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Dietary patterns in cancer prevention and survival

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Dietary patterns in cancer prevention and survival

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Editorial: Dietary patterns in cancer prevention and survival

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Editorial on the Research Topic
Dietary patterns in cancer prevention and survival

Cancer is a major societal, public health, and economic problem worldwide. It is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 (1). While advancements in medical research, including early diagnosis and better personalized treatments, have led to improved survival rates for all cancer types, its global burden is still rapidly growing (1). Although some individuals are at higher risk due to non-modifiable risk factors, between 30%—40% of all cancer cases are estimated to be preventable through healthy lifestyles, including healthy diets. However, little is known on the impact of these preventive measures on cancer survival. In 2018, a report from the World Cancer Research Fund and the American Institute for Cancer Research (2) promoted ten cancer prevention recommendations on diet and nutrition, which are also extendable to improving cancer survival. But characterizing a healthy diet is not easy, since foods and nutrients are not consumed alone and, therefore, they can interact with each other.

Over the past decade, dietary pattern analysis has emerged as an alternative and complementary approach to evaluating the relationship between diet and cancer prevention and survival (3, 4). Instead of looking at individual nutrients or foods, dietary pattern analysis examines the relationships with the overall diet. Conceptually, dietary patterns represent a broader picture of food and nutrient consumption, may provide stronger risk estimates with disease risk, and can be more easily translated into dietary guidelines.

In this Research Topic, we are providing 16 peer-reviewed manuscripts on the associations between dietary patterns (both a priori and a posteriori) and cancer risk and survival. Six of them were meta-analyses investigating the associations with Mediterranean diet (Zhu Q. et al.), nutritional status evaluated by the CONUT score (Liu et al.), and food groups overall (Qi et al.), and in particular, fruits and vegetables (Yao et al.), red and processed meats (Sun et al.), and ultra- processed foods (Lian et al.). According to these studies, high adherence to the Mediterranean diet is associated with a 29% reduction in gastric cancer risk, high (Zhu Q. et al.), a high intake of dietary fiber reduces overall cancer mortality (Yao et al.), and the intake of fruits, vegetables, alcohol, tea, and coffee is associated with a lower risk of both renal cell carcinoma and bladder cancer (Qi et al.). However, processed and red meat intake was linked to a higher renal cell carcinoma risk (Qi et al.), whereas the consumption of these foods was not related to pancreatic cancer risk

in the meta-analysis by Sun et al.. Besides, the consumption of ultra-processed foods was found to increase the risk of colorectal, colon, and breast cancer (Lian et al.). With regard to gastric cancer patient's nutritional status, the meta-analysis of Liu et al. showed that a poor nutritional status or low CONUT score leads to a worse stomach cancer prognosis. In addition, another study evaluating the impact of the nutritional status on the patient's outcome proposed two other tools [Patient-Generated Subjective Global Assessment (PG-SGA) and Nutrition Risk Screening 2002 (NRS-2002)] for malnutrition screening (Chen X. et al.).

Furthermore, three of the studies evaluated several dietary factors using Mendelian randomization analysis, an approach that uses genetic variants associated with a dietary factor exposure to estimate the causal relationship between these variables and cancer risk and prognosis. Results of these studies showed that higher genetic predispositions to intake of dried fruit and oily fish are linked to a reduced risk of breast cancer and its subtypes (Wang et al.), that of cheese, dried fruit, and beer appeared to be associated with lung cancer risk or its subtypes (Yan et al.), whereas there was no significant association between coffee or caffeine consumption and the risk or prognosis of endometrial cancer (Chen Z. et al.).

Five of the included studies investigated the association between a priori dietary patterns (e.g., oxidative stress exposure, dietary total antioxidant capacity, diabetes risk reduction diet, microbial diet, and dietary approaches to stop hypertension eating pattern–DASH) and the risk of several types of cancers in large prospective or retrospective studies. Specifically, two studies highlighted the cancer-preventive effects of antioxidant-related dietary patterns: a higher Oxidative Balance Score (OBS) integrating nutrient antioxidants was associated with a lower risk of colorectal cancer in women but not in men in a large prospective study involving over 1,000 cancer patients (Gu et al.), and an antioxidant-rich diet was significantly linked to a reduced risk of head and neck cancer in an Iranian case-control study (Toorang et al.). Dietary patterns related to the prevention of cardiovascular disease, the DASH diet, and diabetes, were inversely associated with lung cancer risk (Zhu Z. et al.), and with head and neck cancer (Wu et al.), respectively. Also, a higher adherence to a sulfur microbial diet, which is related to the enrichment of sulfur-metabolizing gut bacteria, was associated with an increased risk of colorectal adenoma in older adults (Xiao et al.). These three studies were prospective and evidenced differences in the associations by smoking status.

Finally, the last one studied the associations of maternal a posteriori dietary patterns and the risk of leukemia in children in a case control study from Mexico, where a vegetable-rich diet was found to reduce the risk of this disease in infants (Muñoz-Aguirre et al.).

We sincerely hope that this Research Topic of works from around the world will provide high quality epidemiological evidence and bring some light to the complex relationships between diet and cancer prevention and survival.

Author contributions

RZ-R: Writing – original draft. EM-M: Writing – original draft.

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Conflict of interest

The 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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Associations between diet and incidence risk of lung cancer: A Mendelian randomization study

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Background: Observational studies have revealed associations between diet and lung cancer. However, it is unclear whether the association is disturbed by confounding factors. We used a two-sample Mendelian randomization (MR) method to characterize the associations between diet and the lung cancer risk (including 3 subtypes: lung adenocarcinoma (LA), squamous cell lung carcinoma (SqCLC), and small cell lung cancer (SCLC)).

