothers follow the WHO recommendations in introducing CF to infants at the age of 6 months. Gluten-free cereals are among the most consumed food types by children in the study area. Mothers younger than 20 years old and the employment of mothers outside of the home were factors associated with the timely initiation of the CF of the infant. This finding is noteworthy since it gives updated information on infant feeding and stimulates more research into the frequency, quality, and quantity of food consumed by infants.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Armauer Hansen Research Institute, National Research Ethics Committee of Ethiopia, Lund University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AG conducted the research and statistical analysis and drafted the manuscript. DA and CA contributed to the result interpretation and writing of the manuscript. DA contributed to the study design, editing of the manuscript, and overall supervision of the study. CA and TT contributed to the critical reading and editing of the manuscript. All authors accepted the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.672462/full#supplementary-material

REFERENCES

1. World Health Organization. *Complementary Feeding: Report of the Global Consultation and Summary of Guiding Principles for Complementary Feeding of the Breastfed Child*. Geneva: World Health Organization (2003). Available online at: https://apps.who.int/iris/handle/10665/42739
2. Demilew YM, Tafere TE, Abitew DB. Infant and young child feeding practice among mothers with 0-24 months old children in Slum areas of Bahir Dar City, Ethiopia. *Int Breastfeed J.* (2017) 12:26. doi: 10.1186/s13006-017-0117-x
3. Saha KK. Appropriate infant feeding practices result in better growth of infants and young children in rural Bangladesh. *Am J Clin Nutr.* (2008) 87:1852–9. doi: 10.1093/ajcn/87.6.1852
4. Pearce J, Taylor M, Langley-Evans S. Timing of the introduction of complementary feeding and risk of childhood obesity: a systematic review. *Int J Obes.* (2013) 37:1295–306. doi: 10.1038/ijo.2013.99
5. Biks GA, Tariku A, Wassie MM, Derso T. Mother's Infant and Young Child Feeding (IYCF) knowledge improved timely initiation of complementary feeding of children aged 6–24 months in the rural population of northwest Ethiopia. *BMC Res Notes.* (2018) 11:1–7. doi: 10.1186/s13104-018-3703-0
6. Teji Roba K. Infant and Young Child Feeding (IYCF) practices among mothers of children aged 6–23 months in two agro-ecological zones of rural Ethiopia. *Int J Nutr Food Sci.* (2016) 5:185–94. doi: 10.11648/j.ijnfs.20160503.16
7. Sadauskaite-Kuehne V, Ludvigsson J, Padaiga Ž, Jašinskiene E, Samuelsson U. Longer breastfeeding is an independent protective factor against development of type 1 diabetes mellitus in childhood. *Diabetes Metabol Res Rev.* (2004) 20:150–7. doi: 10.1002/dmrr.425
8. Akobeng AK, Ramanan AV, Buchan I, Heller RF. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. *Arch Dis Childhood.* (2006) 91:39–43. doi: 10.1136/adc.2005.082016
9. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am J Clin Nutr.* (2004) 80:1342–52. doi: 10.1093/ajcn/80.5.1342
10. Mohammed S, Getinet T, Solomon S, Jones AD. Prevalence of initiation of complementary feeding at 6 months of age and associated factors among mothers of children aged 6 to 24 months in Addis Ababa, Ethiopia. *BMC Nutr.* (2018) 4:54. doi: 10.1186/s40795-018-0264-5
11. Teshale AB, Tesema GA. Timely initiation of breastfeeding and associated factors among mothers having children less than two years of age in sub-Saharan Africa: a multilevel analysis using recent demographic and health surveys data. *PLoS ONE.* (2021) 16:e0248976. doi: 10.1371/journal.pone.0248976
12. Nkoka O, Mhone TG, Ntenda PAM. Factors associated with complementary feeding practices among children aged 6-23 mo in Malawi: an analysis of the demographic and health survey 2015-2016. *Int Health.* (2018) 10:466–79. doi: 10.1093/inthealth/ihy047
13. Abeshu MA, Lelisa A, Geleta B. Complementary feeding: review of recommendations, feeding practices, and adequacy of homemade complementary food preparations in developing countries–lessons from Ethiopia. *Front Nutr.* (2016) 3:41. doi: 10.3389/fnut.2016.00041
14. Lee H. Teff, a rising global crop: current status of teff production and value chain. *Open Agric J.* (2018) 12:185–93. doi: 10.2174/1874331501812010185
15. Yilmaz HO, Arslan M. Teff: nutritional compounds and effects on human health. *Acta Sci Med Sci.* (2018) 2:15–8.
16. Shumoy H, Raes K. Tef: The rising ancient cereal: what do we know about its nutritional and health benefits? *Plant Foods Hum Nutr.* (2017) 72:335–44. doi: 10.1007/s11130-017-0641-2
17. Institute EPH ICF. *Ethiopia Mini Demographic and Health Survey 2019: Key Indicators*. EPHI and ICF (2019).
18. Gudeta AN, Ramelius A, Balcha TT, Girma A, Ilonen J, Agardh D. Distribution of HLA-DQ risk genotypes for celiac disease in Ethiopian children. *HLA.* (2020) 96:681–7. doi: 10.1111/tan.14119
19. Björkman P. *Tuberculosis Infection in Women of Reproductive Age and Their Infants.* (2017). Available online at: https://clinicaltrials.gov/ct2/show/NCT03305991 (accessed March 17, 2021).
20. De Onis M, Habicht JP. Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee. *Am J Clin Nutr.* (1996) 64:650–8. doi: 10.1093/ajcn/64.4.650
21. Victora CG, De Onis M, Hallal PC, Blössner M, Shrimpton R. Worldwide timing of growth faltering: revisiting implications for interventions. *Pediatrics.* (2010) 125:e473–e80. doi: 10.1542/peds.2009-1519
22. World Health Organization. *Strengthening Action to Improve Feeding of Infants and Young Children 6-23 Months of Age in Nutrition and Child Health Programmes: Report of Proceedings*. Geneva: World Health Organization (2008). Available online at: https://apps.who.int/iris/handle/10665/44034
23. Shumey A, Demissie M, Berhane Y. Timely initiation of complementary feeding and associated factors among children aged 6 to 12 months in Northern Ethiopia: an institution-based cross-sectional study. *BMC Public Health.* (2013) 13:1050. doi: 10.1186/1471-2458-13-1050
24. Kassa T, Meshesha B, Haji Y, Ebrahim J. Appropriate complementary feeding practices and associated factors among mothers of children

age 6–23 months in Southern Ethiopia, 2015. *BMC Pediatr.* (2016) 16:131. doi: 10.1186/s12887-016-0675-x
25. Chane T, Bitew S, Mekonnen T, Fekadu W. Initiation of complementary feeding and associated factors among children of age 6-23 months in Sodo town, Southern Ethiopia: cross-sectional study. *Pediatr Rep.* (2017) 9:7240. doi: 10.4081/pr.2017.7240
26. Amare ZY, Ahmed ME, Mehari A. Determinants of nutritional status among children under five age in Ethiopia: a further analysis of the Ethiopian Demographic and Health Survey (EDHS) 2016 Data. *bioRxiv.* (2019) 2019:698308. doi: 10.1101/698308
27. Reda EB, Teferra AS, Gebregziabher MG. Time to initiate complementary feeding and associated factors among mothers with children aged 6–24 months in Tahtay Maichew district, Northern Ethiopia. *BMC Res Notes.* (2019) 12:17. doi: 10.1186/s13104-019-4061-2
28. Bazezew K, Worku W, Abebe Z. Timely initiation of complementary feeding practices in Gondar town Northwest Ethiopia: a cross-sectional Study. *Ecol Food Nutr.* (2020) 59:329–41. doi: 10.1080/03670244.2020.1733994
29. Epheson B, Birhanu Z, Tamiru D, Feyissa GT. Complementary feeding practices and associated factors in Damot Weydie District, Welayta zone, South Ethiopia. *BMC Public Health.* (2018) 18:1–7. doi: 10.1186/s12889-018-5245-8
30. Agedew E, Demissie M, Misker D, Haftu D. Early initiation of complementary feeding and associated factors among 6 months to 2 years young children. Kamba Woreda, South West Ethiopia: a community–based cross-sectional study. *J Nutr Food Sci.* (2014) 4:314. doi: 10.4172/2155-9600.1000314
31. Yonas F. Infant and young child feeding practice status and associated factors among mothers of under 24-month-old children in Shashemene Woreda, Oromia region, Ethiopia. *Open Access Libr J.* (2015) 2:1. doi: 10.4236/oalib.1101635
32. Tamiru D, Aragu D, Belachew T. Survey on the introduction of complementary foods to infants within the first six months and associated factors in rural communities of Jimma Arjo. *Int J Nutr Food Sci.* (2013) 2:77–84. doi: 10.11648/j.ijnfs.20130202.18
33. Oladejo T A, Elizabeth T A, Isaac O A, Lavalle T. Role of religion on knowledge, attitude and practices of lactating mothers on infant feeding. *Int J Nutr.* (2019) 4:14–25. doi: 10.14302/issn.2379-7835.ijn-19-2876
34. Saeed G, Fakhar S, Imran T, Abbas LK. The effect of modes of delivery on infants' feeding practices. *Iran J Med Sci.* (2011) 36:131.
35. Saaka M, Hammond AY. Caesarean section delivery and risk of poor childhood growth. *J Nutr Metab.* (2020) 2020:6432754. doi: 10.1155/2020/6432754
36. Ahmadi D, Amarnani E, Sen A, Ebadi N, Cortbaoui P, Melgar-Quiñonez H. Determinants of child anthropometric indicators in Ethiopia. *BMC Public Health.* (2018) 18:626. doi: 10.1186/s12889-018-5541-3
37. Woldeamanuel BT, Tesfaye TT. Risk factors associated with under-five stunting, wasting, and underweight based on Ethiopian demographic health survey datasets in Tigray region, Ethiopia. *J Nutr Metabol.* (2019) 2019:6967170. doi: 10.1155/2019/6967170
38. Thurstans S, Opondo C, Seal A, Wells J, Khara T, Dolan C, et al. Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in under nutrition. *BMJ Global Health.* (2020) 5:e004030. doi: 10.1136/bmjgh-2020-004030

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Assessing Dietary Intake Patterns Through Cluster Analysis Among Adolescents in Selected Districts of Bihar and Assam From India: A Cross-Sectional Survey

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Background: In the recent decade, dietary pattern assessment has evolved as a promising tool to describe the whole diet and represent inter-correlations between different dietary components. We aimed to derive the dietary patterns of adolescents (10–19 years) using cluster analysis on food groups and evaluate these patterns according to their socio-demographic profile.

Methods: This community-based cross-sectional study was conducted in two districts, each from Bihar and Assam in India. Adolescents (10–19 years) were enrolled from both rural and urban areas. The dietary intake was assessed through a pre-validated single food frequency questionnaire. Cluster analysis was performed by a 2-step procedure to explore dietary patterns, pre-fixed at 2 clusters. Clusters were analyzed with respect to socio-demographic characteristics using binomial logistic regression.

Results: A total of 826 girls and 811 boys were enrolled in the study. We found two major dietary patterns, namely a low- and high-mixed diet. The low-mixed diet (76.5% prevalence) had daily consumption of green vegetables, including leafy vegetables, with less frequent consumption of other foods. The high-mixed diet (23.5% prevalence) had more frequent consumption of chicken, meat, egg, and milk/curd apart from green vegetables. Adolescent boys had 3.6 times higher odds of consuming a low-mixed diet compared to girls. Similarly, adolescents with lower education grades and from marginalized social classes had two times higher odds of taking a low-mixed diet than their respective counterparts.

Conclusions: The high consumption of a low-mixed diet and relatively less milk consumption limit the comprehensive growth of adolescents. Improvement in dietary intake of adolescents from marginalized sections of society can prove to be an important deterrent in mitigating India's nutritional challenges.

Keywords: adolescent, diet surveys, food, meat, nutrition assessment, vegetables

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INTRODUCTION

Adolescence, defined by the World Health Organization as the age between 10 and 19, is a period of physical, cognitive, and psychosocial growth and development (1). It is estimated that men and women gain 50% of adult weight and 15% of adult height during adolescence. Hence, it is imperative to understand that adequate nutrition is important for attaining full growth potential, and any insults or poor nutrition during adolescence may have transgenerational consequences (2). Adolescence represents a window of opportunity to recuperate the growth insults that ensued early in life (3). There is a growing interest at the public health and policy levels in understanding the complex adolescent health and nutrition needs (1). Investment in adolescent health and well-being has been recognized as one of the best investments for achieving the United Nation's Sustainable Development Goals (4).

The world's 90% of adolescents are concentrated in low- and middle-income countries (5). India has the largest number of adolescents globally, ∼243 million, and they have a huge potential to generate greater economic dividends for the nation (4). However, a large number of adolescents are vulnerable in India. For instance, 42 and 54% of adolescent girls aged 15–19 are thin (Body Mass Index (BMI) < 18.5 Kg/m^2) and anemic, respectively. Similarly, 45 and 29% of adolescent boys aged 15–19 are thin (BMI < 18.5 Kg/m^2) and anemic in India, respectively (6). According to the recent comprehensive national nutrition survey (2016–2018), 16–37% of adolescents had micronutrient deficiencies of different types, including deficiency of vitamin A, vitamin D, folate, zinc, and vitamin B12 (7).

The prevalence of undernutrition and micronutrient deficiencies is not equitable and differs across geographies, ethnicities, gender, religion, and other socio-demographic attributes (7). For example, adolescents in the early age group (10–14 years) and from marginalized families, rural areas, Hindu families, and the poorest of the poor socio-economic strata had the highest prevalence of vitamin A deficiencies compared to their respective counterparts. Similarly, adolescents with a vegetarian diet have been found to have high probabilities of micronutrient deficiencies (7). This spotlights the influence of various socio-demographic attributes in the nutrition of adolescents, and hence they need to be understood while comprehending the nutrition profile of the population.

For better understanding the nutrition profile of the population, it is imperative to consider the dietary patterns, argued to describe the whole of the diet better, and represent inter-correlations between different dietary components (3). Also, dietary patterns' assessment generates an evidence base and provides public health recommendations to interventionists (8). Many studies in the past have attempted to assess the dietary patterns of the Indian population (9–12). Most of these studies have identified a vegetarian dietary pattern based on fruits, vegetables, pulses, and cereals, with added dairy products, meat, and eggs in many cases. Large variations in the dietary patterns in different geographical regions have been noticed with higher consumption of fish or egg or meat in the Eastern parts compared to the Northern or Western parts of the country. However, it is crucial to note that adolescents have been underrepresented or not included in most of these studies (13).

Furthermore, most of the studies used principal component analysis (PCA) for finding patterns that may not be very useful in terms of interpretation (13). PCA does not represent the whole of the diet; instead, it describes patterns artificially composed of a few distinguishing food items without calculating the consumption of each food group in each pattern (14). On the contrary, cluster analysis groups individuals into distinct dietary patterns who share similar frequency patterns for food consumption. Besides, cluster analysis can be used for both categorical and continuous variables (15).

Considering the abovementioned gaps, we decided to explore dietary patterns among adolescents for developing a nutrition-specific intervention. The present study was a part of the formative assessment to inform the intervention aimed at improving the maternal, child, and adolescent health and nutrition conducted by MAMTA-Health Institute for Mother and Child, a not-for-profit institution. The project, entitled MANCH (Maternal, Adolescent, Newborn, and Child Health), was implemented across two districts, namely Munger and Darrang, each in Bihar and Assam, respectively. The specific objectives of the MANCH project were: (a) to improve the nutritional status of adolescents, pregnant women, and lactating mothers, (b) to improve access to public health services by them, and (c) to enhance self-efficacy of adolescents through life skills to prevent early marriage. The formative assessment was done at the beginning of the project to evaluate the baseline measures of the indicators corresponding to the project's objectives. However, the present study restricts itself to derive the dietary patterns of adolescents (10–19 years) using cluster analysis on different food groups and evaluate these patterns with respect to the selected socio-demographic profile.

METHODS

Study Design

We conducted a community-based cross-sectional study of adolescents (girls and boys) in Bihar and Assam, situated in east and North-east part of India, respectively.

Study Setting and Sampling

Situated to the east of the capital of Bihar, Munger has a population of 1.3 million, a sex ratio of 876 females per 1,000 males, 62% female literacy rate, and 31% of non-pregnant women (15–49 years) with undernutrition and 65% with anemia (6). Similarly, situated to the north of the capital of Assam, Darrang has a population of 0.93 million, a sex ratio of 935 females per 1,000 males, 58% of female literacy rate, and 27.5% of non-pregnant women (15–49 years) with undernutrition and 46% with anemia (6).

The states and districts were purposively selected as both were the part of a larger intervention project. The intervention areas comprised of 45 urban wards and 6 village-level local elected bodies called Gram Panchayats in Munger district of Bihar and; 4 Gram Panchayats in Darang district of Assam. The survey was concluded in 26 villages from 4 Gram panchayats in

Darang (Ramhari, Chamuapara, Chapai, and Dahi). Similarly, survey was conducted in 52 villages from 6 Gram Panchayats of Munger (Shankarpur, Mahuli, Shreematpur, Kataria, Mayee, and Mirzapur Bardeh). Around 8 adolescent boys and 8 girls were selected per village or ward. One adolescent was selected per household, the selection of which is described below.

From the two selected districts, all the target villages and urban wards were listed, and the required numbers of primary sampling units for the survey were selected using probability proportion to size method. Villages or urban wards were the primary sampling units for the survey. In the selected village, the interviewers started the interview from any one side of the village, following the right-hand approach by choosing every second household until the required number is achieved. The selection of households in the village was carried out, considering at least one eligible respondent in the household. The eligible respondents were unmarried adolescents in the age group of 10–19 years residing in the area for the past 6 months. In case a household has more than one eligible respondent then, only one out of the eligible respondents was interviewed, and the selection of such respondent was made through a lottery method.

Similarly, in urban areas from each ward, we selected two colonies (the bigger one) randomly. Similar to rural areas, all other processes of selection of respondents were done in the same fashion. We applied a circular systematic random sampling method to achieve the target sample in each primary sampling unit. It needs mention here that an equal number of both male and female adolescents were selected for the study. Around 78 villages and 45 urban wards were the primary sampling units.

Sample Size

Using a 25.7% prevalence of underweight (BMI < 18.5 kg/m^2) among women of reproductive age (15–49 years) (6), at 95% confidence level, 5% absolute error, design effect of 1.5, and 15% dropout rate, the sample size was calculated at 534. The design effect of 1.5 was considered because of the stratification of the population into districts, blocks, and villages (arising out of stratified random sampling). A dropout rate of 15% was considered amidst the assent or consent required from adolescents and their parents (for which they do not agree at times) and refusal of adolescents to give time for the interviews as they are busy in household chores or agriculture fields or schools. This sample size of adolescents was interviewed at each of the three sites (one rural and urban site in Bihar and one rural site in Assam) and divided equally between boys and girls. The sample size calculation and equal division into girls and boys was a part of the baseline assessment of the project.

Survey Process

A team of 10 investigators at each site identified the eligible respondents through visits to their houses after school hours. An induction training of the investigators on the questionnaire followed by telephonic mentoring on a weekly basis was done. All the interviews were conducted in the local language (Indian languages). For instance, in Bihar and Assam, Hindi and Assamese were used, respectively, for the interview. Data were collected between October and December 2017.

Survey Instrument

Questionnaire: It consisted of questions on socio-demographic characteristics, dietary intake, history of tobacco use, and the consumption of alcohol. The socio-demographic characteristics included questions on age, gender, residence (rural or urban), social class (scheduled caste or tribe or special class or non-marginalized class), religion (Hindu, Muslim, and others), and years of schooling. Furthermore, we asked adolescents about the possession of below the poverty line card (BPL). The households identified after population-based surveys are distributed BPL cards. BPL status is based on socio-economic indicators and a minimum annual family income, which varies across states (16). In India, social class indicates a hereditary, endogenous, closed, and immutable group associated with an occupation and a particular position in the social hierarchy. Social classes such as scheduled caste or tribe or other special classes are considered marginalized classes (17). We asked adolescents if they worked outside the home for money. A structured and interviewer-based food frequency questionnaire (FFQ) of 9 food groups was used to assess the dietary intake. We adopted the pre-validated FFQ questionnaire used in the fourth round of the National Family Health Survey (NFHS-4) (6). The questions in FFQ had four possible responses, namely daily, weekly, occasionally, and never. The nine food groups included pulses (beans), milk (milk products), fruits, green, including leafy vegetables, eggs, fish, meat (chicken), snacks (fried foods), and cold drinks (other beverages). Cereals (wheat/rice/corn) were not included in the original survey, but it is known that wheat and rice consumption forms a major part of the diet of the Indian population (18). Furthermore, the questionnaire did not have any questions pertaining to the quantity or level of food consumption. Hence, portion sizes were not calculated. We employed a single FFQ method to assess the dietary patterns, which has been acknowledged to be sufficient to capture habitual dietary intake in previous studies (19). The respondents were adolescents themselves.