Materials and methods: Data on 20 diets were screened from the UK Biobank. Lung cancer data came from a large meta-analysis of 85,716 individuals. The inverse-variance weighted method was used as the main analysis. Sensitivity analysis was also used to explain the different multiplicity patterns of the final model.

Results: Our results showed significant evidence that 3 diets were associated with lung cancer [odds ratio (OR): 0.271, 95% confidence interval (CI): 0.150–0.488, $p=1.46\times10^{-4}$, dried fruit; OR: 3.010, 95% CI: 1.608–5.632, $p=5.70\times10^{-4}$, beer] and SqCLC (OR: 0.135, 95% CI: 0.062–0.293, $p=2.33\times10^{-5}$, dried fruit; OR: 0.485, 95% CI: 0.328–0.717, $p=2.9\times10^{-4}$, cheese). There were also suggestive correlations between 5 dietary intakes and lung cancer (OR: 0.441, 95% CI: 0.250–0.778, $p=0.008$, cereal; OR: 2.267, 95% CI: 1.126–4.564, $p=0.022$, beef), LA (OR: 0.494, 95% CI: 0.285–0.858, $p=0.012$, dried fruit; OR: 3.536, 95% CI: 1.546–8.085, $p=0.003$, beer) and SCLC (OR: 0.006, 95% CI: 0.000–0.222, $p=0.039$, non-oily fish; OR: 0.239, 95% CI: 0.086–0.664, $p=0.006$, dried fruit). No other association between diet and lung cancer was observed.

Conclusion: Our study preliminary found that cheese, dried fruit, and beer intake were significantly associated with the risk of lung cancer or its subtypes, while cereal, beef, and non-oily fish intake were suggestively associated with the risk of lung cancer or its subtypes. Well-designed prospective studies are still needed to confirm our findings in the future.

KEYWORDS

diet, dietary intake, lung cancer, Mendelian randomization, incidence risk

Introduction

Lung cancer is the second most common cancer and the leading cause of cancer death. According to the latest global cancer statistics, there were 2.2 million new lung cancer cases and 1.8 million deaths in 2020 (1). Most patients with lung cancer are found to be in the advanced stage of the disease, and the 5-year survival rate is less than 20% (2, 3). Therefore, it is essential

to determine the changeable protective or risk factors to prevent the occurrence and development of lung cancer.

As a factor that is easy to obtain and change, many researchers have begun to pay attention to the effect of diet on lung cancer. A sizeable multi-ethnic cohort study showed that a high-quality diet is associated with a lower risk of lung cancer, especially squamous cell lung cancer. However, high-quality dietary assessment is based on various dietary indexes, and it is unclear about the relationship between specific dietary intake and lung cancer (4). Similarly, dietary pattern analysis allows researchers to investigate the comprehensive influence of multiple dietary components on disease. Nevertheless, it also limits the ability to explore the role of individual diets (5, 6). Some meta-analyses based on prospective cohort studies investigated the association between specific diets and lung cancer (7–9). The results showed that increased intake of coffee, tea, red meat and processed meat was associated with an increased risk of lung cancer, while intake of fruits and vegetables protected against lung cancer. However, changes in smoking, environment, lifestyle and dietary intake after registration of the study may cause residual confounding. Therefore, these findings need to be further clarified.

In this case, Mendelian randomization (MR) is a feasible way to infer the correlations between specific dietary intake and disease. MR can use genetic variants as instrumental variables (IVs) for exposure (such as dietary intake) to make associational inferences (10), which largely avoids the interference of confounding factors common in observational studies. Because alleles are randomly assigned to offspring during conception, the association between genetic variation and disease outcomes is not easily affected by environmental and confounding factors (11, 12). Currently, many studies have used MR to explore the correlations between dietary intake and disease, including cardiovascular disease (13), mental illness (14) and cancer (15, 16). Additionally, previous MR studies have demonstrated a link between micronutrients concentration and lung cancer (17–19). Since many foods contain nutrients evaluated in previous studies, it is necessary to further assess the effects of specific dietary intake on lung cancer.

In this study, the authors used summary statistics from genome-wide association studies (GWAS) to conduct a two-sample MR analysis to comprehensively characterize the associations between different specific dietary components and lung cancer risk. This study provided further evidence for the value of diet as a modifiable factor in preventing lung cancer.

Materials and methods

Study design

Two-sample MR method was used to explore the correlations between dietary intake and lung cancer. Our MR study is based on three hypotheses: (1) genetic variants are closely related to the exposure of interest; (2) genetic variants are not related to confounding factors; (3) genetic variants cannot directly affect the outcome but only through the exposure of interest (12). Data used in this study are based on published summary statistics of GWAS, so ethical approval and informed consent are not required. Figure 1 illustrated the flow chart of our study design.

Selection of instrumental variables and data source

The genetic variants of dietary intake were obtained from the UK Biobank cohort of about 500,000 individuals (20). The original list included 26 dietary intakes: coffee, tea, milk, yogurt, cheese, cereal, bread, oily fish, non-oily fish, beef, lamb, pork, bacon, processed meat, cooked vegetable, raw vegetable, fresh fruit, dried fruit, salted nuts, unsalted nuts, salted peanuts, unsalted peanuts, red wine, beer, saturated fatty acids and polyunsaturated fatty acids. To select valid IVs, we included single nucleotide polymorphisms (SNPs) at the genome-wide significant level ($p < 5 \times 10^{-8}$) (21) and used strict cutoff values ($R^2 < 0.01$; region size = 5,000 kb) to remove SNPs that are in linkage disequilibrium (22). Because milk, yogurt, salted nuts, unsalted nuts, salted peanuts and unsalted peanuts have less than 5 SNPs that meet the strict threshold ($p < 5 \times 10^{-8}$). For these diets, we chose to use a relaxed threshold ($p < 1 \times 10^{-5}$; $R^2 < 0.01$; region size = 5,000 kb) to select SNPs. Second, SNPs with a minimum allele frequency (MAF) less than 0.05 were excluded because the association between these SNPs and dietary intake was estimated to be unstable. To satisfy the second critical hypothesis, the subphenotype of the selected SNP was evaluated using the PhenoScanner database ($p < 5 \times 10^{-8}$) (23) (Supplementary Table S3). We excluded SNP associated with smoking, body mass index and type 2 diabetes. In parallel, SNPs directly related to lung cancer were excluded to avoid violating the third critical hypothesis that IVs could not directly relate to the outcome. In addition, we ruled out SNPs associated with multiple diets to reduce potential pleiotropy across the SNPs (Supplementary Table S4). Finally, F statistics are used to evaluate SNPs with weak IVs bias (24). The formula of F statistics is $F = R^2 \times (N-2)/(1-R^2)$, where N represents the sample size and R^2 refers to the variance of exposure explained by IVs. Only the SNP with F statistics >10 is considered to be included in the MR analysis.

Dietary intakes as exposure factors were acquired by asking about the frequency of dietary intake in the questionnaire. Take dried fruit intake as an example; participants were asked, "how many pieces of dried fruit would you eat per day?" (Ten raisins, one prune and one dried apricot are considered as one piece). Answer with the average (integer) of participants' intake in the past year. All dietary ingredients included in this study and the corresponding number of European descent participants include milk ($N = 64,949$), yogurt ($N = 64,949$), salted peanuts ($N = 64,949$), unsalted peanuts ($N = 64,949$), salted nuts ($N = 64,949$), unsalted nuts ($N = 64,949$), coffee ($N = 428,860$), tea ($N = 447,485$), cheese ($N = 451,486$), cereal ($N = 441,640$), bread ($N = 452,236$), oily fish ($N = 460,443$), non-oily fish ($N = 460,880$), beef ($N = 461,053$), lamb ($N = 460,006$), pork ($N = 460,162$), bacon ($N = 64,949$), processed meat ($N = 461,981$), cooked vegetable ($N = 448,651$), raw vegetable ($N = 435,435$), fresh fruit ($N = 446,462$), dried fruit ($N = 421,764$), red wine ($N = 327,026$), beer ($N = 327,634$), saturated fatty acids ($N = 114,999$) and polyunsaturated fatty acids ($N = 114,999$).

Summary-level data on lung cancer were acquired from a large meta-analysis by McKay et al. as the outcome of the current MR analysis (25). This study collected data from the International Lung Cancer Consortium and the OncoArray-TRICL and provided information on genetic variants of three histological subtypes of lung cancer (26–28). Therefore, the related data of four types of lung cancer were included in the analysis, namely lung cancer ($N_{case} = 29,266$ and $N_{control} = 56,450$), lung adenocarcinoma (LA) ($N_{case} = 11,273$ and