Ethical Considerations

We were cognizant of the fact that matters concerning adolescents are very sensitive; therefore, before the administration of the study, ethical clearance was taken by MAMTA Ethical Review Board. The consent and assent forms were developed as per the standard guideline, and due approvals were also taken from the said Board. Before each interview, consent and assent forms were read-out by the investigator, and once agreed by both parents and adolescents, and then only the interview was conducted.

Statistical Analysis

Data were expressed as frequency (percentages) for categorical variables. Besides, cluster analysis was performed to identify the dietary patterns by means of a 2-step procedure. This procedure grouped participants into clusters based on log-likelihood distances between observations, which assumed multinomial distribution for categorical variables. Subsequently, the clusters were treated as separate observations. Schwarz Bayesian Criterion was used to arrive at an initial number of clusters, which were 4 (Silhouette coefficient = 0.2). However, in the subsequent calculations, we pre-fixed the number of clusters based on nine food groups to be 2.

After multiple runs with different food groups in the first place and simultaneously performing a chi-square test to assess if all the food groups varied between different clusters, we decided to take only eight food groups. Pulses/beans category was removed from the final analysis as it did not vary between the two clusters ($p > 0.05$). The ratio of the larger to the smaller cluster, in the final analysis, was 3.25, and the Silhouette coefficient was 0.3. We compared clusters based on socio-demographic characteristics using binomial logistic regression for unadjusted and adjusted associations, respectively. Associations between clusters and socio-demographic characteristics were expressed as odds ratio (OR) and 95% confidence interval (CI). All the statistical analysis was performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A nearly equal number of adolescents belonged to early (46%) and late adolescence (54%) groups (**Table 1**). Around two-thirds of boys and girls were from the rural areas, as only one urban site from Munger was selected. Similarly, 65–63.5% of families of adolescents had below the poverty line card. More than two-thirds of adolescents were Hindus. Among the food groups, nearly 72% of girls and 60% of boys consumed green vegetables, including leafy vegetables, on a daily basis (**Table 2**). Likewise, three-fourths or more adolescent boys and girls consumed pulses/beans on a daily basis. More than two-thirds of boys and girls did not consume fruits even on a weekly basis.

We found two clusters in the analysis (**Table 3**). Fish and chicken/meat had the highest predictor importance in the two-step cluster analysis (**Figure 1**), which means that they are responsible for the wide difference between the clusters and are important predictors in estimating the model. The size of the larger cluster was 1,252 (76.5%), and the smallest cluster was 385 (23.5%). The first cluster had a higher percentage of adolescents consuming green vegetables, including leafy vegetables on a daily basis (68.8 vs. 54.5% in the second cluster), and fruits and fried foods (1.6–1.7 times the second cluster) sometimes than the second cluster. On the contrary, the second cluster had a large number of adolescents consuming meat/chicken, eggs and fishes on a weekly basis (65–80%) and milk/curd on a daily basis ($\sim$40%) compared to the first cluster. Hence, we named the first cluster as "low-mixed diet" and the second cluster as "high-mixed diet." Girls had a higher consumption of fish and chicken/meat compared to boys and also, these two food items had the highest predictor importance in the cluster analysis. Other food items such as milk and curd or green leafy vegetable had similar consumption between the two genders.

Adolescent boys had 3.6 times higher odds of consuming a low-mixed diet compared to girls (**Table 4**). Adolescents who were illiterate or had obtained education up to primary or middle grades had higher odds of having a low-mixed diet as compared to adolescents who obtained education up to senior secondary grade and above. Hindus had higher odds of low-mixed diet than Muslims in the unadjusted analysis, but not so after adjustments for socio-economic parameters. Social marginalization, such as belonging to scheduled caste or scheduled tribe and other special classes, was a significant predictor of the use of a low-mixed diet.

TABLE 1 | Percent distribution of adolescent boys and girls with respect to selected background characteristics in two districts of Bihar and Assam.

Variable	Adolescent girls (n = 826) N (%)	Adolescent boys (n = 811) N (%)
Age groups (years)		
Early adolescence (10–14)	389 (47.0)	365 (45.0)
Late adolescence (15–19)	437 (53.0)	446 (55.0)
Area		
Rural	548 (66.3)	549 (67.7)
Urban	278 (33.7)	262 (32.3)
Religion		
Hindu	555 (67.2)	582 (71.8)
Muslim	266 (32.2)	228 (28.1)
Others	5 (0.6)	1 (0.1)
Education status		
Up to primary (1–5th grade)	150 (19.2)	190 (24.0)
Middle class (6–8th grade)	241 (30.8)	209 (26.4)
Secondary class (9 and 10th grade)	263 (33.6)	263 (33.2)
Senior secondary class and above (11th and above)	129 (16.5)	129 (16.3)
Missing	20	43
Social class		
Scheduled caste/tribe	290 (35.1)	230 (28.4)
Other special class	247 (29.9)	290 (35.8)
Non-marginalized class	289 (35.0)	291 (35.9)
Possess below the poverty line card		
Yes	536 (64.9)	515 (63.5)
No	251 (30.4)	282 (34.8)
Don't know	39 (4.7)	14 (1.7)
Worked outside home		
Yes	96 (11.6)	41 (5.1)
No	730 (88.4)	770 (94.9)

SD, Standard Deviation; p-value < 0.05 was considered statistically significant.

DISCUSSION

In the present study, we found two major dietary patterns, namely a low- and high-mixed diet. The low-mixed diet had daily consumption of green vegetables, including leafy vegetables, with less frequent consumption of other foods. On the other hand, the high-mixed diet had more frequent consumption of chicken/meat, egg, and milk/curd apart from green vegetables. Adolescent boys, and adolescents with lower grades of education, and from marginalized classes had higher odds of low-mixed diet compared to their respective counterparts.

The findings of the present study indicated daily consumption of green vegetables, including leafy vegetables and pulses, among

TABLE 2 | Percent distribution of adolescents by frequency of consumption of specific food groups.

Food groups	Adolescent girls (n = 826) N (%)	Adolescent boys (n = 811) N (%)	P-value
Green, including leafy vegetables			
Daily	592 (71.7)	480 (59.2)	**<0.001**
Weekly	83 (10.0)	101 (12.5)	
Sometimes	124 (15.0)	207 (25.5)	
Never	27 (3.3)	23 (2.8)	
Fruits			
Daily	72 (8.7)	29 (3.6)	**<0.001**
Weekly	162 (19.6)	158 (19.5)	
Sometimes	572 (69.2)	611 (75.3)	
Never	20 (2.4)	13 (1.6)	
Egg			
Daily	55 (6.7)	41 (5.1)	**0.002**
Weekly	218 (26.4)	213 (26.3)	
Sometimes	479 (58.0)	518 (63.9)	
Never	74 (9.0)	39 (4.8)	
Fish			
Daily	44 (5.3)	11 (1.4)	**<0.001**
Weekly	239 (28.9)	109 (13.4)	
Sometimes	458 (55.4)	643 (79.3)	
Never	85 (10.3)	48 (5.9)	
Chicken/meat			
Daily	18 (2.2)	0	**<0.001**
Weekly	207 (25.1)	80 (9.9)	
Sometimes	518 (62.7)	693 (85.5)	
Never	83 (10.0)	38 (4.7)	
Fried foods			
Daily	31 (3.8)	6 (0.7)	**<0.001**
Weekly	78 (9.4)	31 (3.8)	
Sometimes	478 (57.9)	636 (78.4)	
Never	239 (28.9)	138 (17.0)	
Aerated drinks			
Daily	3 (0.4)	0	**<0.001**
Weekly	53 (6.4)	27 (3.3)	
Sometimes	547 (66.2)	744 (91.7)	
Never	223 (27.0)	40 (4.9)	
Milk/curd			
Daily	242 (29.3)	258 (31.8)	**<0.001**
Weekly	91 (11.0)	247 (30.5)	
Sometimes	372 (45.0)	264 (32.6)	
Never	121 (14.6)	42 (5.2)	
Pulses/beans			
Daily	711 (86.1)	608 (75.0)	**<0.001**
Weekly	54 (6.5)	137 (16.9)	
Sometimes	58 (7.0)	56 (6.9)	
Never	3 (0.4)	10 (1.2)	

p-values < 0.05 are highlighted in bold.

more than 60% of adolescents. Similar findings with regard to the consumption of vegetables (both green leafy and other vegetables) among adolescents were reported in another study (20). The NFHS-4 (2015-16) reported at least once a week consumption of both vegetables and pulses among 83–89% of adolescent boys and girls (15–19 years) (6). Another study reported daily consumption of vegetables by only one-third of adolescents (21). The plausible explanation for the frequent consumption of green vegetables in our study could be a single category for all types of green vegetables compared to separate categories in other studies. Furthermore, most of the population in our study (nearly two-thirds) belonged to the rural areas that had easy access to and availability of locally-grown vegetables compared to urban areas. The consumption of fruits was poor in our study. Only one-fifth of adolescents consumed fruits on a weekly basis. Likewise, other studies from Uttar Pradesh and Kolkata reported low consumption of fruits among school-going adolescents (20, 22).

TABLE 3 | Percent distribution of two clusters according to selected food groups.

Food groups	Cluster-1 (Low-mixed diet) Frequency (%)	Cluster-2 (High-mixed diet) Frequency (%)
Green, including leafy vegetables	Daily (68.8)	Daily (54.5)
Fruits	Sometimes (80.3)	Sometimes (46.2)
Egg	Sometimes (75.2)	Weekly (65.5)
Fish	Sometimes (86.3)	Weekly (81.3)
Chicken/meat	Sometimes (88.7)	Weekly (69.6)
Fried foods	Sometimes (74.4)	Sometimes (47.3)
Aerated drinks	Sometimes (84.3)	Sometimes (61.0)
Milk/curd	Sometimes (40.2)	Daily (39.7)

In the present study, the majority of the adolescents consumed egg, fish, or meat sometimes, and 5–10% of adolescents never consumed them. Low consumption of non-vegetarian food items could be partly explained by the cost factor (high cost of non-vegetarian food items) and easy availability of vegetables in villages (67–71%). Furthermore, it has been highlighted in the previous studies that the majority of Indians have a vegetarian dietary pattern influenced by religious beliefs (13, 23). It is surprising to see a low frequency of consumption of milk or milk products during adolescence in our study, which is a period of growth and development and requires a high intake of calcium and proteins. But, unfortunately, previous literature noted similar findings (20, 24). The study based by the National Sample Survey Organization (NSSO) reported that the consumption of milk has increased marginally or reduced in states like Bihar and Assam in the last 25 years (25).

The two clusters defined in the present study have been reported previously in another study using a similar FFQ questionnaire (26). The low-mixed diet was the predominant dietary pattern among adolescents in our study (76.5%). Amongst adolescents in the low-mixed cluster, quite large proportions (68.8%) reported daily consumption of green vegetables, including leafy vegetables, and the consumption of fried foods and aerated drinks (74–84%) sometimes. This may suggest two different possible conditions. Firstly, the high cost of non-vegetarian items, such as fish and meat, and easy availability

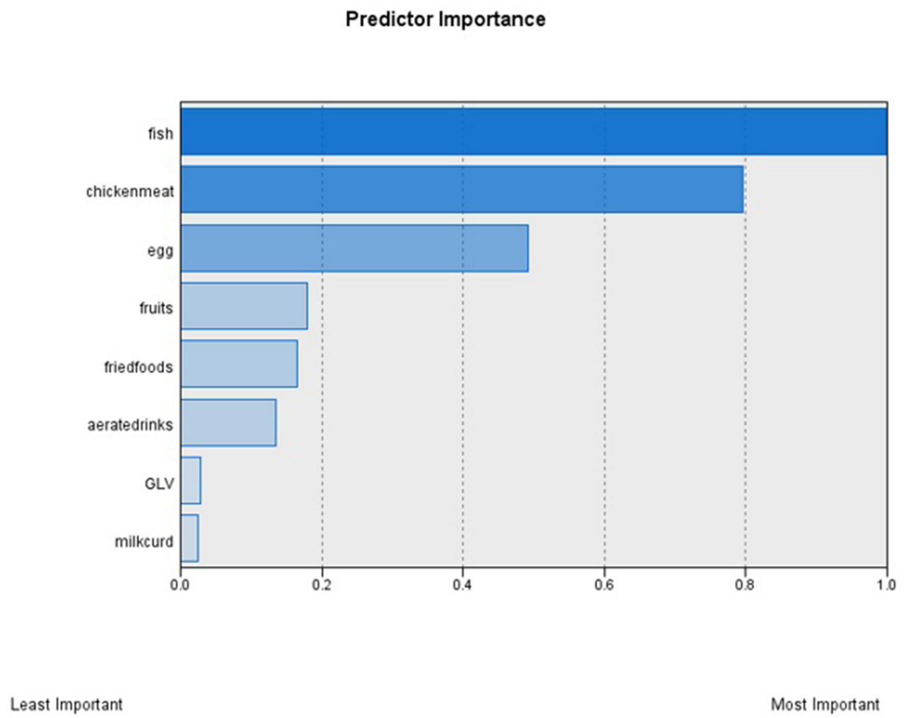

FIGURE 1 | Predictor importance of the selected food groups (*n* = 8). GLV, Green, including leafy vegetables. Contribution of each food item to the clustering solution as reported from the Two-Step cluster analysis. This shows the index of relative importance of each food item as identified by the Two-Step cluster analysis. Fish and chicken/meat had high predictor importance, meaning that they are responsible for the wide difference between the clusters. On the contrary. Green leafy vegetables (GLV) and milk/curd had lowest predictor importance. So, they are important in predicting a model.

of green leafy vegetables in the villages. Secondly, it could be because of the lack of knowledge about a balanced diet and healthy foods, including sources of protein or calcium like milk or curd. Furthermore, fish/meat/egg had the highest contribution in the clustering solution because they are less often eaten by the population in Bihar compared to other states (23, 27, 28). A similar study among rural adolescents and adults informed of lack of food diversity with less frequent consumption of fruits, and non-vegetarian food items in India, leading to nutritional deficiencies and inadequacy (29).

Globally, studies have documented a healthier dietary pattern among females. Multiple assumptions have been stipulated for the gender differences in dietary patterns, including weight-control behaviors and greater health consciousness among girls and masculinity ideation discouraging men from eating a healthy diet (20, 29). However, it will be difficult to conclude in our study that boys had a lower probability of eating a healthy diet compared to girls as both boys and girls consume veggies frequently, girls consume meats and fish more frequently, and both groups consume fried foods and aerated drinks infrequently. Increased access to fish/chicken/meat by girls should not be seen as a proxy for healthier diet consumption; instead, the underlying dynamics of intrahousehold food distribution need to be understood better and figured out why such differentials prevail.

The higher odds of consuming the low-mixed diet among less educated and marginalized populations suggest socio-economic inequalities in food consumption among the Indian population. Our findings are congruent with other studies reporting similar poor intake of nutrition among socially and economically backward populations (30, 31). Similar to our results, education has been found to influence the intake of a variety of food groups more than the economic status in other studies (32, 33). This highlights the need to ensure food security by improving the availability, access, and utilization of food to poor and marginalized populations (34). The targeted public distribution system in India bridged this gap by providing nutrition supplements to poor people. However, multiple challenges, including inaccurate identification of households, leakages, and diversions of food grains, inadequate storage capacity, and poor quality of food grains, exist in the targeted public distribution system (35).

Furthermore, it is acknowledged that regular family meals may promote the uptake and maintenance of healthy eating behaviors among adolescents. Regular family-oriented meals will improve the intake of fruits, vegetables, dietary fiber, and vitamins and cut down the intakes of saturated and trans fats (36).

LIMITATIONS

The study results should be interpreted with caution due to the following limitations. First, we could not include other food groups like roots and tubers, nuts or seeds, cereals, sweets, and milk-based beverages in the analysis due to the lack of questions

TABLE 4 | Logistic regression analysis showing results of unadjusted and adjusted odds ratio of the likelihood of the low-mixed diet with respect to selected background characteristics.

Variables	Unadjusted odds ratio (95% CI)*	*p*-value	Adjusted odds ratio (95% CI)*	*p*-value
Age groups (years)				
10–14	1.09 (0.86–1.37)	0.459	0.88 (0.63–1.23)	0.468
15–19	*Reference*		*Reference*	
Gender				
Male	3.44 (2.68–4.43)	**<0.001**	3.63 (2.79–4.73)	**<0.001**
Female	*Reference*		*Reference*	
Area				
Rural	0.79 (0.61–1.01)	0.063	0.84 (0.64–1.11)	0.239
Urban	*Reference*		*Reference*	
Religion				
Hindu	1.89 (1.49–2.40)	**<0.001**	1.17 (0.81–1.69)	0.404
Others	2.35 (0.27–20.29)	0.437	2.65 (0.28–25.25)	0.397
Muslim	*Reference*		*Reference*	
Education status				
Up to primary (1–5th grade)	1.60 (1.09–2.35)	**0.015**	2.15 (1.32–3.52)	**0.002**
Middle class (6–8th grade)	1.39 (0.98–1.98)	0.067	1.92 (1.22–3.00)	**0.004**
Secondary class (9 and 10th grade)	1.12 (0.80–1.56)	0.504	1.27 (0.88–1.83)	0.190
Senior secondary class and above (11th and above)	*Reference*		*Reference*	
Social class				
Scheduled caste/tribe	1.83 (1.39–2.41)	**<0.001**	1.94 (1.30–2.87)	**0.001**
Other special class	2.33 (1.75–3.10)	**<0.001**	2.26 (1.51–3.39)	**<0.001**
Non-marginalized class	*Reference*		*Reference*	
Possess below poverty line card				
Yes	1.04 (0.81–1.32)	0.757	1.10 (0.84–1.43)	0.481
Don't know	1.56 (0.74–3.28)	0.241	2.27 (1.01–5.07)	0.046
No	*Reference*		*Reference*	
Work outside				
Yes	1.01 (0.67–1.52)	0.963	1.33 (0.85–2.10)	0.208
No	*Reference*		*Reference*	

CI, Confidence interval; p-value < 0.05 was considered statistically significant.
**Cluster 2 was the reference category. p-values < 0.05 are highlighted in bold.*

on each of these groups in the validated NFHS-4 questionnaire. The inclusion of these food groups might have resulted in more distinct clusters. Second, although a single FFQ method is good for exploring the dietary patterns, there could be a recall bias of remembering the consumption of food items over weeks or months. Third, we could not obtain the dietary patterns of adults and reflect how different adolescents are from adults in the same families. Lastly, we could not collect data regarding the intake of cereals in the dietary intakes and quantify energy intakes. This would have explained the gender differences seen in the study.

CONCLUSIONS

In this study, we observed two dietary patterns, low- and high-mixed diets, among adolescents. The low-mixed diet, common among 76% of adolescents, had a low intake of non-vegetarian food items and milk. Adolescent boys and adolescents with lower education status and from marginalized classes had higher odds of consuming a low-mixed diet compared to their counterparts. Although Hindus had higher odds of low-mixed diet in the unadjusted model, the association became insignificant in the adjustment model.