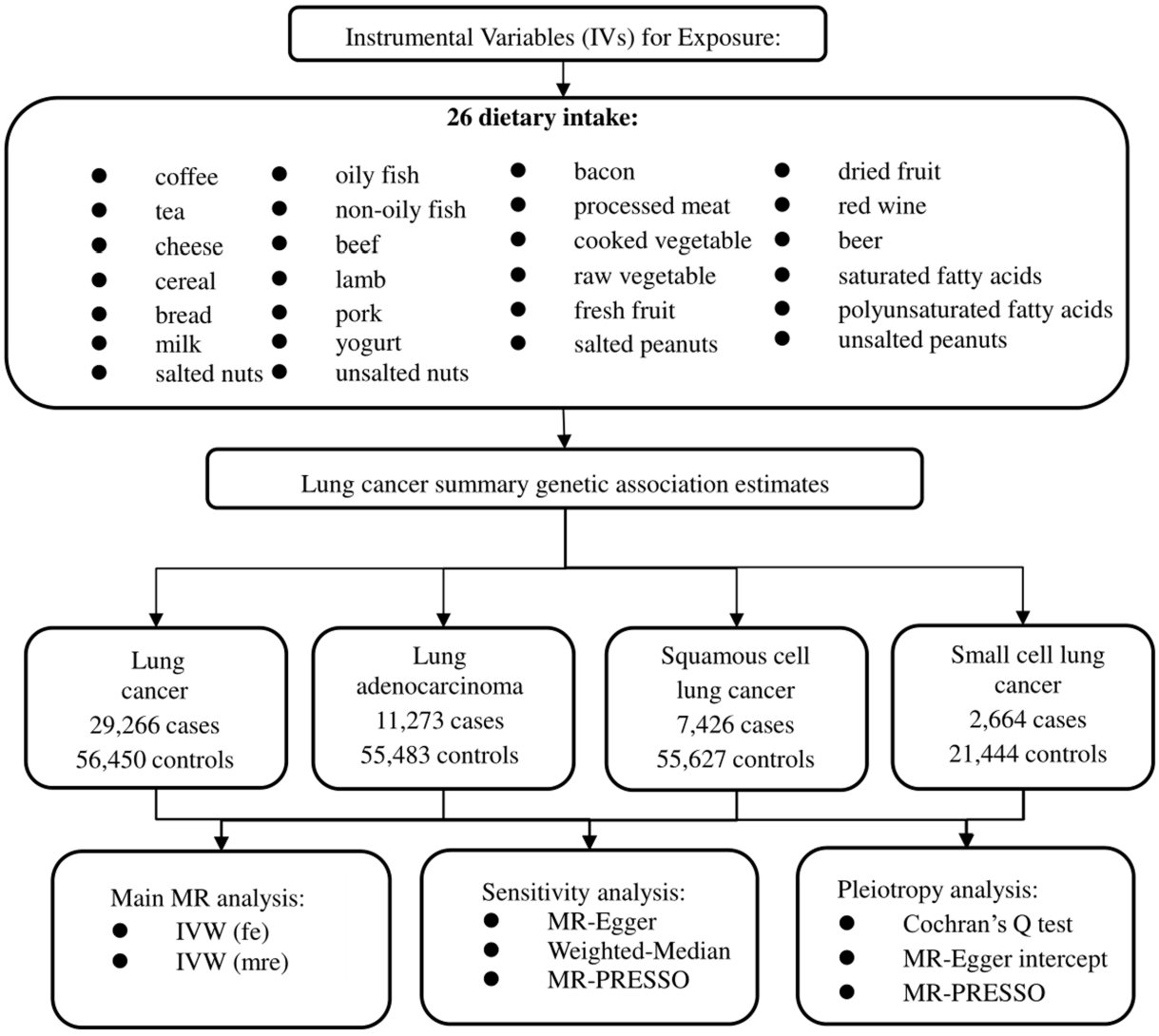

FIGURE 1
The flow chart of our study design.

$N_{control}$ = 55,483), squamous cell lung carcinoma (SqCLC) (N_{case} = 7,426 and $N_{control}$ = 55,627) and small cell lung cancer (SCLC) (N_{case} = 2,664 and $N_{control}$ = 21,444). The specific information of the summary-level data included in this study was shown in Supplementary Table S1.

Statistical analysis

MR used SNPs to represent the genetic prediction level of dietary intake and estimated the association between that level and lung cancer risk. The fixed-effects inverse-variance weighted (IVW) method was used as the primary method (29). IVW uses a meta-analysis method to combine Wald estimates for each SNP to obtain the overall estimate of the effect of diet on lung cancer. IVW can get unbiased associational estimation if no horizontal or horizontal pleiotropy is balanced. Sensitivity analysis was also carried out to explain the different multi-effect modes of the final model. Specifically, the weighted median approach allowed half of the weight to come from invalid genetic variants and provided a consistent point estimate (30). The MR-Egger method is based on the InSIDE hypothesis. Even if all genetic variants are invalid IV, it also gives a valid test of the null associational hypothesis and a consistent associational effect estimation. However, the estimation of MR-Egger may be inaccurate and may be strongly affected by external genetic variants (31). The MR-PRESSO method used the global test to evaluate horizontal pleiotropy and outliers and also provided the distortion test to compare the results before and after outliers are removed (32).

In each analysis of dietary intake and lung cancer, Cochran's Q statistics were used to quantify the heterogeneity between IVs (33). Suppose heterogeneity is detected ($P_{Cochran'sQ} < 0.05$), the multiplicative random-effects IVW model is implemented to avoid the bias towards weaker instrument exposure associations (34). The MR-Egger intercept test used the intercept term to evaluate pleiotropy (35). If there is a significant difference between the intercept term and zero, there may be horizontal pleiotropy between IVs. Moreover, forest plots, scatter plots, funnel plots, and leave-one-out analysis plots were drawn to visualize the results with high confidence. Specifically, forest plot intuitively provides the impact of each SNP on outcome;

leave-one-out analysis determines whether the results are robust visually; scatter plot shows the fitting results of different MR analyses; funnel plot visually judges the heterogeneity of IVs.

The 95% confidence interval (CI) of the odds ratio (OR) was used to estimate the associational effect of dietary intake on lung cancer. $p < 0.05$ was considered to have a suggestive correlation, whereas high-confidence associations were those that survived multiple tests with a threshold of 0.0019 (= 0.05/26) by Bonferroni correction. Use the network tool mRND provided by Stephen Burgess to calculate the statistical power of MR analysis (Supplementary Table S13) (36). The power estimate for each dietary intake is based on a type I error of 5% (37). All data analysis in this study was carried out using R software (version 4.1.3). The R packages used for MR analyses included *TwoSampleMR* (22) and *MR-PRESSO* (32) packages.

Results

Dietary intake and lung cancer

Supplementary Table S2 showed the specific characteristics of 622 IVs by 26 dietary intakes. The F statistics of all IVs are more than 10 (minimum = 20, maximum = 603), which avoids weak instrument bias.

According to Supplementary Table S5 and Figure 2, in the fixed-effects IVW method, we found that cereal intake (OR: 0.487, 95% CI: 0.332–0.714, $p = 2.30 \times 10^{-4}$), non-oily fish (OR: 0.149, 95% CI: 0.054–0.410, $p = 2.31 \times 10^{-4}$), dried fruit intake (OR: 0.266, 95% CI: 0.179–0.394, $p = 4.05 \times 10^{-11}$) and beer intake (OR: 3.010, 95% CI: 1.608–5.632, $p = 5.70 \times 10^{-4}$) were significantly associated with lung cancer risk. In addition, oily fish (OR: 0.657, 95% CI: 0.500–0.862, $p = 0.002$), beef (OR: 2.267, 95% CI: 1.126–4.564, $p = 0.022$), raw vegetable (OR: 0.352, 95% CI: 0.160–0.774, $p = 0.009$) were nominally associated with lung cancer. Except for beef and beer, we found evidence of heterogeneity in the other five dietary intakes ($P_{Cochran's\ Q} < 0.05$), indicating that the estimation of fixed-effects IVW may be biased (Supplementary Table S6). The random-effects IVW method showed that the suggestive association between oily fish, non-oily fish, raw vegetable intake and lung cancer disappeared. The significant association between cereal and lung cancer is weakened to a suggestive association. In the sensitivity analysis, only MR-Egger showed that the point estimation of the association between cereal and lung cancer was contrary to the main analysis (IVW method). Other sensitivity analyses were directionally consistent with the IVW method. No horizontal pleiotropy was detected in the MR-Egger intercept test (Supplementary Table S6). Additionally, except for beef and beer intake, the MR-PRESSO Global Test found outliers in the other five dietary intakes (Supplementary Table S6). After excluding outliers, the nominal association between oily fish, non-oily fish, raw vegetable intake and lung cancer disappeared. The significant correlation between dry fruit intake (OR: 0.343, 95% CI: 0.193–0.611, $p = 9.10 \times 10^{-4}$) and lung cancer remained. Finally, the visualization results of a significant connection between dried fruit and beer and lung cancer were drawn (Supplementary Figures S1, S2).