The low-mixed diet with less frequent consumption of non-vegetarian food and milk can lead to micronutrient deficiencies and undernutrition among adolescents. Socio-cultural influences on the dietary intakes of Indian populations are significant and inevitable. Taking cognizance of these findings, public health interventions should target behavior change communication that aims to increase dietary diversity along with the intake of nutrients. This should involve a comprehensive health promotion strategy of educating adolescents and their parents/teachers on nutrition, besides strengthening nutrition supplementation programs of the government, such as mid-day meals and weekly iron-folic acid supplementation. Furthermore, food supplementation programs can ensure the provision of costly protein-rich food items (non-vegetarian) and milk through *Anganwadi* centers or mid-day meals in schools. Since adolescent boys had a higher consumption of the low-mixed diet, the reasons of the same should be explored, and the gaps need to be addressed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by MAMTA Ethical Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SMa and JK contributed to the conceptualization and design of the study, training of the field investigators on the questionnaire, monitoring the data collection, and reviewing or editing of the final manuscript. SS led the statistical analysis, interpretation of the data, and wrote the draft manuscript. SMe contributed to the conceptualization of the study and reviewed and edited the manuscript. C was involved in statistical analysis and editing of the final manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Patton GC, Sawyer SM, Santelli JS, Ross DA, Afifi R, Allen NB, et al. Ourfuture: a Lancet commission on adolescent health and well-being. *Lancet.* (2016) 387:2423–78. doi: 10.1016/S0140-6736(16)00579-1
2. Leroy JL, Ruel M, Sununtnasuk C, Ahmed A. Understanding the determinants of adolescent nutrition in Bangladesh. *Ann NY Acad Sci.* (2018) 1416:18–30. doi: 10.1111/nyas.13530
3. Andrew L, Thorne-Lyman SS, Mehra S, Wu LSF, Ali H, Alland K, et al. Dietary patterns of >30,000 adolescents 9-15 years of age in rural Bangladesh. *Ann NY Acad Sci.* (2019) 1468:3–15. doi: 10.1111/nyas.14207
4. Mehra S, Dharal S, Sharma S. Investing in our adolescents: assertions of the 11th world congress on adolescent health. *J Adol Health.* (2018) 63:9–11. doi: 10.1016/j.jadohealth.2018.05.005
5. Keats ECR, Rappaport AI, Shah S, Oh C, Jain R, Bhutta ZA. The dietary intake and practices of adolescent girls in low- and middle-income countries: a systematic review. *Nutrients.* (2018) 10:1978. doi: 10.3390/nu10121978
6. International Institute for Population Sciences (IIPS) and ICF. *National Family Health Survey (NFHS-4), 2015-16*: Mumbai: IIPS (2017).
7. Ministry of Health and Family Welfare (MoHFW) GoI, UNICEF and Population Council. *Comprehensive National Nutrition Survey (CNNS) National Report*. Ministry of Health and Family Welfare (MoHFW) GoI: New Delhi (2019).
8. Cespedes EM, Hu FB. Dietary patterns: from nutritional epidemiologic analysis to national guidelines. *Am J Clin Nutr.* (2015) 101:899–900. doi: 10.3945/ajcn.115.110213
9. Daniel CR, Prabhakaran D, Kapur K, Graubard BI, Devasenapathy N, Ramakrishnan L, et al. A cross-sectional investigation of regional patterns of diet and cardio-metabolic risk in India. *Nutr J.* (2011) 10:12. doi: 10.1186/1475-2891-10-12
10. Venkaiah K, Brahmam GNV, Vijayaraghavan K. Application of factor analysis to identify dietary patterns and use of factor scores to study their relationship with nutritional status of adult rural populations. *J Health Popul Nutr.* (2011) 29:327. doi: 10.3329/jhpn.v29i4.8448
11. Joy EJ, Green R, Agrawal S, Aleksandrowicz L, Bowen L, Kinra S, et al. Dietary patterns and non-communicable disease risk in Indian adults: secondary analysis of Indian Migration Study data. *Public Health Nutr.* (2017) 20:1963–72. doi: 10.1017/S1368980017000416
12. Kehoe SH, Krishnaveni GV, Veena SR, Guntupalli AM, Margetts BM, Fall CH, et al. Diet patterns are associated with demographic factors and nutritional status in South Indian children. *Matern Child Nutr.* (2014) 10:145–58. doi: 10.1111/mcn.12046
13. Green R, Milner J, Joy EJM, Agrawal S, Dangour AD. Dietary patterns in India: a systematic review. *Br J Nutr.* (2016) 116:142–8. doi: 10.1017/S0007114516001598
14. Hearty Á, Gibney M. Comparison of cluster and principal component analysis techniques to derive dietary patterns in Irish adults. *Br J Nutr.* (2008) 101:598–608. doi: 10.1017/S0007114508014128
15. Benassi M, Garofalo S, Ambrosini F, Sant'Angelo RP, Raggini R, De Paoli G, et al. Using two-step cluster analysis and latent class cluster analysis to classify the cognitive heterogeneity of cross-diagnostic psychiatric inpatients. *Front Psychol.* (2020) 11:e01085. doi: 10.3389/fpsyg.2020.01085
16. Ram F, Mohanty SK, Ram U. Understanding the distribution of BPL cards: all-India and selected states. *Econ Polit Wkly.* (2009) 14:66–71. Available online at: https://www.epw.in/journal/2009/07/special-articles/understanding-distribution-bpl-cards-all-india-and-selected-states
17. Mukherjee S, Haddad S, Narayana, D. Social class related inequalities in household health expenditure and economic burden: evidence from Kerala, south India. *Int J Equity Health.* (2011) 10:1. doi: 10.1186/1475-9276-10-1
18. DeFries R, Chhatre A, Davis KF, Dutta A, Fanzo J, Ghosh-Jerath S, et al. Impact of historical changes in coarse cereals consumption in India on micronutrient intake and anemia prevalence. *Food Nutr Bull.* (2018) 39:377–92. doi: 10.1177/0379572118783492
19. Whitton C, Ho JC, Tay Z, Rebello SA, Lu Y, Ong CN, et al. Relative validity and reproducibility of a food frequency questionnaire for assessing dietary intakes in a multi-ethnic Asian population using 24-h dietary recalls and biomarkers. *Nutrients.* (2017) 9:1059. doi: 10.3390/nu9101059
20. Rathi N, Riddell L, Worsley A. Food consumption patterns of adolescents aged 14-16 years in Kolkata, India. *Nutr J.* (2017) 16:50. doi: 10.1186/s12937-017-0272-3
21. Rao DR, Vijayapushpam T, Subba Rao GM, Antony GM, Sarma KV. Dietary habits and effect of two different educational tools on nutrition knowledge

of school going adolescent girls in Hyderabad, India. *Eur J Clin Nutr.* (2007) 61:1081–5. doi: 10.1038/sj.ejcn.1602622
22. Deka MK, Malhotra AK, Yadav R, Gupta S. Dietary pattern and nutritional deficiencies among urban adolescents. *J Family Med Prim Care.* (2015) 4:364–8. doi: 10.4103/2249-4863.161319
23. Raghunathan K, Headey D, Herforth A. Affordability of nutritious diets in rural India. *Food Policy*. (2021) 99:101982. doi: 10.1016/j.foodpol.2020.101982
24. Jain A, Jain A, Pankaj JP, Sharma BN, Paliwal A. The study of obesity among children aged 5-18 years in Jaipur, Rajasthan. *Muller J Med Sci Res.* (2016) 7:125–30. doi: 10.4103/0975-9727.185013
25. Kumar A, Joshi PK, Kumar P. Parappurathu S. Trends in the consumption of milk and milk products in India: implications for self-sufficiency in milk production. *Food security.* (2014) 6:719–26. doi: 10.1007/s12571-014-0376-y
26. Padmadas SS, Dias JG, Willekens FJ. Disentangling women's responses on complex dietary intake patterns from an Indian cross-sectional survey: a latent class analysis. *Public Health Nutr.* (2005) 9:204–11. doi: 10.1079/PHN2005842
27. Rehman M. *A Study of Food Security in Rural Assam: Are Food-Based Welfare Programs Doing Enough?* Guwahati: Indian Institute of Technology (2017).
28. Soumya Gupta VS, Naveen S, Singh D. *TARINA District Fact Sheet on Dietary Diversity*. New Delhi: Tata-Cornell Institute for Agriculture and Nutrition (2018).
29. Nithya DJ, Bhavani RV. Dietary diversity and its relationship with nutritional status among adolescents and adults in rural India. *J Biosoc Sci.* (2018) 50:397–413. doi: 10.1017/S0021932017000463
30. Singh S, Srivastava S, Upadhyay AK. Socio-economic inequality in malnutrition among children in India: an analysis of 640 districts from National Family Health Survey (2015-16). *Int J Equity Health*. (2019) 18:1–9. doi: 10.1186/s12939-019-1093-0
31. Mayén AL, Marques-Vidal P, Paccaud F, Bovet P, Stringhini S. Socioeconomic determinants of dietary patterns in low- and middle-income countries: a systematic review. *Am J Clin Nutr.* (2014) 100:1520–31. doi: 10.3945/ajcn.114.089029
32. Agrawal S, Kim R, Gausman J, Sharma S, Sankar R, Joe W, et al. Socio-economic patterning of food consumption and dietary diversity among Indian children: evidence from NFHS-4. *Eur J Clin Nutr.* (2019) 73:1361–72. doi: 10.1038/s41430-019-0406-0
33. Nguyen PH, Avula R, Headey D, Tran LM, Ruel MT, Menon P. Progress and inequalities in infant and young child feeding practices in India between 2006 and (2016). *Matern Child Nutr.* (2018) 14:e12663. doi: 10.1111/mcn.12663
34. Ministry of Statistics and Programme Implementation and The World Food Programme. *Food and Nutrition Security Analysis: India.* (2019). New Delhi: Ministry of Statistics and Programme Implementation and The World Food Programme (2019).
35. Gopal GM, Ganga D, Nilam R. Public distribution system in india: key issues and challenges. *Indian J Econ Dev*. (2017) 13:747–54. doi: 10.5958/2322-0430.2017.00240.2
36. Gulati S, Misra A, Colles SL, Kondal D, Gupta N, Goel K, et al. Dietary intakes and familial correlates of overweight/obesity: a four-cities study in India. *Ann Nutr Metab.* (2013) 62:279–90. doi: 10.1159/000346554

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Association Between Dietary Patterns and Plasma Lipid Biomarker and Female Breast Cancer Risk: Comparison of Latent Class Analysis (LCA) and Factor Analysis (FA)

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Background: Diet research focuses on the characteristics of "dietary patterns" regardless of the statistical methods used to derive them. However, the solutions to these methods are both conceptually and statistically different.

Methods: We compared factor analysis (FA) and latent class analysis (LCA) methods to identify the dietary patterns of participants in the Chinese Wuxi Exposure and Breast Cancer Study, a population-based case-control study that included 818 patients and 935 healthy controls. We examined the association between dietary patterns and plasma lipid markers and the breast cancer risk.

Results: Factor analysis grouped correlated food items into five factors, while LCA classified the subjects into four mutually exclusive classes. For FA, we found that the *Prudent*-factor was associated with a lower risk of breast cancer [4th vs. 1st quartile: odds ratio (OR) for 0.70, 95% CI = 0.52, 0.95], whereas the *Picky*-factor was associated with a higher risk (4th vs. 1st quartile: OR for 1.35, 95% CI = 1.00, 1.81). For LCA, using the *Prudent*-class as the reference, the *Picky*-class has a positive association with the risk of breast cancer (OR for 1.42, 95% CI = 1.06, 1.90). The multivariate-adjusted model containing all of the factors was better than that containing all of the classes in predicting HDL cholesterol ($p = 0.04$), triacylglycerols ($p = 0.03$), blood glucose ($p = 0.04$), apolipoprotein A1 ($p = 0.02$), and high-sensitivity C-reactive protein ($p = 0.02$), but was weaker than that in predicting the breast cancer risk ($p = 0.03$).

Conclusion: Factor analysis is useful for understanding which foods are consumed in combination and for studying the associations with biomarkers, while LCA is useful for classifying individuals into mutually exclusive subgroups and compares the disease risk between the groups.

Keywords: dietary patterns, latent class analysis (LCA), factor analysis (FA), plasma lipid biomarkers, breast cancer

INTRODUCTION

The interest in dietary patterns is well-founded in nutritional epidemiology, in light of the limitation of the traditional single-nutrient approach (1–6). Dietary patterns can integrate complex interactions of diet exposures and bypass problems generated due to multiple testing and a high correlation among these exposures (1, 7). Due to the presence of dietary patterns, a relationship between diet and health outcomes is simplified and robust (2, 8, 9).

Generally, two main ideas are used to derive dietary patterns, *a priori* methods by using a predefined dietary pattern and fitting the data into the indices, namely the diet quality index (DQI) (10–12), or posterior methods by data-driven reduction techniques to explore dietary patterns, namely factor analysis (FA), principal component analysis (PCA), and cluster analysis (CA) (12, 13). The dietary patterns derived from "*a priori*" method have a clear explanation in the biological sense, while the "posterior" methods can obtain more information.

In the "posterior" methods, FA simplifies the diet data into dietary patterns based on the correlation between foods. It postulates that the created statistical model can explain this correlation through a limited number of underlying factors, and give factor scores to individuals for all the derived factors (13, 14). PCA and FA are closely related, the main difference is that FA assumes a certain statistical model for the existing data sets, while PCA does not rely on statistical assumptions and is mainly a mathematical method (15). CA simplifies the diet data into dietary patterns based on the differences of individuals in the mean dietary intake, and each individual belongs to only one cluster (13, 16). Recently, a novel CA method, latent class analysis (LCA) originating from psychology (17, 18), has been used in nutritional epidemiology (19, 20). LCA is similar to a non-hierarchical clustering analysis, but LCA is a model-based clustering method not a partition optimized based on numerical criteria (21). Because LCA relaxes the strict assumptions on conditional independence and the same error variance of all outcomes in clustering, it shows a better model fit (19). The main difference in concepts between FA and LCA is based on "person-centered" or "variable-oriented" [(22); **Figure 1**]. FA explains the correlations between many observed variables through few underlying continuous latent variables. LCA classifies participants into mutually exclusive groups, rather than a joint classification of the factors (23).

However, most diet studies focus on the characteristics of "dietary patterns," such as the "*Western*" or "*Prudent*" dietary pattern, and regardless of what statistical methods are used to derive them. The effects are combined based only on the term of dietary pattern in some meta-analyses studies (24, 25). In fact, these approaches are both conceptually and technically different (4). When applied indiscriminately to the studies of associations with health outcomes, it may affect the reliability and generality of the results. In addition, the relationship between dietary effects, plasma lipids, and the breast cancer risk is complex, plasma lipids and lipoprotein are influenced by weight and diet and may be related to breast cancer risk factors. For example, the higher mammography density is considered to be a strong risk factor for breast cancer (26), which is related to increased levels of HDL-C and decreased levels of LDL-C (27). Some prospective clinical research suggested that high levels of TC and HDL-C increased the incidence of breast cancer (28–30). However, the conclusion is not consistent. A recent meta-analysis of the association between blood lipid levels and female breast cancer implicated no significant differences in the levels of total cholesterol, low-density lipoprotein cholesterol between cases and controls (31). Therefore, a direct comparison of methods of deriving dietary patterns is necessary, which would be useful to unravel the obscured relationship between diet, lipid profile levels, and the disease status and in moving the field forward. This study aimed to compare the dietary patterns derived from LCA and FA methods and their relation to plasma lipid biomarkers and female breast cancer risk.

METHODS

Study Design and Subjects

Subjects came from a population-based case-control study involving biology, diet, lifestyle, and environmental factors impact on the risk of breast cancer in Asian women. All subjects were adult women and restricted to local residents who have lived in Wuxi for at least 5 years. All newly diagnosed female breast cancers (ICD code: C50) among local residents identified by cancer registries are eligible to be included as cases. Secondary and recurrent cancers will be excluded. Controls were derived from the local area as cases and will be 1:1 individually matched with cases by age (±2 years) and residence. As personal information such as name, address, date of birth, and sex for all residents is available in the local demographic information database, eligible controls are randomly identified from this database. For choosing each control, two additional subjects will be selected as a backup at the same time. When the first control could not be interviewed, an alternative will be enrolled in the study. The selection procedure will be repeated until an eligible subject is interviewed. A total of 1,042 eligible breast cancer cases and 1,042 health controls were identified during the study period. About 818 cases and 935 controls agreed to participate, with a frequency match (cases and controls have the same distributions over age and residence). We excluded 77 cases and 75 controls because of extreme values in total calorie intake ($<$500 or $>$5,000 kcal) and 46 cases and 56 controls missing the information on adjusting covariant variables. A total of 695 cases and 804 controls were finally included in this study. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Jiangsu Center for Disease Control and Prevention ethical committee. Written informed consent was obtained from all subjects/patients.

Plasma Lipid Measurements

In the blood samples of all subjects, a series of plasma lipid biomarkers, including LDL cholesterol, HDL cholesterol, total cholesterol, triacylglycerols, blood glucose, apolipoprotein

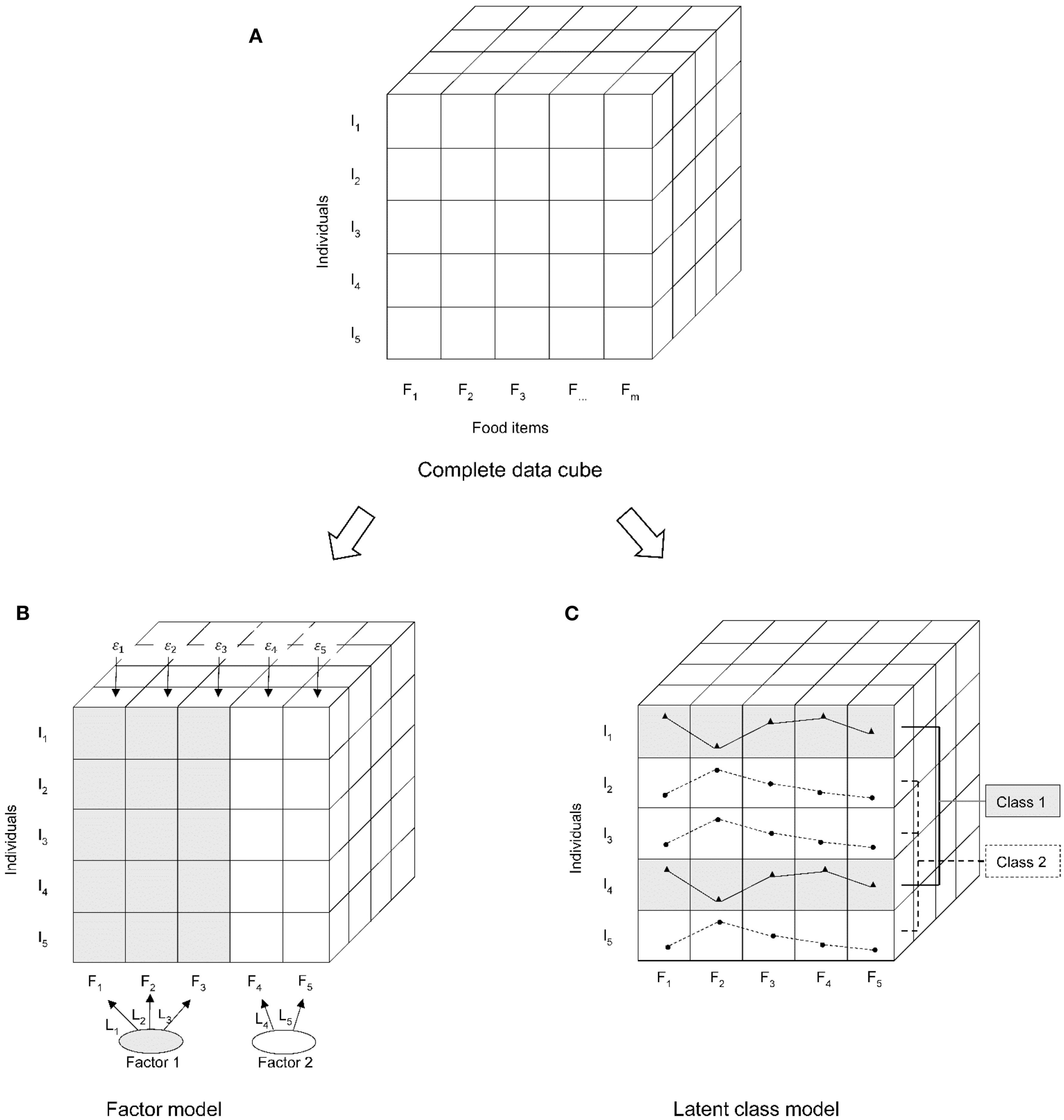

FIGURE 1 | Differences in technical processing between the latent class analysis (LCA) and factor analysis (FA). **(A)** Data structure; **(B)** FA is a variable-oriented data reduction technique; **(C)** LCA is a person-centered classification technique. I, individuals; F, food items.