Dietary intake and lung adenocarcinoma

As shown in Supplementary Table S7 and Figure 3, genetically predicted beer intake (OR: 3.536, 95% CI: 1.546–8.085, $p = 0.003$) was nominally associated with increased risk of LA, while dried fruit intake (OR: 0.512, 95% CI: 0.303–0.866, $p = 0.013$) was suggestively associated with a low LA risk. Cochran's Q test only found no heterogeneity between the IVs of beer and dried fruit intake (Supplementary Table S8). When sensitivity analysis is carried out, the point estimation of dried fruit in the MR-Egger method is opposite to that of the IVW method. However, no horizontal pleiotropy was detected by the MR-Egger regression intercept (Supplementary Table S8). Further global tests found no outliers (Supplementary Table S8).

Dietary intake and squamous cell lung carcinoma

The fixed-effects IVW method showed that genetically predicted cheese intake (OR: 0.485, 95% CI: 0.328–0.717, $p = 2.9 \times 10^{-4}$), raw vegetable intake (OR: 0.103, 95% CI: 0.031–0.340, $p = 1.93 \times 10^{-4}$), dried fruit intake (OR: 0.120, 95% CI: 0.063–0.288, $p = 9.06 \times 10^{-11}$) and red wine intake (OR: 0.199, 95% CI: 0.079–0.502, $p = 6.21 \times 10^{-4}$) was significantly correlated with the risk of SqCLC, while oily fish intake (OR: 0.648, 95% CI: 0.423–0.994, $p = 0.047$), non-oily fish (OR: 0.106, 95% CI: 0.024–0.470, $p = 0.003$), pork intake (OR: 4.099, 95% CI: 1.003–16.744, $p = 0.049$) and beer intake (OR: 3.418, 95% CI: 1.210–9.660, $p = 0.020$) were nominally associated with the risk of SqCLC (Supplementary Table S9; Figure 4). However, heterogeneity and outliers were detected in all seven dietary intakes except cheese (Supplementary Table S10). When using the random-effects IVW method or the MR-PRESSO method to exclude outliers, only the relationship between dried fruit intake and SqCLC remained unchanged. In contrast, all the associations between oily fish, non-oily fish, pork, raw vegetable, red wine, beer and SqCLC disappeared (Supplementary Table S9; Figure 4). Additionally, the connection between raw vegetable intake and SqCLC was suggestive in random-effects IVW but not in the MR-PRESSO method (Supplementary Table S9; Figure 4). In most of the results, sensitivity analysis is directionally consistent with the IVW method. In addition, the MR-Egger regression of all results was close to zero, indicating no horizontal pleiotropy interference (Supplementary Table S10). Finally, the visualization results show that the significant association between cheese and dried fruit and SqCLC is robust and is not disturbed by heterogeneity (Supplementary Figures S3, S4).

Dietary intake and small cell lung cancer

There was no significant evidence of a link between genetically predicted dietary intake and SCLC. However, we found a nominal association between genetically predicted non-oily fish intake (OR: 0.035, 95% CI: 0.003–0.365, $p = 0.005$), pork intake (OR: 8.597, 95% CI: 1.045–70.748, $p = 0.045$) and dried fruits (OR: 0.239, 95% CI: 0.086–0.664, $p = 0.006$) and SCLC risk (Supplementary Table S11; Figure 5). Heterogeneity and outliers were found in non-oily fish and pork intake (Supplementary Table S12). No evidence of associations between non-oily fish and pork intake and SCLC were detected after implementing the random-effects IVW model. However, after using global test to exclude outliers, the association between pork and SCLC disappeared, and the nominal association between non-oily fish and