A1, apolipoprotein B, and high-sensitivity C-reactive protein, were measured. Anantecubital venous blood sample was drawn from the study subjects after they had fasted overnight. Blood glucose, concentrations of triacylglycerols, and total cholesterol were measured by using an enzymatic method (GPO-POD method and GHOD-POD method), HDL cholesterol and LDL cholesterol were measured by a homogeneous enzymatic method, apolipoprotein A1, apolipoprotein B, and high-sensitivity C-reactive protein were measured by an immunoturbidimetric method, and all plasma lipid measurements were done using the Roche Chemistry Analyzer (cobas c701).

Dietary Assessment

The diet was measured by a validated, semi-quantitative food frequency questionnaire (FFQ), which included 149 food items. The 149 food items can be further classified into 18 predefined food groups based on similarities in nutrient profile and culinary usage. A detailed description and reliability verification of the FFQ can be found in the previously published study (32). Total energy intake is based on the Chinese Food Composition Database (2018, 6th version).

Dietary Pattern Analysis

Latent class analysis: LCA for dietary pattern derivation is described briefly as follows:

Latent class analysis is a conditional Gaussian finite mixture model [FMM; (19)]. The identification of dietary patterns can be considered as there are subgroups who are distinguished by their dietary profiles in the population and have different food consumption probability distributions. FMM is particularly suited to the problem of identifying the subgroups that are defined in this manner. In FMM, the overall population probability density is expressed as a finite sum of well-defined component densities, with each density representing a subgroup.

An FMM can be written as

$$f\left(y_i|\theta\right) = \sum\nolimits_{k=1}^{K} \pi_k f_k(y_i|\theta_k) \quad (1)$$

In Equation (1), y_i is a vector of observations on J feature variables for the ith subject, K is the chosen number of subgroups, π_k is the probability of subgroup membership (or mixing proportion) which sums to 1 over subgroups and θ is the set of model parameters that are to be estimated. If the feature variables are continuous, it is usually assumed that the K probability densities $f_1,\ldots,f_k$ are multivariate normal. The most general solution involves estimating a separate set of means, variances, and covariances for each component density, as well as the mixing proportions.

The details please refer to our previous study (33). The dietary classes derived from LCA adjusted the energy intake of each subject and were interpreted and named according to the conditional probabilities of food group intake, using controls only. The number of classes was determined by the Bayesian Information Criterion (BIC), Lo–Mendel–Rubin likelihood ratio (LMR) test, and entropy value (34, 35). The dietary classes were derived from LCA.

Factor analysis: FA is the most commonly used method to derive dietary patterns, briefly described as follows.

The identification of dietary patterns in FA can be regarded as a problem of few latent variables to explain the correlation between many observed variables, which is achieved by dividing a covariance between the observed variables. These continuous explanatory latent variables are called "factors."

Assuming that the intake of n subjects in P dietary variables $X_1, X_2, \ldots, X_P$ is measured, where i variables can be written as a linear combination based on m factors $F_1, F_2, ..., F_m$. When $m < p$, a FA can be expressed in Equation (2) as

$$X_i = a_{i1}F_1 + a_{i2}F_2 + \ldots + a_{im}F_m + e_i \quad (2)$$

a_{is} is the factor loading of the variable i, and e_i is the part of the variable X_i that cannot be "explained" by the factors.

We first performed an exploratory factor analysis (EFA) on 18 food groups using weighted least squares and derived the factors by orthogonal Varimax rotation. The number of factors left is based on the characteristic root and the variance interpretation. Next, we constructed a confirmatory factor analysis (CFA) model that only included food groups with the loading value ≥ 0.25 in EFA, allowing food groups to load on multiple factors. Both EFA and CFA analyses use controls only and adjust each subject's energy intake.

Statistical Analysis

To compare the characteristics of the dietary patterns derived from LCA and FA, we calculated consumption conditional probabilities and factor loadings for each food group and compared factor scores' means ($\pm$SD) for each class.

To compare the association between the dietary patterns derived by LCA or FA and plasma lipid biomarkers, we used a multivariate-adjusted linear regression to examine individual associations between each class or each factor with each plasma lipid biomarker. Indicator variables (aka, dummy variables) were created for each class, while the factors remained as continuous variables (z-scores). A separate linear regression model was constructed for each individual class or factor for each plasma lipid biomarker (plasma lipid biomarker as an outcome variable). Each dietary pattern (derived by LCA or FA) will be tested in eight separate regression models to examine the associations between a dietary pattern and LDL cholesterol, HDL cholesterol, total cholesterol, triacylglycerols, blood glucose, apolipoprotein A1, apolipoprotein B, and high-sensitivity C-reactive protein, respectively. The multi-regression analysis of each dietary pattern derived by FA or LCA will be performed two times. We will first adjust age (age at diagnosis for cases or enrollment for controls, by years) and BMI (kg/m^2) and further adjust area (urban and rural), education (ordered as illiterate and primary, middle, and high school, University and above), smoking (no or yes: including smoking and second-hand smoking $\geq$ 3 day/week), moderate physical activity (min/day), oral contraceptive use (no or yes: current use or ever use), hormone replacement therapy (no or yes: current use or ever use), age at menarche (by years), age at first full-term delivery (by years), parity (ordered as 0, 1, 2, or $\geq$3), family history of breast cancer (no or yes: in a first-degree relative), history of benign breast disease (no or yes: including lactation mastitis, plasma cell mastitis, cyclomastopathy, fibroadenoma of breast, and galactocele), breastfeeding (no or yes), height (in cm), energy intake (kcal/extra-administrative) and menopausal status (premenopausal, postmenopausal, postmenopausal as the absence of menstruation in the past 12 months). To further compare dietary patterns in relation to health outcomes (included plasma lipid biomarkers and breast cancer risk), we built a linear regression model that included all the factors and another linear regression model that included all the classes and then compared them using *Pitman's* test to see which solution better predicted the outcomes.

To examine the association between dietary patterns and the disease risk, we calculated standardized factor scores and Bayesian posterior probability for each subject, so that all the subjects were assigned with a score for each dietary pattern, and all the subjects were assigned with a latent class, based on their FFQ intake. The logistic regression models were used to estimate the odds ratio (OR) and their 95% CIs. For FA, because the factors are not mutually exclusive and the factor scores are continuous variables, we divided the factor score of each dietary pattern into quartiles and examined their association with the breast cancer risk, with a reference of the lowest quartile. For LCA, because the classes are mutually exclusive, we estimate the risk of breast cancer directly for mutually exclusive classes compared with a reference class.

Latent class analysis and FA were conducted using MPLUS (V8.3; Muthén & Muthén, Los Angeles, CA, USA) (36), and other statistical analyses were conducted using R version 4.0.2 (The R Project for Statistical Computing, USA; https://www.r-project.org/).

RESULTS

Dietary Derived by LCA

The dietary patterns derived from LCA were described in our previous studies (33). As described briefly below, latent class models were fitted for two to six classes, and the four classes were chosen. The food consumption conditional probability from the selected food groups for the four classes was presented in **Table 1**. We named the classes as follows: *Prudent, Chinese traditional* (short for *Chinese* below)*, Western*, and *Picky*. The *Prudent* class was characterized by a high probability of consuming healthy foods like cereals, aquatic products, fruits, vegetables, soy foods, and nuts. Compared with the other three classes, women in the *Picky*-class were characterized by higher extreme probabilities of non-consumption of specific foods.

Dietary Derived by FA

According to the scree plot and characteristic root from EFA (the first six eigen values were 2.57, 1.66, 1.44, 1.29, 1.18, and 1.01), we extracted five factors, which explain ∼45.21% of the total variance. Factor 1 with a high factor loading in cereals, aquatics, milk, fruits, soy foods, nuts, cakes, and fresh juice, named as *Prudent*-factor; Factor 2 with a high factor loading in cakes, sugar strengthened beverage (SSB), fresh juice, soft drinks, pickled foods, and coffee, named as *Sugar*-factor. Factor 3 with a high factor loading in fried foods and red meat, named as *Western*-factor; Factor 4 with a high factor loading in poultry, eggs, and soy foods, named as *Chinese traditional*-factor (short for *Chinese*); Factor 5 with a high factor loading in vegetables, soy foods, and pickled foods, named as *Picky*-factor.

The CFA model only included food groups with loading $\geq$0.25 in EFA. The factor loadings from EFA and CFA were almost similar except for coffee for *Picky*-factor and fresh juice for *Sugar*-factor (**Table 2**). Therefore, we kept the names given from EFA for the dietary patterns assessed by CFA. After excluding food groups with the factor loading <0.25, the model was more concise and the goodness of fit did not decrease (results not shown). We examined the overall correlations among the

TABLE 1 | Food consumption level conditional probabilities of dietary pattern classes, latent class analysis (LCA)[a,b].

Food group	Class 1: *Prudent*		Class 2: *Western*		Class 3: *Chinese*		Class 4: *Picky*	
	High consumption	No consumption	High consumption	No consumption	High consumption	No consumption	High consumption	No consumption
Rice/Flour	0.08	0.25	0.16	0.40	0.10	0.26	0.24	0.17
Cereals	0.35	0.24	0.28	0.15	0.25	0.12	0.17	0.56
Fried food	0.13	0.24	0.46	0.12	0.00	0.50	0.02	0.73
Meat	0.47	0.03	0.79	0.01	0.03	0.00	0.15	0.10
Poultry	0.46	0.26	0.71	0.00	0.29	0.05	0.23	0.36
Aquatics	0.56	0.02	0.55	0.00	0.29	0.01	0.27	0.13
Eggs	0.05	0.25	0.22	0.01	0.06	0.03	0.07	0.36
Milk	0.01	0.47	0.04	0.26	0.01	0.38	0.01	0.85
Fruits	0.25	0.04	0.18	0.00	0.30	0.01	0.14	0.32
Vegetables	0.26	0.01	0.27	0.00	0.17	0.00	0.37	0.04
Soy foods	0.40	0.17	0.49	0.09	0.25	0.06	0.18	0.38
Nuts	0.26	0.34	0.25	0.08	0.14	0.15	0.11	0.67
Cakes	0.23	0.51	0.33	0.15	0.13	0.31	0.10	0.76
SSB	0.02	0.98	0.25	0.75	0.11	0.89	0.05	0.95
Fresh juice	0.06	0.94	0.27	0.73	0.11	0.89	0.02	0.98
Soft drink	0.06	0.94	0.47	0.53	0.18	0.82	0.07	0.93
Pickled foods	0.12	0.44	0.25	0.19	0.16	0.32	0.24	0.33
Coffee	0.08	0.92	0.26	0.74	0.08	0.92	0.02	0.99

[a] *Classes were derived using LCA on 18 food groups based on 804 controls.*

[b] *Conditional probabilities of food group consumption were categorized into four levels: tertiles of non-zero consumption and no consumption (calculated from controls). Because there were <20% of women consumed sugar strengthened beverage (SSB), fresh juice, soft drink, or coffee, we set the consumption of these foods as binary variables (consumed or no). While rice/flour was consumed almost ubiquitously, there were only tertiles of consumption and no non-consumption category.*

TABLE 2 | Selected exploratory and confirmatory factor loadings for the five-factor model, factor analysis (FA)[a].

	EFA					CFA[b]				
Food group	**Factor 1: *Prudent***	**Factor 2: *Sugar***	**Factor 3: *Western***	**Factor 4: *Chinese***	**Factor 5: *Picky***	**Factor 1: *Prudent***	**Factor 2: *Sugar***	**Factor 3: *Western***	**Factor 4: *Chinese***	**Factor 5: *Picky***
Rice/Flour	−0.12	−0.02	−0.02	0.03	0.46	–	–	–	–	0.54
Cereals	0.45	−0.11	−0.06	0.07	0.07	0.35	–	–	–	–
Fried food	0.10	0.17	0.78	0.03	0.01	–	–	0.78	–	–
Meat	0.03	0.04	0.88	0.24	0.05	–	–	0.89	–	–
Poultry	0.08	0.04	0.10	0.92	−0.18	–	–	–	0.61	–
Aquatics	0.24	0.01	0.10	0.13	−0.01	0.30	–	–	–	
Eggs	0.20	0.15	0.12	0.41	0.08		–	–	0.64	–
Milk	0.48	0.10	0.03	0.01	−0.23	0.49	–	–	–	–
Fruits	0.48	−0.08	−0.02	0.07	−0.16	0.43	–	–	–	–
Vegetables	0.02	0.01	0.04	−0.07	0.41		–	–	–	0.35
Soy foods	0.32	0.13	0.09	0.26	0.25	0.33	–	–	0.29	0.30
Nuts	0.50	0.15	0.11	0.05	0.08	0.55	–	–	–	–
Cakes	0.42	0.32	0.14	0.01	−0.02	0.43	0.25	–	–	–
SSB	0.04	0.76	0.08	0.01	0.06		0.72	–	–	–
Fresh juice	0.48	0.31	−0.04	0.01	−0.20	0.56	–	–	–	
Soft drink	0.11	0.79	0.04	0.14	−0.04	–	0.86	–	–	–
Pickled foods	−0.09	0.34	0.04	0.12	0.24	–	0.34	–	–	0.27
Coffee	0.33	0.45	0.17	0.01	−0.26	0.37	0.36	–	–	–

[a] Factors were derived using FA on 18 food groups based on 804 controls.
[b] Food groups with factor loading <0.25 are excluded for simplicity.

five factors and found a significant difference ($p < 0.001$) compared to the hypothesis of being zero (for details see **Supplementary Figure 1**).

Comparison Between LCA and FA

Latent class analysis and FA methods identified similar dietary patterns based on the same data sets, which have similar diet characteristics from the conditional probabilities of LCA and factor loadings of FA (**Tables 1**, **2**). Latent classes derived from LCA have higher factor scores on corresponding latent factors, as shown in **Figure 2**. Besides, the *Western*-class also had the highest factor score for *Sugar*-factor. The *Picky*-class had the lowest factor score for *Prudent*-factor and also had the factor score less than zero for *Western*-factor, *Chinese*-factor, *Prudent*-factor, and *Sugar*-factor. Although the *Prudent*-class had higher means for the *Prudent*-factor score, the factor score between the *Chinese*-class and *Western*-class was not significantly different (results not shown).

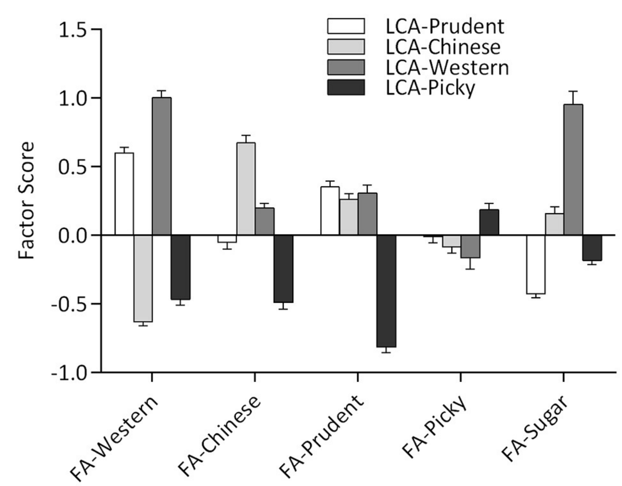

FIGURE 2 | Factor scores' means by latent class, four classes on five factor scores.

Dietary Patterns and Plasma Lipid Biomarkers

In the multivariate-adjusted regression models for the classes derived by LCA, individuals in the *Western*-class had higher total cholesterol ($\beta = 0.23$; $p < 0.01$), triacylglycerols ($\beta = 0.28$; $p < 0.01$), blood glucose ($\beta = 0.29$; $p < 0.01$), and apolipoprotein B ($\beta = 0.08$; $p < 0.01$) than those who are not in the *Western*-class. Individuals in the *Picky*-class had higher triacylglycerols ($\beta = 0.23$; $p < 0.01$) and blood glucose ($\beta = 0.29$; $p < 0.01$) than those who are not in the *Picky*-class (**Table 3**).

In multivariate-adjusted regression models for the factors derived by FA, the *Prudent*-factor was inversely related to triacylglycerols ($\beta = -0.12$; $p < 0.01$), blood glucose ($\beta = -0.13$; $p < 0.01$), apolipoprotein B ($\beta = -0.02$; $p < 0.01$), and high-sensitivity C-reactive protein ($\beta = -0.13$; p

TABLE 3 | Association between dietary patterns (classes) and plasma lipid biomarkers, regression coefficients (β)[a].

Dietary pattern[e]	LDL cholesterol	HDL cholesterol	Total cholesterol	Triacylglycerols	Blood glucose	Apolipoprotein A1	Apolipoprotein B	High-sensitivity C-reactive Protein
Class 1: *Prudent*								
Adjusted for age and BMI	−0.01 (0.07)	0.02 (0.03)	−0.05 (0.08)	−0.07 (0.07)	−0.11 (0.10)	−0.00 (0.02)	−0.02 (0.02)	−0.03 (0.13)
Multivariate adjusted[d]	−0.01 (0.07)	0.02 (0.03)	−0.04 (0.08)	−0.08 (0.07)	−0.11 (0.10)	−0.00 (0.02)	−0.02 (0.02)	−0.04 (0.14)
Class 2: *Western*								
Adjusted for age and BMI	0.15 (0.09)	−0.03 (0.04)	0.22 (0.10)[b]	0.27 (0.09)[c]	0.26 (0.13)[b]	0.03 (0.02)	0.07 (0.03)[c]	0.03 (0.17)
Multivariate adjusted[d]	0.17 (0.09)	−0.03 (0.04)	0.23 (0.10)[b]	0.28 (0.09)[c]	0.29 (0.13)[b]	0.03 (0.02)	0.08 (0.03)[c]	0.03 (0.17)
Class 3: *Chinese*								
Adjusted for age and BMI	0.06 (0.07)	0.03 (0.03)	0.04 (0.07)	−0.10 (0.07)	−0.17 (0.10)	0.01 (0.02)	0.01 (0.02)	0.01 (0.13)
Multivariate adjusted[d]	0.06 (0.07)	0.03 (0.03)	0.04 (0.07)	−0.10 (0.07)	−0.16 (0.10)	0.02 (0.02)	0.01 (0.02)	0.01 (0.13)
Class 4: *Picky*								
Adjusted for age and BMI	0.03 (0.08)	−0.04 (0.03)	0.06 (0.08)	0.23 (0.07)[c]	0.27 (0.11)[b]	0.00 (0.02)	0.02 (0.02)	0.05 (0.15)
Multivariate adjusted[d]	0.04 (0.08)	−0.03 (0.03)	0.07 (0.08)	0.23 (0.07)[c]	0.29 (0.11)[b]	0.00 (0.02)	0.02 (0.02)	0.06 (0.15)

[a] *SE in parentheses.*
[b] $p < 0.05$.
[c] $p < 0.01$.
[d] *Multivariate models were adjusted for age, BMI, area, education, smoking, age at menarche, age at first full–term delivery, parity, age at menopause, parity, family history of breast cancer, history of benign breast disease, use of HRT, use of oral contraceptives, breastfeeding, moderate physical activity, height, body mass index, total energy intake, and menopausal status.*
[e] *Association between dietary patterns (classes) and plasma lipid biomarkers based on 804 controls.*

TABLE 4 | Association between dietary patterns (factors) and plasma lipid biomarkers, regression coefficients (β)[a].