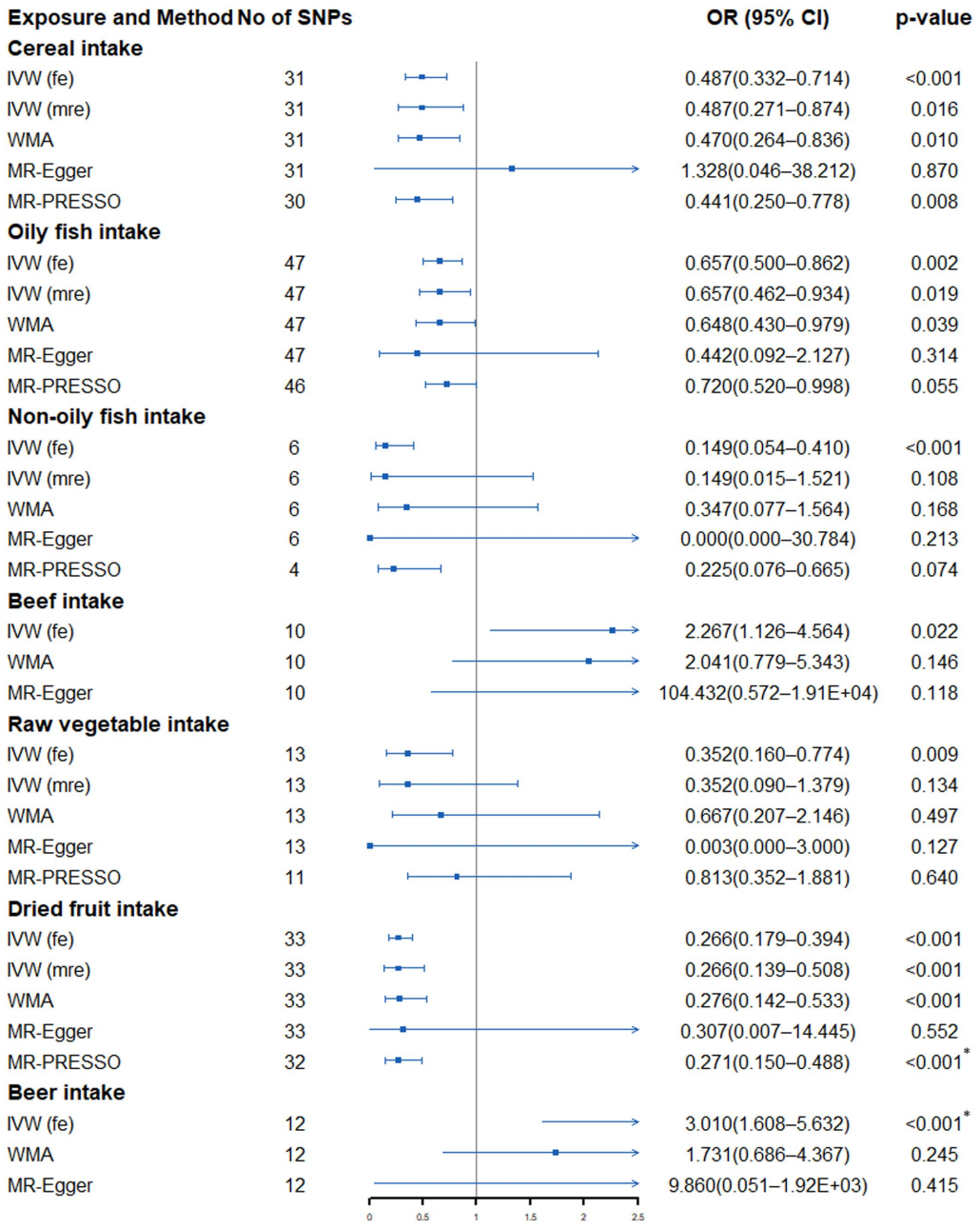

FIGURE 2
Forest plot showing results from Mendelian randomization study to assess associations between dietary intake and lung cancer. SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IVW (fe), fixed-effects inverse-variance weighted; IVW (mre), multiplicative random-effects inverse-variance weighted; WMA, weighted median approach; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.
*p value is still significant after multiple corrections.

SCLC still existed. All sensitivity analysis is consistent with the direction of the primary analysis. Moreover, the MR-Egger intercept test did not detect the existence of horizontal pleiotropy that might affect the results (Supplementary Table S12).

Discussion

In this two-sample MR study, we characterized the association between 26 dietary intakes and the risk of lung cancer or its subtypes. We observed highly confident associations between dried fruit, beer and cheese intake and lung cancer. Suggestive associations between beef, non-oily fish, and cereal intake and lung cancer were also detected.

Dried fruit is favored because it can fully retain the nutrients in the fruit and is easy to carry and preserve (38, 39). Dried fruit contains various macronutrients, micronutrients and health-promoting bioactive substances, which can prevent the development of many chronic diseases by regulating cellular responses and metabolism (40, 41). The consumption of dried fruits in western countries is low;

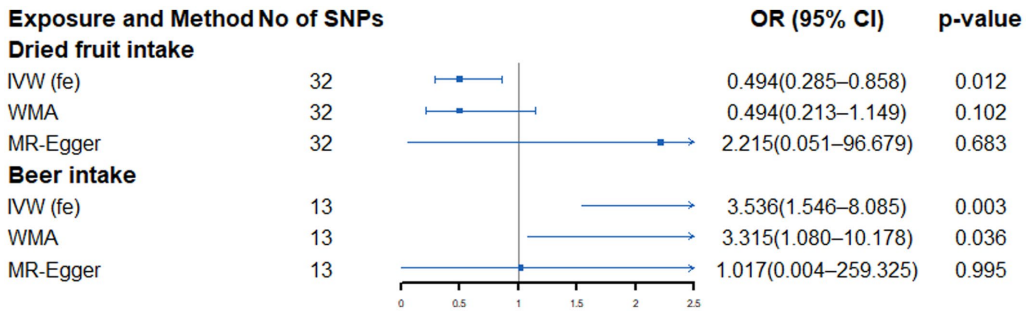

FIGURE 3
Forest plot showing results from Mendelian randomization study to assess associations between dietary intake and lung adenocarcinoma. SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IVW (fe), fixed-effects inverse-variance weighted; WMA, weighted median approach.

however, studies have shown that eating dried fruits can help reduce people's inadequate intake of nutrients and improve the quality of their diet (42). A meta-analysis has shown that dried fruit has preventive value for some cancers, particularly those of the digestive system (43). However, few observational studies have explored the effects of dried fruit on lung cancer. A cohort study involving 34,198 individuals indicated that consuming dried fruit 3 or more times per week was associated with a lower lung cancer risk (relative risk 0.89) (44). A recent MR study by Jin et al. explored the correlations between dried fruit and lung cancer using data from the International Lung Cancer Consortium ($N = 27{,}209$) (45). Their results showed that dried fruit significantly reduced the risk of lung cancer and SqCLC but not LA. Our analysis used larger lung cancer data ($N = 85{,}716$) and included the SCLC subtype. Similar to Jin et al. 's results (45), our study found a significant protective effect of dried fruit on lung cancer and SqCLC. Moreover, we also found evidence of a suggestive protective effect of dried fruit against LA and SCLC, which suggests that dried fruit intake may have a potential preventive value for both lung cancer and all its subtypes. In the future, the mechanism of dried fruit prevention of lung cancer should be further explored to provide a new means to prevent lung cancer.

The link between alcohol and lung cancer has long been suspected, and there has been some evidence from observational studies. A pooled analysis of seven prospective studies found that subjects who consumed more than 30 grams of alcohol per day had a slightly higher lung cancer risk than those who did not drink (46). Another prospective Chinese study also suggested a dose–response association between alcohol intake and lung cancer risk (hazard ratio 1.25, 95CI [1.10–1.42]) (47). However, other studies suggested that different types of alcoholic beverage consumption may have diverse effects on lung cancer (48, 49). Although ethanol is an essential component of alcoholic beverages, the existence and concentration of some carcinogens such as nitrosamines, polycyclic aromatic hydrocarbons and asbestos are different in the manufacturing process of alcoholic beverages (50–52). According to a meta-analysis, drinking large amounts of beer and liquor increases men's risk of lung cancer, while red wine intake may prevent lung cancer (53). Nevertheless, another pooled analysis of 22 cohort studies and case–control studies suggested that red wine and liquor were negatively correlated with lung cancer risk, and no association was found between beer and lung cancer (54). It is worth noting that avoiding residual confounding in observational studies is a challenging task, and conflicting findings may also be attributed to inherent heterogeneity between studies. In our study, the MR method can effectively avoid the impact of residual confounding. Our results supported a significant association between beer intake and increased risk of lung cancer.

Fermented dairy products are rich in nutrients and probiotics. Therefore, people pay much attention to its potential for cancer prevention (55) because some nutrients and probiotics may promote human health by regulating the immune system (56, 57). A meta-analysis of fermented dairy products and pan-cancer risk suggested that fermented dairy product intake is significantly associated with overall cancer risk reduction (58). Subgroup analysis showed that the effects of fermented dairy products were mainly reflected in esophageal cancer, colorectal cancer and bladder cancer but not significant in lung cancer. Another meta-analysis after adjusting for confounding factors also indicated no statistical correlation between cheese, yogurt and other fermented dairy products and lung cancer risk (59). Notably, these meta-analyses do not investigate the effects of fermented dairy products on lung cancer subtypes, which may lead people to ignore the possible association between fermented dairy product intake and some lung cancer subtypes. Although our study found no effect of cheese on lung cancer, we observed that cheese intake significantly reduced the risk of SqCLC. Moreover, although the mechanism is unknown, some observational studies have found that diet is associated with different lung cancer subtypes (60, 61). Therefore, it should not be ignored that diet may have different effects on lung cancer subtypes.

Red meat contains high hemoglobin and iron, and its catalytic oxidation can destroy various components of the human body and cause oxidative stress damage (62). N-nitroso compounds and heterocyclic aromatic amines may be produced in cooked red meat, which can cause cancer (63). Consistent with previous observational studies (9, 64), our study found nominal evidence of a link between beef intake and an increased lung cancer risk. Jayedi et al. conducted a meta-analysis of 33 prospective studies on fish consumption and the risk of chronic diseases (65). Their findings showed that increased fish intake was associated with a lower liver cancer risk but not in other cancers. However, the quality of this evidence was rated as low or very low. Our results suggested that non-oily fish intake has a nominally protective effect on SCLC. Additionally, we found a suggestive association between cereal intake and a decreased LC risk. Studies