Dietary pattern[e]	LDL cholesterol	HDL cholesterol	Total cholesterol	Triacylglycerols	Blood glucose	Apolipoprotein A1	Apolipoprotein B	High-sensitivity C-reactive Protein
Factor 1: *Prudent*								
Adjusted for age and BMI	−0.04 (0.03)	0.03 (0.01)[b]	−0.03 (0.03)	−0.12 (0.03)[c]	−0.13 (0.05)[c]	0.00 (0.01)	−0.02 (0.01)[b]	−0.13 (0.06)[b]
Multivariate adjusted[d]	−0.04 (0.03)	0.02 (0.01)	−0.03 (0.03)	−0.12 (0.03)[c]	−0.13 (0.05)[c]	0.00 (0.01)	−0.02 (0.01)[b]	−0.13 (0.06)[b]
Factor 2: *Sugar*								
Adjusted for age and BMI	0.09 (0.03)[c]	−0.02 (0.01)	0.10 (0.03)[c]	0.06 (0.03)[b]	0.15 (0.05)[c]	0.01 (0.01)	0.03 (0.01)[c]	0.04 (0.06)
Multivariate adjusted[d]	0.09 (0.03)[c]	−0.02 (0.01)	0.10 (0.03)[c]	0.06 (0.03)[b]	0.15 (0.05)[c]	0.01 (0.01)	0.03 (0.01)[c]	0.02 (0.06)
Factor 3: *Western*								
Adjusted for age and BMI	−0.03 (0.03)	−0.01 (0.01)	0.00 (0.03)	0.05 (0.05)	−0.01 (0.01)	−0.01 (0.01)	0.05 (0.06)	0.05 (0.06)
Multivariate adjusted[d]	−0.03 (0.03)	−0.01 (0.01)	−0.04 (0.03)	0.00 (0.03)	0.04 (0.05)	−0.01 (0.01)	−0.01 (0.01)	0.05 (0.06)
Factor 4: *Chinese*								
Adjusted for age and BMI	0.03 (0.03)	0.02 (0.01)	0.03 (0.04)	−0.05 (0.03)	−0.00 (0.05)	0.02 (0.01)	0.01 (0.01)	−0.06 (0.06)
Multivariate adjusted[d]	0.02 (0.03)	0.02 (0.01)	0.02 (0.04)	−0.05 (0.03)	−0.01 (0.05)	0.02 (0.01)	0.00 (0.00)	−0.06 (0.06)
Factor 5: *Picky*								
Adjusted for age and BMI	−0.01 (0.03)	0.01 (0.01)	0.02 (0.03)	0.07 (0.03)[b]	−0.01 (0.04)	0.02 (0.01)[b]	0.00 (0.01)	0.14 (0.06)[b]
Multivariate adjusted[d]	−0.01 (0.03)	0.01 (0.01)	0.02 (0.03)	0.07 (0.03)[b]	−0.01 (0.04)	0.02 (0.01)[b]	0.00 (0.01)	0.14 (0.06)[b]

[a] *SE in parentheses.*
[b] $p < 0.05$.
[c] $p < 0.01$.
[d] *Multivariate models were adjusted for age, BMI, area, education, smoking, age at menarche, age at first full-term delivery, parity, age at menopause, parity, family history of breast cancer, history of benign breast disease, use of HRT, use of oral contraceptives, breastfeeding, moderate physical activity, height, body mass index, total energy intake, and menopausal status.*
[e] *Association between dietary patterns (factors) and plasma lipid biomarkers based on 804 controls.*

< 0.01), whereas the *Picky*-factor was directly associated with triacylglycerols ($\beta = 0.07$; $p < 0.05$), apolipoprotein A1($\beta = 0.02$; $p < 0.05$), and high-sensitivity C-reactive protein ($\beta = 0.14$; $p < 0.05$). Individuals in the *Sugar*-factor had higher LDL cholesterol ($\beta = 0.09$; $p < 0.01$), total cholesterol ($\beta = 0.10$; $p < 0.01$), triacylglycerols ($\beta = 0.06$; $p < 0.01$), blood glucose ($\beta = 0.15$; $p < 0.01$), and apolipoprotein B ($\beta = 0.03$; $p < 0.01$; **Table 4**). Because the factors are continuous variables (z-scores), β here means 1 mg/dl for a 1-unit increase in z-score.

TABLE 5 | The proportion of variability explained (R^2) by regression models containing all classes or all factors in predicting plasma lipid biomarkers and *Pitman's* test.

Dietary pattern[a]	LDL cholesterol	HDL cholesterol	Total cholesterol	Triacylglycerols	Blood glucose	Apolipoprotein A1	Apolipoprotein B	High-sensitivity C-reactive Protein	Breast cancer
Model 1: all classes									
Classes only[b]	0.005	0.003	0.007	0.023	0.014	0.002	0.011	0.000	0.005
Adjusted for age and BMI	0.014	0.005	0.018	0.023	0.017	0.005	0.016	0.001	0.009
Multivariate adjusted[c]	0.112	0.023	0.141	0.091	0.055	0.039	0.131	0.021	0.023
Model 2: all factors									
Factors only	0.014	0.011	0.021	0.069	0.024	0.012	0.020	0.015	0.008
Adjusted for age and BMI	0.024	0.012	0.024	0.034	0.027	0.015	0.026	0.017	0.011
Multivariate adjusted[c]	0.114	0.031	0.141	0.099	0.063	0.049	0.131	0.031	0.014
P-value for Pitman's test	0.42	0.04	1.00	0.03	0.04	0.02	1.00	0.02	0.03

[a]*Association between dietary patterns (classes) and plasma lipid biomarkers and the breast cancer risk based on all subjects (695 cases, 804 controls).*
[b]*Because the classes are categorical variables, regression models contain only three classes because one class as the reference.*
[c]*Multivariate models were adjusted for age, BMI, area, education, smoking, age at menarche, age at first full-term delivery, parity, age at menopause, parity, family history of breast cancer, history of benign breast disease, use of HRT, use of oral contraceptives, breastfeeding, moderate physical activity, height, body mass index, total energy intake, and menopausal status.*

TABLE 6 | Associations between the dietary patterns derived by FA and LCA and health outcome (breast cancer)[a], adjusted OR and 95% CI[b].

Factor analysis	Factor 1: *Prudent*	Factor 2: *Sugar*	Factor 3: *Western*	Factor 4: *Chinese*	Factor 5: *Picky*
Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	1.12 (0.83, 1.50)	1.03 (0.77, 1.39)	0.81 (0.60, 1.09)	1.15 (0.80, 1.66)	1.39 (1.03, 1.86)
Quartile 3	0.77 (0.57, 1.03)	1.05 (0.78, 1.42)	1.05 (0.78, 1.42)	0.94 (0.63, 1.40)	1.19 (0.88, 1.60)
Quartile 4	0.70 (0.52, 0.95)	1.06 (0.79, 1.43)	0.95 (0.70, 1.28)	0.71 (0.46, 1.09)	1.35 (1.00, 1.81)
P for trend	0.0029	0.6832	0.8270	0.0940	0.1220
Latent class analysis	**Class 1:** *Prudent*	– –	**Class 2:** *Western*	**Class 3:** *Chinese*	**Class 4:** *Picky*
	1.00 (reference)	–	0.76 (0.53, 1.09)	0.86 (0.65, 1.14)	1.42 (1.06, 1.90)

[a]*Association between dietary patterns (classes) and plasma lipid biomarkers and the breast cancer risk based on all subjects (695 cases, 804 controls).*
[b]*Adjusted for or age, BMI, area, education, smoking, age at menarche, age at first full-term delivery, parity, age at menopause, parity, family history of breast cancer, history of benign breast disease, use of HRT, use of oral contraceptives, breastfeeding, moderate physical activity, height, body mass index, total energy intake, and menopausal status.*

From the *Pitman's* test results, we found that the model containing all of the factors was slightly better than the model containing all of the classes in predicting HDL cholesterol ($p = 0.04$), triacylglycerols ($p = 0.03$), blood glucose ($p = 0.04$), apolipoprotein A1 ($p = 0.02$), high-sensitivity C-reactive protein ($p = 0.02$), but was weaker than that in predicting the breast cancer risk ($p = 0.03$; **Table 5**).

Dietary Patterns and Health Outcomes

For FA, the *Prudent*-factor was associated with a lower breast cancer risk (4th vs. 1st quartile: OR for 0.70, 95% CI: 0.52–0.95, p-trend = 0.0029), while the *Picky*-factor was associated with a higher breast cancer risk (4th vs. 1st quartile: OR for 1.35, 95% CI: 1.00–1.81, p-trend = 0.1220; **Table 6**). For LCA, we found that the *Prudent*-class was similar to the Mediterranean pattern in terms of the correlation with food intake. Using the *Prudent*-class as the reference, we found that individuals belonging to the *Picky*-class have a significant higher breast cancer risk (OR for 1.42, 95% CI = 1.06, 1.90) (**Table 6**).

DISCUSSION

Nutritional studies have historically been focusing on specific nutrients or foods in isolation and oversimplified the complexity of foods (3, 6). A high degree of intercorrelation among various nutrients and foods makes it difficult to attribute effects to a single independent component, and the interpretation and application of results were limited (1, 5). Now, in nutrition epidemiology, the concept of food synergy has been convinced that nutrients exist in a purposeful biological sense in food. The dietary patterns that inherently account for interactions among nutrients and estimate overall dietary effects may provide a more robust approach for determining associations between diet and health outcomes (8, 9).

Although various methods have been developed to derive dietary patterns, there are still many challenges in an accurate

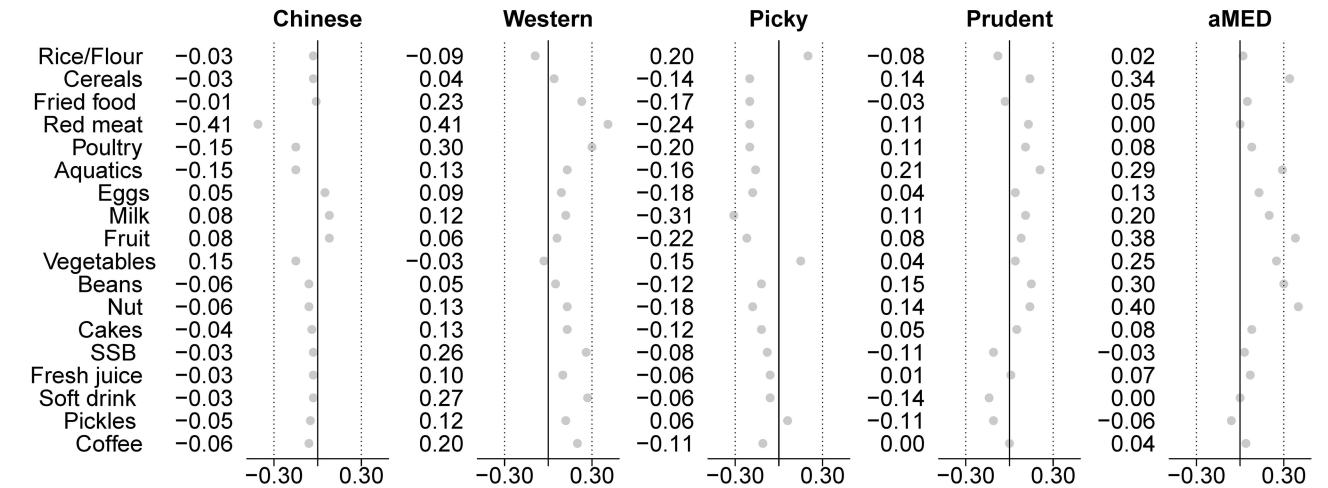

FIGURE 3 | Correlations between food consumption and the dietary pattern, based on the posterior LCA method and the prior diet quality index (DQI) method. Compared with the data-driven "posterior" method, the "*a priori*" method has a clearer biological meaning under a certain diet pattern. This study found that in terms of its relevance to the specific food group, the *Prudent*-dietary pattern from LCA is similar to the Mediterranean dietary pattern.

identification of dietary patterns (37). Different statistical methods use different concepts and techniques to reduce the complex multidimensional nutritional data down to meaningfully observed dietary patterns. For example, the most commonly used FA method is "variance-oriented," which is achieved by partitioning variances among variables and explaining the correlations between many observed variables through few underlying continuous latent variables. In contrast, LCA is a "person-oriented" approach, which models the distinct configurations of heterogeneity within a sample and divides the sample into mutually exclusive subgroups with different dietary structures (38, 39). When applying the dietary patterns derived from different methods indiscriminately to studies, it may affect the reliability and generalizability of the results.

The results of this study show that the dietary patterns derived from the different methods are both formally and biologically different. The FA approach summarizes five factors ("*Prudent,*" "*Western,*" "*Chinese traditional,*" "*Picky,*" and "*Sugar*") based on the correlation of food group intake, LCA approach derives four classes ("*Prudent,*" "*Western,*" "*Chinese traditional,*" and "*Picky*") based on the differences in a dietary structure of the study population. Despite on the basis of characteristics of the conditional probability of LCA and factor loading of FA as well as the factor scores of the latent class on the corresponding factors, the same-named dietary patterns are similar in diet characteristics. However, the FA method identified a typical food combination from a strong preference for sweet foods, while the LCA method did not derive the "pure" *Sugar*-class. On another side, the characteristics of the *Picky* pattern were high extreme probabilities of non-consumption on specific foods, which was only reflected in the LCA result.

Through examining the associations between dietary patterns and plasma lipid biomarkers, we found that the *Prudent*-dietary pattern characteristic of cereal, aquatics, fruits, soy foods, and nuts in case of its derivation by LCA or FA was inversely associated with triacylglycerols, blood glucose, and apolipoprotein B. While the *Picky* pattern was associated with triacylglycerols and blood glucose when derived by LCA and was associated with triacylglycerols, apolipoprotein A1, and high-sensitivity C-reactive protein when derived by FA. *Chinese traditional* and *Western* patterns were not significantly associated with any of the plasma lipid biomarkers regardless of using the LCA or FA method. Although the coefficients of pattern-plasma lipid biomarker regression from LCA and FA cannot be compared directly because the dietary patterns (classes) derived by LCA were treated as indicator variables and are dichotomous, whereas the dietary patterns (factors) derived by FA were treated as continuous variables (z-scores), the associations between dietary patterns and biomarkers were in a similar direction for both LCA and FA methods. When we compared a model containing all the classes with a model containing all the factors, we found that FA is slightly better than LCA in predicting some plasma lipid biomarkers (HDL cholesterol, triacylglycerols, blood glucose, apolipoprotein A1, and high-sensitivity C-reactive protein), while LCA is better than FA in predicting the breast cancer risk. Furthermore, we examined the dietary patterns-health outcome associations. Because the factors derived by FA are not mutually exclusive, an individual's dietary pattern can only be inferred by her factor score of the derived factors (40). We found that women with the highest quartile score of the *Prudent*-factor decreased 30% risk compared to women with the lowest quartile, and with robust linearity (p-trend = 0.0029). While women who follow a *Picky*-factor increase 35% risk of breast cancer, but there is insufficient evidence for considerable linearity

(p-trend = 0.1220). In contrast, LCA classifies participants into mutually exclusive groups, the disease risk can be directly compared between groups, but need to select a reference first. We used the *Prudent*-class as the reference, which was similar to the recognized healthy dietary pattern (Mediterranean diet, **Figure 3**) and found that individuals belonging to the *Picky*-class have a 42% higher risk of breast cancer than those belonging to the *Prudent*-class.

The difference between the dietary patterns derived from LCA and FA methods can be explained by their concept and technology. FA summaries dietary patterns based on the correlation between foods intake. The methodological characteristics of FA may explain why the dietary patterns derived by FA are more closely related to plasma lipid biomarkers than those derived by LCA, and the synergy produced by highly correlated foods strengthens the relationship between dietary patterns and plasma lipid biomarkers (**Figure 1**). However, we cannot make a direct comparison of the risk of disease between individuals using the FA approach (40), which needs mutually exclusive subgroups and a chosen reference group. The challenge is that when the number of factors is more than 2, the number of derived cells from the cross-tabulation of the quantiles of all factor scores might be too large, which needs strong subjective decisions to collapse them into mutually exclusive groups (1, 19, 41). In contrast, LCA is well-suited to an issue of identifying the heterogeneity embedded in the sample and classifying the sample into mutually exclusive subgroups. Because LCA is based on the FMM, which postulates that there are subgroups with different dietary structures, and these subgroups should have different food consumption probability distributions (**Figure 1**) (19, 42, 43). Through FMM, the distribution is heterogeneous across the overall sample but homogeneous within subgroups, which maximize the differences of the dietary patterns derived by LCA in the food consumption probability (44). The characteristics of LCA make it easier to compare the health outcome between the individuals because an individual belongs to only one class and the health outcome is also specific to individuals within each class.

Most previous research on dietary patterns and the breast cancer risk was conducted by the FA method in Western populations. An inverse association with the *Prudent*-dietary pattern and a positive correlation with the *Western*-dietary pattern of the breast cancer risk have been found in most studies (45–47). However, the results were not consistent. Although there were a few studies on dietary patterns and the breast cancer risk in Asian women, conflicting results were also noted (48–52). In this study, based on LCA results, there is no significant difference between breast cancer and the *Prudent*-class, *Western*-class, or *Chinese traditional*-class. What deserves attention is the *Picky*-class, which is similar to the "*Salty*-pattern" in a previous study (53), women in the *Picky*-class were characterized by higher extreme probabilities of non-consumption on specific foods, the highest probabilities in consumption of pickled foods, and the lowest probabilities in consumption of cereals, soy foods, and nuts. The risk of the *Picky*-class may come from an imbalance diet that could lead to the loss of certain vital nutrients and a high consumption of pickled foods that are prone to inflammation (33).

The strength of this study included the study design that allows us to compare the predictability and comparability of biomarkers and the disease risk between the dietary patterns derived from different posterior methods, and this study provides evidence that the dietary patterns derived from posterior methods are biologically meaningful and demonstrates the role of dietary patterns in the disease risk. A understanding of the derivation of dietary patterns will advance the application of dietary patterns in nutrition research. The results of this study indicated that the dietary pattern derived from the FA is suitable for analyzing the synergistic effect of food effects on biomarkers, while the dietary patterns derived from LCA were used to compare the disease risk among people with a different diet structure. The limitation of the study is that both LCA and FA methods are highly data-driven, and a cross-validation with other independent samples in the future is required (54, 55). The next work is to compare the dietary patterns derived by FA and LAC concerning other biomarkers and health outcomes for a better understanding of the utility of these methods in nutritional epidemiology research.

CONCLUSION

In conclusion, FA is suitable for an understanding of the correlations between dietary intake and analyzing the synergistic effect of food intake; LCA divides people into mutually exclusive subgroups with different diet structures, which is conducive to compare the disease risk between the groups. We recommend the use of flexible modeling approaches capable of being adapted to specific research.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Jiangsu Center for Disease Control and Prevention Ethical Committee. The subjects/patients provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation of the manuscript. MW, SC, and PMW: designed and conducted the study. QRZ, ZZ, and JYZ: developed diet indices and data collection. SC and LCL: performed the statistical analyses and drafted the manuscript. PMW and MW: interpreted the data, critically revised the manuscript, and had full responsibility for the analyses and interpretation of the data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.645398/full#supplementary-material

REFERENCES

1. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol.* (2002) 13:3–9. doi: 10.1097/00041433-200202000-00002
2. Kant AK. Dietary patterns and health outcomes. *J Am Diet Assoc.* (2004) 104:615–35. doi: 10.1016/j.jada.2004.01.010
3. Michels KB, Mohllajee AP, Roset-Bahmanyar E, Beehler GP, Moysich KB. Diet and breast cancer: a review of the prospective observational studies. *Cancer.* (2007) 109:2712–49. doi: 10.1002/cncr.22654
4. Moeller SM, Reedy J, Millen AE, Dixon LB, Newby PK, Tucker KL, et al. Dietary patterns: challenges and opportunities in dietary patterns research an Experimental Biology workshop, April 1, 2006. *J Am Diet Assoc.* (2007) 107:1233–9. doi: 10.1016/j.jada.2007.03.014
5. Tapsell LC. Foods and food components in the Mediterranean diet: supporting overall effects. *BMC Med.* (2014) 12:100. doi: 10.1186/1741-7015-12-100
6. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. *Lancet Oncol.* (2017) 18:e457–71. doi: 10.1016/S1470-2045(17)30411-4
7. Costacou T, Bamia C, Ferrari P, Riboli E, Trichopoulos D, Trichopoulou AJE, et al. Tracing the Mediterranean diet through principal components and cluster analyses in the Greek population. *Eur J Clin Nutr.* (2003) 57:1378–85. doi: 10.1038/sj.ejcn.1601699
8. Gleason PM, Boushey CJ, Harris JE, Zoellner J. Publishing nutrition research: a review of multivariate techniques–part 3: data reduction methods. *J Acad Nutr Diet.* (2015) 115:1072–82. doi: 10.1016/j.jand.2015.03.011
9. Castello A, Buijsse B, Martin M, Ruiz A, Casas AM, Baena-Canada JM, et al. Evaluating the applicability of data-driven dietary patterns to independent samples with a focus on measurement tools for pattern similarity. *J Acad Nutr Diet.* (2016) 116:1914–24 e1916. doi: 10.1016/j.jand.2016.05.008
10. Kant AK. Indexes of overall diet quality: a review. *J Am Diet Assoc.* (1996) 96:785–91. doi: 10.1016/S0002-8223(96)00217-9
11. Trichopoulos D, Lagiou PJB. Dietary patterns and mortality. *Br J Nutr*. (2001) 85:133–4. doi: 10.1079/BJN2000282
12. Ocke MC. Evaluation of methodologies for assessing the overall diet: dietary quality scores and dietary pattern analysis. *Proc Nutr Soc.* (2013) 72:191–9. doi: 10.1017/S0029665113000013
13. Newby PK, Tucker KL. Empirically derived eating patterns using factor or cluster analysis: a review. *Nutr Rev.* (2004) 62:177–203. doi: 10.1111/j.1753-4887.2004.tb00040.x
14. Newby PK, Muller D, Tucker KL. Associations of empirically derived eating patterns with plasma lipid biomarkers: a comparison of factor and cluster analysis methods. *Am J Clin Nutr.* (2004) 80:759–767. doi: 10.1093/ajcn/80.3.759
15. Chatfied C, Collins A. *Introduction to Multivariate Analysis*. Boca Raton: Routledge (2018).
16. Everitt BS, Landau S, Leese M, Stahl D. *Cluster Analysis 5th ed.* London: Wiley (2011). doi: 10.1002/9780470977811
17. Berlin KS, Parra GR, Williams NA. An introduction to latent variable mixture modeling (part 2): longitudinal latent class growth analysis and growth mixture models. *J Pediatr Psychol.* (2014) 39:188–203. doi: 10.1093/jpepsy/jst085
18. Berlin KS, Williams NA, Parra GR. An introduction to latent variable mixture modeling (part 1): overview and cross-sectional latent class and latent profile analyses. *J Pediatr Psychol.* (2014) 39:174–87. doi: 10.1093/jpepsy/jst084
19. Fahey MT, Thane CW, Bramwell GD, Coward WA. Conditional gaussian mixture modelling for dietary pattern analysis. *J R Statist Soc.* (2007) 170:149–66. doi: 10.1111/j.1467-985X.2006.00452.x
20. Rabe-Hesketh S, Skrondal A. Classical latent variable models for medical research. *Stat Methods Med Res.* (2008) 17:5–32. doi: 10.1177/0962280207081236
21. Sotres-Alvarez D, Herring AH, Siega-Riz A. Latent class analysis is useful to classify pregnant women into dietary patterns. *J Nutr.* (2010) 140:2253–9. doi: 10.3945/jn.110.124909
22. de Vos S, Wardenaar KJ, Bos EH, Wit EC, de Jonge PJB. Decomposing the heterogeneity of depression at the person-, symptom-, and time-level: latent variable models versus multimode principal component analysis. *BMC Med Res Methodol.* (2015) 15:88. doi: 10.1186/s12874-015-0080-4
23. Wardenaar KJ, de Jonge. P. Diagnostic heterogeneity in psychiatry: towards an empirical solution. *BMC Med.* (2013) 11:201. doi: 10.1186/1741-7015-11-201
24. Fabiani R, Minelli L, Bertarelli G, Bacci S. A western dietary pattern increases prostate cancer risk: a systematic review and meta-analysis. *Nutrients.* (2016) 8:626. doi: 10.3390/nu8100626
25. Sun Y, Li Z, Li J, Li Z, Han J. A healthy dietary pattern reduces lung cancer risk: A systematic review and meta-analysis. *Nutrients.* (2016) 8:134. doi: 10.3390/nu8030134
26. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. *New Engl J Med.* (2007) 356:227–36. doi: 10.1056/NEJMoa062790
27. Boyd NF, Connelly P, Byng J, Yaffe M, Draper H, Little L, et al. Plasma lipids, lipoproteins, mammographic densities. *Cancer Epidemiol Prevent Biomark.* (1995) 4:727–33.
28. Boyd N, McGuire V. Evidence of association between plasma high-density lipoprotein cholesterol and risk factors for breast cancer. *J Natl Cancer Inst.* (1990) 82:460–8. doi: 10.1093/jnci/82.6.460
29. Kaye J, Meier C, Walker A, Jick H. Statin use, hyperlipidaemia, and the risk of breast cancer. *Br J Cancer.* (2002) 86:1436–9. doi: 10.1038/sj.bjc.6600267
30. Kitahara CM, De González AB, Freedman ND, Huxley R, Mok Y, Jee SH, et al. Total cholesterol and cancer risk in a large prospective study in Korea. *J Clin Oncol.* (2011) 29:1592. doi: 10.1200/JCO.2010.31.5200
31. Zhao Y, Wang H, Pan Y, Li N, Bian C. Association of lipid profile levels in premenopausal and postmenopausal women with breast cancer: a meta-analysis. *Int J Clin Exp Med.* (2016) 9:552–63.
32. Zhao W, Hasegawa K, Chen J. The use of food-frequency questionnaires for various purposes in China. *Public Health Nutr.* (2002) 5:829–33. doi: 10.1079/PHN2002374
33. Cao S, Lu S, Zhou J, Zhu Z, Li W, Su J, et al. Association between dietary patterns and risk of breast cancer in Chinese female population: a latent class analysis. *Public Health Nutr*. (2020) 24:4918–28. doi: 10.1017/S1368980020004826
34. Tibshirani R, Walther G, Hastie T. Estimating the number of clusters in a data set via the gap statistic. *J R Statist Soc B.* (2001) 63:411–23. doi: 10.1111/1467-9868.00293
35. Geiser C. *Data Analysis With Mplus*. New York: Guilford (2012).
36. Muthen LK, Muthen BO. *The comprehensive modeling program for applied researchers user guide.* Los Angeles: Muthén & Muthén (2003).
37. Edefonti V, Randi G, La Vecchia C, Ferraroni M, Decarli A. Dietary patterns and breast cancer: a review with focus on methodological issues. *J Nutr Rev.* (2009) 67:297–314. doi: 10.1111/j.1753-4887.2009.00203.x

38. von Eye A, Bergman LR. Research strategies in developmental psychopathology: Dimensional identity and the person-oriented approach. *J Dev Psychopathol.* (2003) 15:553–80. doi: 10.1017/S0954579403000294
39. Nurius PS, Macy RJ. Heterogeneity among violence-exposed women: applying person-oriented research methods. *J Interpers Viol.* (2008) 23:389–415. doi: 10.1177/0886260507312297
40. Newby PK, Muller D, Hallfrisch J, Andres R, Tucker KL. Food patterns measured by factor analysis and anthropometric changes in adults. *Am J Clin Nutr.* (2004) 80:504–13. doi: 10.1093/ajcn/80.2.504
41. Knudsen VK, Orozova-Bekkevold IM, Mikkelsen TB, Wolff S, Olsen SF. Major dietary patterns in pregnancy and fetal growth. *Eur J Clin Nutr.* (2008) 62:463–70. doi: 10.1038/sj.ejcn.1602745
42. McLachlan GJ, Peel D. *Finite Mixture Models*. New York: John Wiley & Sons (2000).
43. Everitt BS. *Finite Mixture Distributions*. Wiley StatsRef: Statistics Reference Online (2014).
44. Rosato NS, Baer JC. Latent class analysis: a method for capturing heterogeneity. *Soc Work Res.* (2012) 36:61–9. doi: 10.1093/swr/svs006
45. Brennan SF, Cantwell MM, Cardwell CR, Velentzis LS, Woodside JV. Dietary patterns and breast cancer risk: a systematic review and meta-analysis. *Am J Clin Nutr.* (2010) 91:1294–302. doi: 10.3945/ajcn.2009.28796
46. Albuquerque RC, Baltar VT, Marchioni DM. Breast cancer and dietary patterns: a systematic review. *Nutr Rev.* (2014) 72:1–17. doi: 10.1111/nure.12083
47. Dandamudi A, Tommie J, Nommsen-Rivers L, Couch S. Dietary patterns and breast cancer risk: a systematic review. *Anticancer Res.* (2018) 38:3209–22. doi: 10.21873/anticanres.12586
48. Cui X, Dai Q, Tseng M, Shu XO, Gao YT, Zheng W. Dietary patterns and breast cancer risk in the shanghai breast cancer study. *Cancer Epidemiol Prevent Biomark.* (2007) 16:1443–8. doi: 10.1158/1055-9965.EPI-07-0059
49. Butler LM, Wu AH, Wang R, Koh WP, Yuan JM, Yu MC. A vegetable-fruit-soy dietary pattern protects against breast cancer among postmenopausal Singapore Chinese women. *Am J Clin Nutr.* (2010) 91:1013–9. doi: 10.3945/ajcn.2009.28572
50. Zhang CX, Ho SC, Fu JH, Cheng SZ, Chen YM, Lin FY. Dietary patterns and breast cancer risk among Chinese women. *Cancer Causes Contl.* (2011) 22:115–24. doi: 10.1007/s10552-010-9681-8
51. Shin S, Saito E, Inoue M, Sawada N, Ishihara J, Takachi R, et al. Dietary pattern and breast cancer risk in Japanese women: the Japan Public Health Center-based Prospective Study (JPHC Study). *Br J Nutr.* (2016) 115:1769–79. doi: 10.1017/S0007114516000684
52. Kojima R, Okada E, Ukawa S, Mori M, Wakai K, Date C, et al. Dietary patterns and breast cancer risk in a prospective Japanese study. *Breast cancer.* (2017) 24:152–60. doi: 10.1007/s12282-016-0689-0
53. Lu S, Qian Y, Huang X, Yu H, Yang J, Han R, et al. The association of dietary pattern and breast cancer in Jiangsu, China: A population-based case-control study. *PLoS ONE.* (2017) 12:e0184453. doi: 10.1371/journal.pone.0184453
54. Bauer DJ, Curran PJ. Overextraction of latent trajectory classes: much ado about nothing? Reply to Rindskopf (2003), Muthén (2003), and Cudeck and Henly (2003). *Psychol Methods.* (2003) 8:384–93. doi: 10.1037/1082-989X.8.3.384
55. van de Schoot R, Sijbrandij M, Winter SD, Depaoli S, Vermunt JK. The GRoLTS-checklist: guidelines for reporting on latent trajectory studies. *Struct Eq Model.* (2017) 24:451–67. doi: 10.1080/10705511.2016.1247646

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Association of Dietary Calcium Intake With Bone Health and Chronic Diseases: Two Prospective Cohort Studies in China

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Background: Calcium is an essential element in our diet and the most abundant mineral in the body. A high proportion of Chinese residents are not meeting dietary calcium recommendations. The purpose of this study was to investigate the relationship between calcium intake and the health of residents in two longitudinal studies of Chinese residents.

Methods: This study used nationally representative data from the Harbin Cohort Study on Diet, Nutrition, and Chronic Non-communicable Disease Study (HDNNCDS) and China Health Nutrition Survey (CHNS), including 6,499 and 8,140 Chinese adults, respectively, who were free of chronic diseases at recruitment, with mean values of 4.2- and 5.3-year follow-up. Cox's proportional-hazards regression was conducted to explore the relationship between dietary calcium intake and the incidence of obesity, type 2 diabetes, hypertension, and cardiovascular disease (CVD) with adjustment for covariates.

Results: Calcium intakes were 451.35 ± 203.56 and 484.32 ± 198.61 (mean ± SD) mg/day in HDNNCDS and CHNS. After adjusting the covariates, the relationship between dietary calcium intake and bone mineral density (BMD) was not statistically significant ($p = 0.110$). In the multivariate-adjusted Cox's proportional-hazards regression model, dietary calcium intakes were inversely associated with obesity incidence in both cohorts (HR [95% CI]: 0.61 [0.48–0.77] and p trend < 0.001 in fixed-effects model); nevertheless, there was no correlation between dietary calcium intake and the risk of type 2 diabetes (p trend $= 0.442$ and 0.759) and CVD (p trend $= 0.826$ and 0.072). The relationship between dietary calcium intake and the risk of hypertension in the two cohorts was inconsistent (p trend $= 0.012$ and 0.559). Additionally, after further adjusting the vegetable intake in the original multivariate model, both cohorts found no association between dietary calcium intake and the risk of developing obesity (p trend $= 0.084$ and 0.444).

Conclusions: Our data suggest that the current calcium intake of Chinese residents was inversely associated with obesity, which may be related to consumption of vegetables. Meanwhile, the current calcium intake does not increase the risk of type 2 diabetes, CVD, and bone health burden. This research suggested that the Chinese current calcium intake level may have met the needs of the body.

Keywords: dietary calcium intake, chronic disease, cohort study, dietary reference intakes (DRI), bone mineral density (BMD)

INTRODUCTION

Calcium is an essential nutrient in the human body. Adequate calcium intake is essential for the normal growth and development of bones and the necessary physiological functions (1). Although short-term dietary calcium deficiency will not lead to a significant decrease in blood calcium levels, long-term dietary calcium deficiency will eventually lead to bone weakness and easy fracture (2, 3). Recent evidence suggests that calcium may also have non-skeletal effects. To date, numerous epidemiological studies and meta-analyses have found that there seems to be a close link between dietary calcium deficiency and the prevalence of chronic disease (4, 5).

Despite this, according to the China Nutrition and Health Status Survey, the average dietary calcium intake of Chinese residents in 2002 and 2012 was 389 and 364 mg/d, respectively, which is only about 50% of the recommended intake (6, 7). The current reference recommended intake of dietary calcium for Chinese residents is 800 mg/day (8). Notably, the Chinese recommended intake of calcium has been formulated based primarily on reference to the US standard, which is only slightly lower than the US at the time of formulation given the differences in bone mass between the Chinese and US populations (9). Due to ethnic differences in calcium absorption, metabolism, and dietary habits, the reference intake based on the western population may not be fully applicable to the Chinese population (10, 11). Moreover, a meta-analysis including 11 calcium balance studies showed that the calcium requirement for Chinese adults approximately ranged between 400 and 500 mg/d (9), which was close to the average dietary calcium intake of Chinese residents. Given the limitation and inconsistency of evidence, the relationship between dietary calcium and health in the normal population remains unclear. Meanwhile, most previous studies on the association between calcium intake and chronic disease have been conducted in Western populations (12), with only limited evidence in Chinese, despite a steadily increasing prevalence of chronic disease over the past decade.

Therefore, it is necessary to study the relationship between dietary calcium intake and bone health and non-bone health on the premise that the calcium intake of Chinese residents is generally lower than the recommended intake. In this research, two prospective cohorts from the Harbin Cohort Study on Diet, Nutrition, and Chronic Non-communicable Disease Study (HDNNCDS) and the China Health and Nutrition Survey (CHNS) were used to investigate the association of calcium intake with bone health and the incidence of chronic diseases including obesity, type 2 diabetes, hypertension, and cardiovascular disease (CVD).

METHODS

Study Populations

Harbin Cohort Study on Diet, Nutrition, and Chronic Non-communicable Disease Study is an ongoing prospective cohort study launched in 2010. The study's design and implementation have been described (13). In brief, at baseline, 9,734 participants aged 20–74 years old had lived in Harbin for more than 2 years, without type 1 diabetes and malignancies were recruited. From 2015 to 2016, a total of 8,913 participants finished the first follow-up survey with a response rate of 91.6%. In this study, first, we excluded the following individuals: those who were taking vitamin D supplementation or calcium gluconate injection at either the baseline or the follow-up; those with dietary restriction for diseases or weight loss; those with extremely high or low total energy intake (>4,000 or <800 kcal); and also those with more than 10 blank items in the dietary questionnaire. Furthermore, when analyzing the relationship between calcium and obesity, we further exclude those with obesity (self-reported or diagnosed based on BMI) at baseline; Similarly, when analyzing the relationship between calcium and hypertension, CVD, and type 2 diabetes, we also excluded participants with these diseases at baseline, respectively (**Figure S1**). The study was carried out at Harbin Medical University in Harbin and approved by the ethics committee of Harbin Medical University and conducted in accordance with the Declaration of Helsinki (ChiCTRECH-12002721).

China Health and Nutrition Survey is a nationwide ongoing longitudinal prospective cohort study of nine waves (1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, and 2011). A multistage, random cluster process was used to obtain the representative samples of 228 communities from nine diverse provinces in China, and new participants have been recruited as replenishment samples since 1997 (14). The overall response rate was 93%, based on those who were followed up at least once.

As hematological specimens were only collected and detected in the 2009 survey, to accurately measure the occurrence of chronic diseases, only participants who provided hematological specimens during the follow-up period in 2009 and complete information at any of the four baseline surveys in 1997, 2000, 2004, and 2006 were included in this study. After excluding those with implausible or missing values for the intake of dietary, or total energy intake and dietary calcium (the upper and lower 0.5% of the intakes), and also those with type 2 diabetes, hypertension, obesity, and CVD at baseline, 6,499 participants were included in the final analyses. The survey protocols, instruments, and the process for obtaining informed consent were approved by the Institutional Review Committees of the University of North Carolina at Chapel Hill, NC, USA, and the China National Institute of Nutrition and Food Safety at the Chinese Center for

Disease Control and Prevention, Beijing, China. All participants provided written informed consent prior to the surveys.

Assessment of Diet

In the HDNNCDS, baseline dietary intake was evaluated using a validated food frequency questionnaire (FFQ) consisting of 103 food items divided into 14 food groups to assess habitual dietary intakes over the past year. To evaluate the validity and repeatability of the FFQ, we have conducted a small-scale study in 2009 and found that FFQ used in HDNNCDS was a reliable method for assessing dietary intake (13). In this study, each participant was asked about the frequency and quantity of each food item that they have consumed by trained nutrition professionals. Daily nutrient intake from the diet was calculated in accordance with the Chinese Food Composition Table (FCT). For the CHNS, to assess individual diet in each survey, the researchers repeatedly performed a 24-h review of individual diet and measured household oil and condiment consumption for three consecutive days. We calculated nutrient intakes as the nutrient content of standard portion size of 100 g multiplied by the consumption of each food item and used China FCTs were utilized to obtain the nutrient intake data of each participant.

Basic Information Collection and Biochemical Assessments

In both cohorts, all the participants were interviewed face-to-face by trained personnel using a structured questionnaire to collect demographic and lifestyle information, mainly including physical activity level, educational status, smoking, drinking status, family history of diseases, and medical history. At the same time, anthropometric indices, body weight, and height were taken in agreement with standardized procedures. Blood pressure was measured 3 times on the right arm, with a standard mercury sphygmomanometer after a 10-min rest before measurement, and the mean values were used for statistical analysis.

Blood samples, including fasting and postprandial (2 h after drinking 75 g of water containing glucose), were collected by professional nurses at the follow-up survey in both HDNNCDS and CHNS. Additionally, in HDNNCDS, blood samples were also collected at the baseline survey. Serum fasting blood glucose and 2-h glucose were measured using an automatic analyzer (Hitachi 7100, and Hitachi 7100, Tokyo, Japan, respectively). In addition, in HDNNCDS, the serum level of $25OHD_3$ was measured based on UPLC (Waters Corporation, Milford, MA, USA) (15).

During the follow-up period of HDNNCDS, the bone mineral density (BMD) of 1,640 subjects without fractures and bone metabolic diseases was measured by dual-energy X-ray absorptiometry Hologic QDR 4500 (DEXA). Measurements were taken at the following sites: femoral neck, intertrochanter, ward triangle, greater trochanter, and total hip. All measurements were collected by trained staff using standard methods.

Outcome Identification

Obesity was defined as BMI $\geq$ 28 kg/cm^2, according to the guidelines for prevention and control of overweight and obesity in Chinese adults (16). Type 2 diabetes at follow-up was defined by ADA criteria as FBG $\geq$ 7.0 mmol/L, and/or 2-h PG $\geq$ 11.1 mmol/L, and/or receiving treatment for type 2 diabetes (17). Diagnostic criteria for hypertension defined by evidence-based guidelines for the management of high blood pressure in adults were as follows: SBP $\geq$ 140 mmHg, and/or DBP $\geq$ 90 mmHg, and/or receiving treatment for hypertension (18). CVD was diagnosed by self-reported information of the history of stroke and/or myocardial infarction (19).

Statistical Analysis

Dietary calcium intakes were energy-adjusted using the residuals calculated from the linear regression for data analysis. Participants were categorized into quartile groups according to their calcium intake levels at the baseline from the lowest intake (quartile 1) to the highest intake (quartile 4). The mean $\pm$ SD was expressed for each continuous data. Category value was expressed as a proportion. Using a general linear model to compare differences in BMD between different dietary calcium intake levels with adjustment for age, sex, BMI, alcohol consumption, smoking, education level, physical activities, dietary total energy, and menopause in the case of women, Cox's proportional-hazards regression was performed to analyze the association of calcium intake and the incidence of obesity, type 2 diabetes, hypertension, and CVD with adjustment for covariates. We used restricted cubic spline (RCS) as a tool available for characterizing dose–response associations between dietary calcium intake with incidence of obesity and hypertension, using 3 knots at pre-specified locations according to the percentiles of the distribution of dietary calcium, the 5, 50, and 95th percentiles. The reference value for calcium intake was chosen to be the median value (20). Stratified analysis was conducted among adults of different genders and ages. Meta-analysis was performed using comprehensive meta-analysis (CMA) V3.0 software (https://www.meta-analysis.com/) with fixed-effects model, and other statistical analyses were performed using R 3.2.5 (http://www.r-project.org/) and SPSS software version 22.0 (SPSS; Beijing Stats Data Mining Co. Ltd). A two-tailed value of $p < 0.05$ was considered significant.

RESULTS

Baseline Characteristics of Subjects Based on Calcium Intake

Table 1 showed the baseline characteristics of the population of these two studies, which were described by quartiles of dietary calcium intake. With the increase in dietary calcium intake, in both studies, the age and proportion of women gradually increased. The individuals in the highest quartile of dietary calcium intake were less likely to smoke and drink alcohol than those in the lowest quartile. High calcium intake was associated with high education level. In addition, there were significant differences in physical activity levels among the four groups in two cohort studies.

TABLE 1 | Baseline characteristics according to quartiles of dietary calcium intake at baseline of the population in two cohort studies.

Characteristics	Dietary calcium intake				P^b
	Q1[a]	Q2	Q3	Q4	
HDNNCDS					
Participants (*n*)	2,036	2,034	2,036	2,034	
Dietary Ca intake[c] (mg/d)	256.62 ± 60.93	377.51 ± 26.89	484.79 ± 36.26	704.77 ± 149.87	
Age (years)	51.13 ± 9.23	51.45 ± 9.46	52.36 ± 9.55	52.65 ± 9.34	<0.01
Female (%)	56.2	66.9	67.8	71.5	<0.01
Smoking (%)					<0.01
Current	22.8	15.0	14.0	12.6	
Ever	4.9	2.8	3.9	2.5	
Never	72.4	82.2	82.1	84.9	
Alcohol consumption (%)	39.5	30.9	32.4	28.5	<0.01
Education (%)					0.01
<9 years	36.1	33.8	30.4	29.2	
10–12 years	30.6	32.1	34.7	35.4	
>12 years	27.5	27.4	28.7	28.9	
Physical activity (%)					<0.01
Light	77.7	82.0	85.0	84.8	
Middle	19.2	17.1	13.5	13.9	
Heavy	3.1	0.9	1.5	1.3	
CHNS					
Participants (n)	1,624	1,626	1,624	1,625	
Dietary Ca intake[c] (mg/d)	283.08 ± 125.12	395.30 ± 129.36	528.21 ± 134.56	795.50 ± 184.20	
Age (years)	42.00 ± 12.90	43.20 ± 13.03	43.92 ± 13.10	44.07 ± 12.92	<0.01
Female (%)	49.7	55.5	56.2	54.6	0.01
Smoking (%)					<0.01
Current	34.6	29.6	30.2	27.3	
Ever	0.4	0.6	0.6	0.9	
Never	65.0	69.8	69.2	71.8	
Alcohol consumption (%)	34.1	29.6	30.7	27.0	<0.01
Education (%)					<0.01
<9 years	27.8	27.6	27.6	26.3	
10–12 years	55.8	54.0	53.3	52.1	
>12 years	14.7	15.6	16.3	18.6	
Physical activity (%)					<0.01
Light	19.3	21.6	22.7	25.8	
Middle	10.3	12.0	13.7	14.0	
Heavy	42.1	31.1	26.4	25.2	

[a]All values represent means ± SD for continuous variables and proportions for categorical variables. [b]Differences between four groups were tested by using ANOVA and chi-squared test for continuous and categorical variables, respectively. [c]Energy-adjusted by using the residual method.

Associations Between Calcium Intake and BMD

Due to the lack of bone health data in CHNS, research on the relationship between dietary calcium and bone health was only conducted in HDNNCDS. After adjusting for covariates, there was no significant difference in BMD of the femoral neck, femoral intertrochanteric, ward triangle, greater trochanter, and total hip among different dietary calcium intake groups (**Table 2**).

Association Between Calcium Intake and Chronic Disease

Table 3 showed the association between calcium intake and four common chronic diseases in HDNNCDS study. During 5.3-year of follow-up, we identified 506 incident cases of obesity, 1,378 incident cases of hypertension, 614 incident cases of type 2 diabetes, and 898 incident cases of CVD. By comparing quartile 4 with quartile 1, we observed that

TABLE 2 | Comparison of BMD in different dietary calcium intake groups.

Variables	Dietary calcium intake (mg/d)				p^{b}_{trend}
	Q1[a]	Q2	Q3	Q4	
Participants (*n*)	409	410	411	410	
Bone mineral density (g/cm^2)					
Femoral neck	0.75 ± 0.01	0.75 ± 0.01	0.76 ± 0.01	0.75 ± 0.01	0.523
Intertrochanter	0.93 ± 0.01	0.95 ± 0.01	0.97 ± 0.01	0.95 ± 0.01	0.168
Ward triangle	0.54 ± 0.01	0.54 ± 0.02	0.57 ± 0.02	0.56 ± 0.01	0.292
Greater trochanter	0.59 ± 0.01	0.60 ± 0.01	0.62 ± 0.01	0.60 ± 0.01	0.158
Total hip	0.80 ± 0.01	0.82 ± 0.01	0.83 ± 0.01	0.81 ± 0.01	0.110

[a]Continuous variables were shown as means ± standard error. [b]Model were adjusted by age, sex, BMI, alcohol consumption, smoking, education, physical activities, dietary total energy, and menopause in case of women. BMI, body mass index.

TABLE 3 | Hazard ratios (HRs) and 95% CIs of chronic disease according to energy-adjusted dietary calcium intake in HDNNCDS (2010–2016).

Variables	Energy-adjusted dietary calcium intake				p_{trend}
	Q1	Q2	Q3	Q4	
Obesity					
Intake (mg/d)	294.81 ± 124.12	342.72 ± 125.76	464.67 ± 128.95	720.74 ± 210.09	
Case/N	176/1,650	112/1,654	126/1,652	92/1,650	
Model 1[a]	Reference	0.68 (0.49–0.95)	0.77 (0.56–1.07)	0.58 (0.41–0.83)	0.006
Model 2[b]	Reference	0.67 (0.47–0.95)	0.78 (0.56–1.10)	0.60 (0.42–0.87)	0.016
Model 3[c]	Reference	0.65 (0.46–0.93)	0.76 (0.54–1.07)	0.58 (0.40–0.83)	0.015
Hypertension					
Intake (mg/d)	255.78 ± 59.74	379.47 ± 27.40	486.59 ± 36.75	704.54 ± 144.90	
Case/N	356/1,332	360/1,336	342/1,334	320/1,332	
Model 1	Reference	1.05 (0.85–1.29)	0.97 (0.78–1.20)	0.90 (0.72–1.11)	0.224
Model 2	Reference	1.06 (0.85-1.33)	1.01 (0.81-1.27)	0.95 (0.76-1.19)	0.539
Model 3	Reference	1.04 (0.83–1.30)	0.99 (0.79–1.24)	0.95 (0.76–1.19)	0.559
Type 2 diabetes					
Intake (mg/d)	256.41 ± 60.75	376.10 ± 26.50	483.60 ± 36.92	704.12 ± 149.67	
Case/*N*	158/1,874	154/1,876	62/1,876	140/1,874	
Model 1	Reference	0.99 (0.73–1.36)	1.02 (0.75–1.40)	0.88 (0.64–1.22)	0.428
Model 2	Reference	1.00 (0.73–1.38)	1.04 (0.76–1.43)	0.88 (0.63–1.23)	0.444
Model 3	Reference	1.02 (0.73–1.41)	1.05 (0.76–1.44)	0.88 (0.63–1.23)	0.442
Cardiovascular disease					
Intake (mg/d)	266.22 ± 76.05	399.74 ± 27.54	503.26 ± 37.15	731.80 ± 164.39	
Case/*N*	208/1,316	208/1,314	246/1,312	236/1,316	
Model 1	Reference	0.98 (0.75–1.29)	1.08 (0.83–1.40)	1.00 (0.77–1.31)	0.887
Model 2	Reference	0.98 (0.74–1.29)	1.09 (0.83–1.42)	1.02 (0.78–1.34)	0.776
Model 3	Reference	1.03 (0.77–1.36)	1.13 (0.86–1.49)	1.02 (0.78–1.34)	0.826

[a]Model 1 adjusted with age and gender; [b]Model 2 adjusted with age, gender, BMI, alcohol consumption rate, smoking rate, physical activity, and education; [c]Model 3 adjusted with age, gender, BMI, alcohol consumption rate, smoking rate, physical activity, education, dietary energy intake, and AHEI. BMI, body mass index; AHEI, alternative healthy eating index.

obesity risk decreased with dietary calcium intake (HR: 0.58, 95% CI: 0.40–0.83, p for trend = 0.015). In addition, we found no appreciable association between dietary calcium intake and the risk of hypertension, type 2 diabetes, and CVD. We modeled the relationship between dietary calcium intake and obesity risk using the RCS model with 3 knots (**Figure 1A**). There was a significant linear dose–response association visually, but not non-linear relationship (p for linear = 0.020; p for non-linear = 0.067).

In CHNS study, during 4.2-year of follow-up, we identified 337 incident cases of obesity, 1,228 incident cases of hypertension, 501 incident cases of type 2 diabetes, and 150 incident cases of CVD (**Table 4**). For the risk of obesity, compared with the lowest quartile, no statistically significant

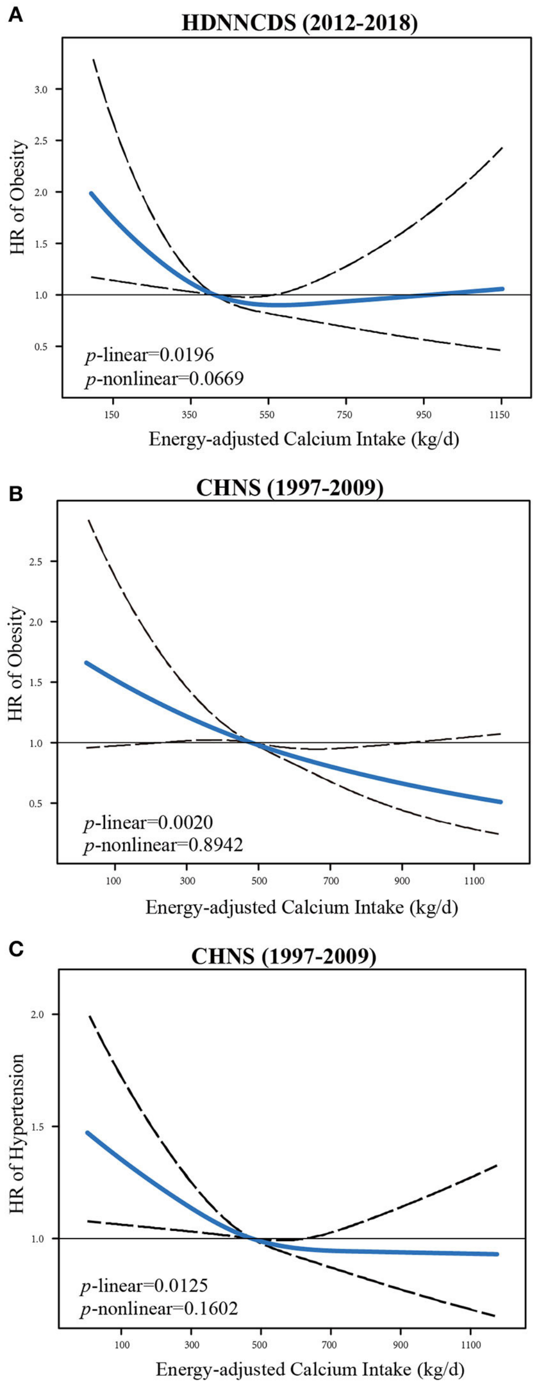

FIGURE 1 | Association between dietary calcium intake and the risk of obesity in HDNNCDS **(A)** and CHNS study **(B)**, and the risks of obesity and hypertension in CHNS study **(C)**, allowing for linear effects, with 95% CIs. The models with 3 knots RCS for calcium intake adjusting for age, sex, BMI, alcohol consumption, smoking, education, physical activities, dietary total energy, and menopause in case of women. Curves showed HRs of obesity or hypertension compared with the chosen reference medians of calcium intakes. BMI, body mass index; HRs, hazard risk.

association was observed between calcium intake and obesity with adjustment for age and sex (p for trend = 0.050). However, after adjustment for potential confounders and related dietary factors, dietary calcium intake was associated with a depressed risk of obesity. In Model 3, the hazard ratio of the highest quartile of calcium intake was 0.63 (95% CI: 0.46–0.85, p for trend = 0.001). Similarly, we found the same negative correlation in the HDNNCDS study, so we used a fixed-effects model to comprehensively analyze the results of the two cohort studies. We further determined the negative correlation between dietary calcium and obesity risk. Likewise, there was no significant association between calcium and the risk of hypertension after adjusted age and sex. But in multivariate analysis, the HR (95% CI) of the highest quartile of calcium intake was 0.82 (95% CI: 0.69–0.97), compared with the lowest quartile. No statistically significant association was observed between calcium intake and type 2 diabetes, or CVD in any model. We also used RCS to model the linear or non-linear relationships between calcium intake and the risks of obesity and hypertension (**Figures 1B,C**). There were both significant linear dose–response associations between calcium and obesity (p for linear = 0.0020; p for non-linear = 0.8942) and hypertension (p for linear = 0.0125; p for non-linear = 0.1602).

Association Between Dietary Sources of Calcium With Obesity and Hypertension

According to the dietary surveys, the main food sources of dietary calcium were grain, beans, vegetables, fruit, meat, dairy, eggs, and seafood in HDNNCDS and CHNS. After adjusting potential confounders and related dietary factors, in HDNNCDS, we found that dietary calcium from the vegetable source was negatively associated with the risk of obesity (p for trend = 0.036) (**Figure 2**). In the multivariate-adjusted model, the hazard risk of the highest quartile of calcium intake from vegetables was 0.86 (95% CI: 0.78–0.98, p = 0.045). Likewise, in CHNS, dietary calcium from the vegetable source was associated with a depressed incidence of obesity (p for trend = 0.029, HR of highest quartile: 0.67, 95% CI: 0.49–0.91, p = 0.011). For hypertension in CHNS, we did not find a significant linear trend between calcium from the vegetable source and the incidence of hypertension (p for trend = 0.190). However, the hazard ratio of hypertension in the third quartile of dietary calcium from vegetables relative to that in the lowest quartile was 0.82 (95% CI: 0.70–0.98, p = 0.033). After further adjusting the vegetable intake in the model, the relationship between dietary calcium intake and obesity and hypertension was not significant (p for trend = 0.084 and 0.444 for obesity in HDNNCDS and CHNS, respectively; p for trend = 0.221 for hypertension in CHNS) (**Table 5**). Otherwise, **Table S1** shows the differences in incidences of obesity and hypertension between people who consumed and did not consume fruit or dairy in CHNS. We found that people who consumed fruit had a significantly lower incidence of hypertension than people who did not consume

TABLE 4 | Hazard ratios (HRs) and 95% CIs of chronic disease according to energy-adjusted dietary calcium intake in CHNS (1997–2009).

Variables	Energy-adjusted dietary calcium intake				p_{trend}
	Q1	Q2	Q3	Q4	
Obesity					
Intake (mg/d)	234.71 ± 126.58	348.41 ± 127.89	479.57 ± 134.04	747.18 ± 181.76	
Case/*N*	88/1,385	97/1,385	75/1,385	77/1,385	
Model 1[a]	Reference	1.06 (0.80–1.42)	0.77 (0.57–1.06)	0.80 (0.59–1.08)	0.050
Model 2[b]	Reference	0.93 (0.70–1.25)	0.66 (0.48–0.90)	0.63 (0.47–0.87)	0.001
Model 3[c]	Reference	0.93 (0.70–1.25)	0.65 (0.47–0.89)	0.63 (0.46–0.85)	0.001
Hypertension					
Intake (mg/d)	230.67 ± 125.54	243.58 ± 130.47	473.72 ± 132.59	740.52 ± 180.90	
Case/*N*	306/1,334	302/1,332	302/1,334	318/1,333	
Model 1	Reference	0.99 (0.84–1.16)	0.89 (0.76–1.04)	0.95 (0.81–1.11)	0.352
Model 2	Reference	0.93 (0.78–1.10)	0.80 (0.66–0.92)	0.84 (0.71–0.99)	0.024
Model 3	Reference	0.92 (0.78–1.09)	0.77 (0.65–0.92)	0.82 (0.69–0.97)	0.012
Type 2 diabetes					
Intake (mg/d)	213.90 ± 72.55	367.48 ± 34.49	494.17 ± 39.52	726.18 ± 132.12	
Case/*N*	117/1,554	119/1,554	132/1,554	133/1,554	
Model 1	Reference	1.01 (0.78–1.30)	1.04 (0.81–1.34)	1.04 (0.81–1.34)	0.700
Model 2	Reference	0.97 (0.74–1.28)	1.03 (0.79–1.34)	0.93 (0.71–1.21)	0.609
Model 3	Reference	0.96 (0.72–1.26)	1.02 (0.78–1.33)	0.95 (0.73–1.24)	0.759
Cardiovascular disease					
Intake (mg/d)	233.57 ± 126.05	343.01 ± 129.64	478.79 ± 134.70	746.91 ± 183.90	
Case/N	39/1,562	42/1,561	35/1,562	34/1,561	
Model 1	Reference	1.05 (0.68–1.62)	0.80 (0.50–1.26)	0.77 (0.49–1.23)	0.166
Model 2	Reference	0.95 (0.60–1.50)	0.70 (0.43–1.13)	0.68 (0.42–1.09)	0.065
Model 3	Reference	0.87 (0.55–1.39)	0.66 (0.40–1.06)	0.67 (0.41–1.09)	0.072

[a]Model 1 adjusted with age and gender; [b]Model 2 adjusted with age, gender, BMI, alcohol consumption rate, smoking rate, physical activity, and education; [c]Model 3 adjusted with age, gender, BMI, alcohol consumption rate, smoking rate, physical activity, education, dietary energy intake, and AHEI. BMI, body mass index; AHEI, alternative healthy eating index.

fruit (20.0% vs. 23.5%, $p = 0.008$). In addition, we did not find significant associations between other food sources of dietary calcium with the incidences of obesity and hypertension in HDNNCDS and CHNS (**Supplementary Figures S5, S6**).

DISCUSSION

In HDNNCDS and CHNS, we found dietary calcium was inversely associated with the incidence of obesity; nevertheless, there was no correlation between dietary calcium intake and bone density, and also the incidence of T2DM and CVD. Meanwhile, the relationship between dietary calcium intake and the risk of hypertension in the two cohorts was inconsistent.

Dietary calcium intakes were 484.32 ± 198.61 and 451.35 ± 203.56 (mean ± SD) mg/d in HDNNCDS and CHNS, respectively. According to the survey, in 2012, the average daily calcium intake of Chinese residents was 366.1, 412.4 mg in urban areas, and 321.4 mg in rural areas (21). These were similar to the mean dietary calcium in the two cohort surveys in our study, both well below the recommended calcium intake of 800 mg/d, while it must be noted that Chinese dietary reference intakes for calcium were largely based on calcium balance data and clinical trials derived from the developed country (22). Measures of calcium balance have limitations and their precision is difficult to ascertain (23). Ideally, each nation should establish its own RDA of calcium based on the ethnic make-up of its population (24). Due to different dietary cultures, genetics, lifestyles, and food production histories, environments, despite the adjustment of sizes, the recommended calcium intake in western countries may not be entirely applicable to Chinese (25, 26). Meanwhile, a meta-analysis for Chinese adults of calcium balance studies found across all the Chinese balance studies, after adjustment for calcium intake, region, gender, diet, adaptation duration, and balance period, calcium intake equaled calcium output at intakes of 400–500 mg/d (9). It was suggested that the current calcium recommended intake based on western countries may not be suitable for the Chinese population.

In HDNNCDS, after adjusting the covariates, the relationship between dietary calcium intake and BMD was not statistically significant. Our finding appears to be consistent with the results from studies in premenopausal women showing that daily dietary calcium intake did not correlate with BMD (27). Moreover, a number of the high-quality meta-analyses that found calcium supplementation alone or with vitamin D were not associated with reduced fracture incidence among community-dwelling adults (28, 29). One possible explanation for this study is that

Calcium from Vegetable

HDNNCDS Study

Obesity

	Vegetable Intake	Case/N	HR (95%CI)	*p*
Q1 (190.51±90.24mg/d)	(213.68±114.62g/d)	74/814	1	0.087
Q2 (299.63±59.59mg/d)	(293.80±116.39g/d)	63/815	0.98 (0.80−1.16)	0.291
Q3 (387.39±76.9mg/d)	(419.62±153.83g/d)	61/815	0.98 (0.80−1.12)	0.126
Q4 (662.2±151.31mg/d)	(495.37±214.69g/d)	53/814	0.86 (0.78−0.98)	**0.045**
p for trend			**0.036**	

CHNS Study

Obesity

	Vegetable Intake	Case/N	HR (95%CI)	*p*
Q1 (144.50±97.27mg/d)	(198.43±121.24g/d)	92/1359	1	0.065
Q2 (233.54±94.42mg/d)	(270.38±115.43g/d)	79/1352	0.73 (0.54−0.99)	**0.049**
Q3 (322.44±97.98mg/d)	(341.93±124.31g/d)	86/1367	0.78 (0.58−1.07)	0.126
Q4 (597.06±104.42mg/d)	(452.22±169.79g/d)	80/1363	0.67 (0.49−0.91)	**0.011**
p for trend			**0.029**	

Hypertension

	Vegetable Intake	Case/N	HR (95%CI)	*p*
Q1 (147.98±102.25mg/d)	(177.75±96.19g/d)	312/1333	1	0.182
Q2 (238.71±97.01mg/d)	(280.15±125.07g/d)	301/1334	0.88 (0.74−1.04)	0.143
Q3 (327.36±99.88mg/d)	(345.96±107.14g/d)	296/1333	0.82 (0.70−0.98)	**0.033**
Q4 (611.32±117.49mg/d)	(458.56±195.11g/d)	319/1333	0.87 (0.74−1.04)	0.133
p for trend			0.190	

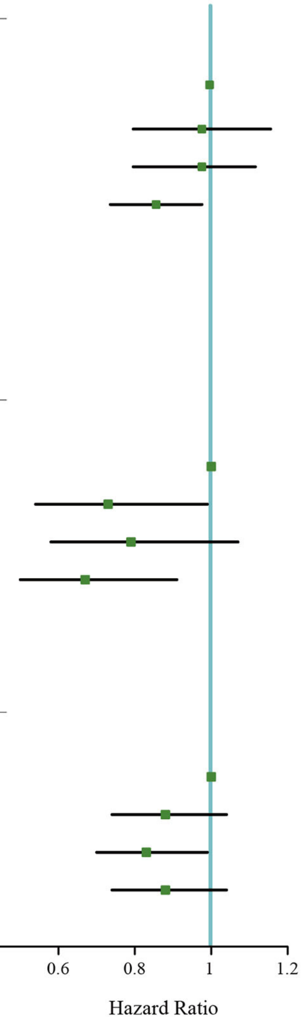

FIGURE 2 | Association between calcium intake from vegetable with the risks of obesity and hypertension in HDNNCDS study and CHNS study. Models adjusted with age, gender, body mass index, alcohol consumption rate, smoking rate, physical activity, education, dietary energy intake, and alternative healthy eating index.

calcium intake has already met the bone requirements in the lowest quantile group, so increasing calcium intake cannot continue to increase bone density.

Apart from that, we used the same statistical model to study the relationship between dietary calcium and disease in two large prospective cohorts of the same race. The results indicated that the association between dietary calcium intake and the risk of obesity was significant in both HDNNCDS and CHNS. To enhance the credibility of the results, in our study, stratified analyses were performed based on age (**Supplementary Figures S2, S3**) and serum 25OHD$_3$ levels (**Figure S4**). Interestingly, we found that this kind of protective relationship exists only in middle-aged people and is independent of serum vitamin D levels. In a cohort study of middle-aged women, the decrease in annual average weight gain was related to the increase in calcium intake (30). Epidemiologic studies based on the National Health and Nutrition Examination Study III (NHANES III) also have found that there was a reduction in risk for obesity with each increasing quartile of calcium intake (31).

However, it is worth noting that Chinese people live on plant-based diets poor in calcium quantity. If residents rely on the traditional Chinese diet, it is hard to reach 800 mg/d calcium intake, unless calcium supplements are used. Although milk and dairy products are the main sources of calcium (32), the Chinese intake of calcium from eggs, fish, shrimp, and milk is <5%, whereas vegetables, cereals, and legumes are the main sources of dietary calcium (28, 33). However, more than 80% of dietary calcium in westerners was derived from dairy and meat products (34). To explore the relationship between major food sources of dietary calcium and chronic diseases, we further analyzed the association of calcium intake in vegetables, fruit, dairy, and other foods with the incidences of obesity and hypertension. We found

TABLE 5 | Hazard ratios (HRs) and 95% CIs of obesity and hypertension according to energy-adjusted dietary calcium intake in HDNNCDS and CHNS.

Variables	Energy-adjusted dietary calcium intake				*p* trend
	Q1	Q2	Q3	Q4	
HDNNCDS					
Obesity					
Case/*N*	176/1,650	112/1,654	126/1,652	92/1,650	
Multivariate-adjusted[a]	Reference	0.65 (0.46–0.93)	0.76 (0.54–1.07)	0.58 (0.40–0.83)	0.015
Added adjusted for vegetable intake	Reference	0.79 (0.52–1.18)	0.73 (0.48–1.10)	0.67 (0.42–1.08)	0.084
CHNS					
Obesity					
Case/*N*	88/1,385	97/1,385	75/1,385	77/1,385	
Multivariate-adjusted	Reference	0.93 (0.70–1.25)	0.65 (0.47–0.89)	0.63 (0.46–0.85)	0.001
Added adjusted for vegetable intake	Reference	1.04 (0.77–1.40)	0.80 (0.58–1.11)	0.92 (0.64–1.32)	0.444
Hypertension					
Case/*N*	306/1,334	302/1,332	302/1,334	318/1,333	
Multivariate-adjusted	Reference	0.92 (0.78–1.09)	0.77 (0.65–0.92)	0.82 (0.69–0.97)	0.012
Added adjusted for vegetable intake	Reference	1.01 (0.85–1.20)	0.93 (0.77–1.11)	1.15 (0.94–1.40)	0.221

[a]*Multivariate-model adjusted with age, gender, BMI, alcohol consumption rate, smoking rate, physical activity, education, dietary energy intake and AHEI. BMI, body mass index; AHEI, alternative healthy eating index.*

that only calcium consumption in vegetables was consistent with total calcium intake, that the higher the calcium intake in vegetables, the lower the risk of obesity and hypertension. Simultaneously, as calcium consumption in vegetable increases, the intake of calcium and vegetables increased together, which possibly contributes to a protective effect on the risk of obesity and hypertension. Therefore, in other to exclude the influence of vegetable intake on the relationship between calcium intake and obesity and hypertension, we further adjusted the vegetable intake in the model. We found that the relationship between dietary calcium intake and obesity and hypertension was strongly attenuated, after further adjustment for the intake of vegetables. Besides, we divided the participants into two groups according to the energy-adjusted vegetable consumption level. We separately analyzed the relationship between dietary calcium and obesity at different levels in the two cohorts (**Figure S7**). We found that dietary calcium was still negatively correlated with obesity risk at higher vegetable consumption levels, but there was no statistically significant relationship between dietary calcium and obesity when vegetable consumption was lower. In any case, such results indicated although the association between dietary calcium intake and obesity and hypertension has been found, it is probably due to the beneficial effects of vegetables on body weight and blood pressure (35–37). Besides, due to the difference in the research methods of the dietary surveys in the two cohort studies, FFQ in HDNNCDS and 3-day 24-h retrospective in CHNS respectively, which led to the intake of dairy and fruits as the main dietary sources of calcium in CHNS, may be underestimated. Since fewer people consumed fruits and dairy products, we compared the incidence of obesity or hypertension in people who consumed fruit and dairy with those who did not (**Table S1**). Even though we found a significantly different incidence of hypertension between the people who consumed fruit and those who did not in CHNS, owing to the number of people who consume fruit is too small, accounting for only 14% of the total number of people, the statistically significant difference between the incidence rates has no actual clinical significance.

To the best of our knowledge, this study is the first attempt to comprehensively explore the relationship between different calcium intake and health in Chinese residents in both a community prospective cohort and a national prospective cohort. We used the same statistical model to study the relationship between dietary calcium and disease in two large prospective cohorts of the same race and reached similar conclusions, which increased the credibility of our findings. In addition, this study also adopted two dietary survey methods to assess dietary calcium intake, with one being relatively accurate (24 h recorded), and another reflecting long-term dietary habits (FFQ), and found no significant correlation between dietary calcium and the risk of chronic diseases. Besides, we measured serum $25OHD_3$ levels based on UPLC, enhancing our ability to entirely evaluate the associations among calcium, vitamin D, and chronic diseases. Nevertheless, there are also some limitations to our study. In the CHNS, CVD is diagnosed by self-reported information of the history of stroke and/or myocardial infarction, and there is no detection of related metabolic indicators. Although this is one of the limitations of the CHNS survey, this standard has also been used in previous articles about CVD research. Additionally, although we have adjusted for many potential confounders including demographic, lifestyle, and diet, our results were also limited by the possibility of unaccounted for confounders.

CONCLUSIONS

In conclusion, this study explored the relationship between calcium intake and the health of Chinese residents from different angles. Although according to our results, the current calcium intake of Chinese residents is negatively correlated with obesity and high blood pressure, the relationship between them is unstable and may be related to the intake of vegetables. Furthermore, we demonstrated that an additional increase in dietary calcium intake may not have significant benefits for bone health, type 2 diabetes, and CVD, on the premise that the calcium intake of Chinese people is generally lower than the recommended intake. Based on our findings to date, although the current calcium intake of Chinese residents is lower than the recommended intake, the calcium concentration in the human body may have reached a balanced state and can meet the needs of the body. It is, thus, not reasonable to emphasize additional calcium supplementation.

DATA AVAILABILITY STATEMENT

For HDNNCDS, the anonymized raw data supporting the conclusions of this article can be obtained upon reasonable request to the corresponding author. For CHNS, the dataset presented in this study can be found in online repositories. The name of the repository/repositories and accession number(s) can be found here: https://www.cpc.unc.edu/projects/china.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YL, CS, and XM contributed to the design and conduct of the research. XG and JG carried out data analysis and the initial draft of the paper. JW, ZZ, QS, and KH conducted the data collection and advised on statistical analysis. All authors reviewed and edited the draft, and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.683918/full#supplementary-material

REFERENCES

1. Uush T. Calcium intake and serum calcium status in Mongolian children. *J Steroid Biochem Mol Biol.* (2014) 144 Pt A:167–71. doi: 10.1016/j.jsbmb.2014.01.010
2. Vannucci L, Masi L, Gronchi G, Fossi C, Carossino A, Brandi M. Calcium intake, bone mineral density, and fragility fractures: evidence from an Italian outpatient population. *Arch Osteoporos.* (2017) 12:40. doi: 10.1007/s11657-017-0333-4
3. Closa-Monasterolo R, Zaragoza-Jordana M, Ferré N, Luque V, Grote V, Koletzko B, et al. Adequate calcium intake during long periods improves bone mineral density in healthy children. Data from the childhood obesity project. *Clin Nutr.* (2018) 37:890–6. doi: 10.1016/j.clnu.2017.03.011
4. Nappo A, Sparano S, Intemann T, Kourides Y, Lissner L, Molnar D. et al. Dietary calcium intake and adiposity in children and adolescents: Cross-sectional and longitudinal results from IDEFICS/IFamily cohort. *Nutr Metab Cardiovasc Dis: NMCD.* (2019) 29:440–9. doi: 10.1016/j.numecd.2019.01.015
5. Jayedi A, Zargar M. Dietary calcium intake and hypertension risk: a dose-response meta-analysis of prospective cohort studies. *Eur J Clin Nutr.* (2019) 73:969–78. doi: 10.1038/s41430-018-0275-y
6. Li S, Na L, Li Y, Gong L, Yuan F, Niu Y, et al. Long-term calcium supplementation may have adverse effects on serum cholesterol and carotid intima-media thickness in postmenopausal women: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr.* (2013) 98:1353–9. doi: 10.3945/ajcn.113.062844
7. Guo Q, Zhao L, He Y, Fang Y, Fang H, Xu X, et al. Survey on dietary nutrients intake of Chinese residents between 2010 and 2012. *Chin J Prevent Med.* (2017) 51:519–22. doi: 10.3760/cma.j.issn.0253-9624.2017.06.012
8. Yang Y, Yang X, Zhai F, Cheng Y. Dietary guidelines for Chinese. J Acad Nutr Diet. (2016) 116:A37-A doi: 10.1016/j.jand.2016.06.127
9. Fang A, Li K, Shi H, He J, Li H. Calcium requirements for Chinese adults by cross-sectional statistical analyses of calcium balance studies: an individual participant data and aggregate data meta-regression. *Chin Med J.* (2014) 127:4250–7.
10. Abelow BJ, Holford TR, Insogna KL. Cross-cultural association between dietary animal protein and hip fracture: a hypothesis. *Calcif Tissue Int.* (1992) 50:14–8. doi: 10.1007/BF00297291
11. Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C, et al. systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos Int.* (2012) 23:2239–56. doi: 10.1007/s00198-012-1964-3
12. Newberry SJ, Chung M, Shekelle PG, Booth MS, Liu JL, Maher AR, et al. Vitamin D and calcium: a systematic review of health outcomes (Update). *Evid Rep Technol Assess (Full Rep).* (2014) 217:1–929. doi: 10.23970/AHRQEPCERTA217
13. Na L, Wu X, Feng R, Li J, Han T, Lin L, et al. The Harbin cohort study on diet, nutrition and chronic non-communicable diseases: study design and baseline characteristics. *PLoS ONE.* (2015) 10:e0122598. doi: 10.1371/journal.pone.0122598
14. Zhang B, Zhai F, Du S, Popkin B. The China Health and Nutrition Survey, 1989-2011. *Obes Rev.* (2014) 15:2-7. doi: 10.1111/obr.12119

15. Wang M, Chen H, Du S, Guo X, Zhao J, Sun C, et al. Nutrition assessment of vitamin A and vitamin D in northeast Chinese population based-on SPE/UPLC/PDA. *BMC Nutr.* (2018) 4:12. doi: 10.1186/s40795-018-0219-x
16. Chen C, Lu FC. The guidelines for prevention and control of overweight and obesity in Chinese adults. *Biomed Environ Sci: BES*. (2004) 17:1–36
17. Standards of medical care in diabetes-−2014. *Diabetes Care*. (2014) 37:S14–80. doi: 10.2337/dc14-S014
18. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. (2014) 311:507–20. doi: 10.1001/jama.2013.284427
19. Reynolds K. Epidemiology of obesity and metabolic syndrome in China. *Curr Cardiovasc Risk Rep.* (2012) 6:109–11. doi: 10.1007/s12170-012-0226-4
20. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med.* (2010) 29:1037–57. doi: 10.1002/sim.3841
21. *National Health and Family Planning Commission, PRC*. Available online at: http://www.nhc.gov.cn/jkj/s5879/201506/4505528e65f3460fb88685081ff158a2.shtml (Accessed June 30,2015) (2015).
22. Bergman C, Gray-Scott D, Chen J, Meacham S. What is next for the Dietary Reference Intakes for bone metabolism related nutrients beyond calcium: phosphorus, magnesium, vitamin D, and fluoride? *Crit Rev Food Sci Nutr.* (2009) 49:136–44. doi: 10.1080/10408390701764468
23. Ross AC, Taylor CL, Yaktine AL, Valle HBD. Overview of calcium—dietary reference intakes for calcium and vitamin D—NCBI bookshelf. *Pediatrics.* (2012) 130:1427. doi: 10.1542/peds.2012-2590
24. Redmond J, Jarjou L, Zhou B, Prentice A, Schoenmakers I. Ethnic differences in calcium, phosphate and bone metabolism. *Proc Nutr Soc.* (2014) 73:340–51. doi: 10.1017/S0029665114000068
25. Geneva World Health Organization. *Vitamin and Mineral Requirements in Human Nutrition*. Switzerland:Geneva World Health Organization (2005). p. 176926.
26. Lee W, Jiang J. Calcium requirements for Asian children and adolescents. *Asia Pacific J Clin Nutr*. (2008) 17:33-6.
27. Chong H, Chee S, Goh E, Chow S, Yeap S. Dietary calcium and bone mineral density in premenopausal women with systemic lupus erythematosus. *Clin Rheumatol.* (2007) 26:182–5. doi: 10.1007/s10067-006-0258-6
28. Tai V, Leung W, Grey A, Reid I, Bolland M. Calcium intake and bone mineral density: systematic review and meta-analysis. *BMJ.* (2015) 351:h4183. doi: 10.1136/bmj.h4183
29. Zhao JG, Zeng XT, Wang J, Liu L. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA*. (2017) 318:2466–82. doi: 10.1001/jama.2017.19344
30. Heaney R. Normalizing calcium intake: projected population effects for body weight. *J Nutr*. (2003) 133:268S−70S. doi: 10.1093/jn/133.1.268S
31. Zemel M, Shi H, Greer B, Dirienzo D, Zemel P. Regulation of adiposity by dietary calcium. *FASEB J.* (2000) 14:1132–8. doi: 10.1096/fasebj.14.9.1132
32. Murakami K, Okubo H, Sasaki S. No relation between intakes of calcium and dairy products and body mass index in Japanese women aged 18 to 20 y. *Nutrition.* (2006) 22:490–5. doi: 10.1016/j.nut.2005.12.003
33. Zhang J, Wang HJ, Wang ZH, Zhang JG, Zhang B. Trend in dietary calcium intake among Chinese elderly aged 50 years and over in nine provinces, from 1991 to 2009. *Zhonghua Liu Xing Bing Xue Za Zhi.* (2012) 33:1119–22.
34. Nancy A, Judith H, Victor F, Cindy S. Contribution of food groups to energy and nutrient intakes in five developed countries. *Nutrients*. (2015) 7:4593–618. doi: 10.3390/nu7064593
35. Wang T, Heianza Y, Sun D, Zheng Y, Huang T, Ma W, et al. Improving fruit and vegetable intake attenuates the genetic association with long-term weight gain. *Am J Clin Nutr.* (2019) 110:759–68. doi: 10.1093/ajcn/nqz136
36. Heo M, Kim R, Wylie-Rosett J, Allison D, Heymsfield S, Faith M. Inverse association between fruit and vegetable intake and BMI even after controlling for demographic, socioeconomic and lifestyle factors. *Obes Facts.* (2011) 4:449–55. doi: 10.1159/000335279
37. John J, Ziebland S, Yudkin P, Roe L, Neil H. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet.* (2002) 359:1969–74. doi: 10.1016/S0140-6736(02)98858-6

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