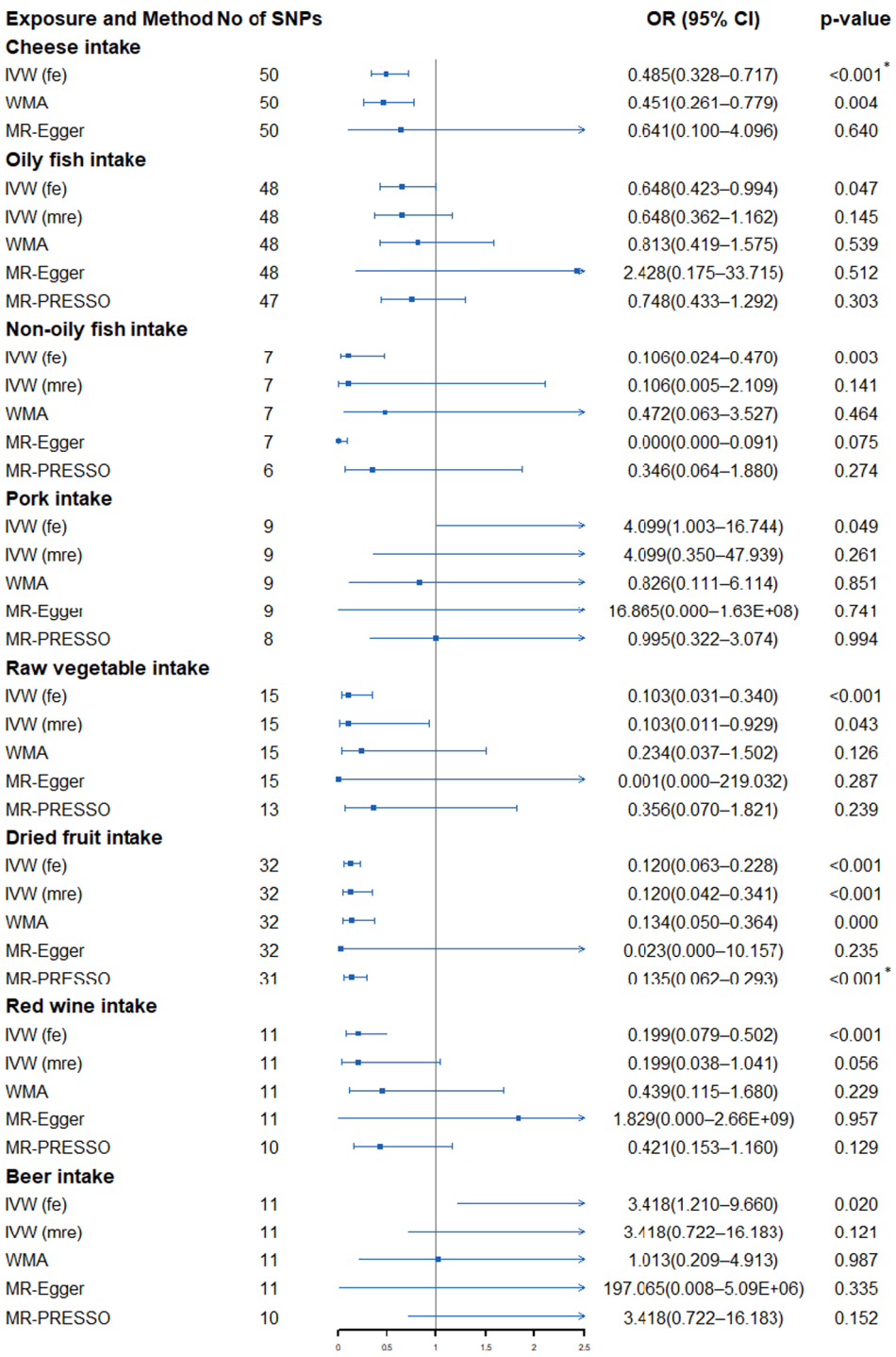

FIGURE 4
Forest plot showing results from Mendelian randomization study to assess associations between dietary intake and squamous cell lung carcinoma. SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IVW (fe), fixed-effects inverse-variance weighted; IVW (mre), multiplicative random-effects inverse-variance weighted; WMA, weighted median approach; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier. **p* value is still significant after multiple corrections.

have shown that cereal fiber can increase fecal bulk and reduce intestinal transport time, thus affecting the absorption of carcinogens (66). Some cereals, such as wheat, can increase the yield of butyrate, which has been shown to inhibit the growth of cancer cells and protect against various cancers (67). A recent prospective cohort study also supported the protective effect of breakfast cereal intake on lung cancer (68). Our results further support a relationship between cereal intake and lung cancer. Notably, this study only found the suggestive effects of beef, non-oily fish and cereal on lung cancer. Considering the modest effect size, our results should be interpreted cautiously.

One of the advantages of this study is to investigate the relationship between multiple dietary intakes and lung cancer through MR

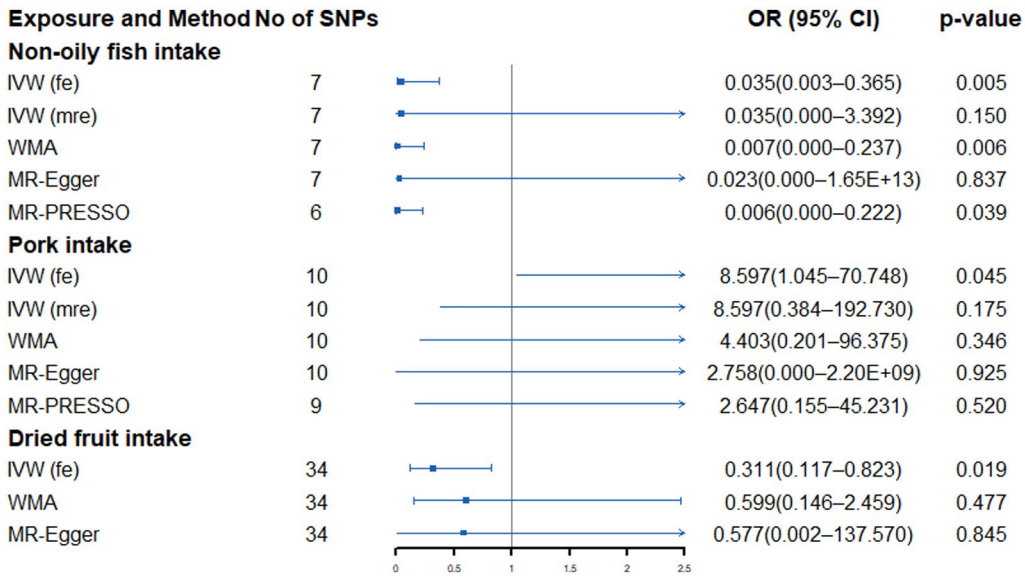

FIGURE 5
Forest plot showing results from Mendelian randomization study to assess associations between dietary intake and small cell lung cancer. SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IVW (fe), fixed-effects inverse-variance weighted; IVW (mre), multiplicative random-effects inverse-variance weighted; WMA, weighted median approach; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

analysis, which is the most comprehensive study to characterize the correlations between diet and lung cancer. Additionally, the MR design itself is not vulnerable to residual clutter. We eliminated the effects of potential pleiotropy on results by using multiple MR methods, PhenoScanner databases, and removing SNPs associated with multiple diets. Therefore, our results are less likely to be disturbed by horizontal pleiotropy. Another advantage of this study is that genetic variants in dietary intake and lung cancer come from summary-level data from GWAS with large sample sizes. The statistical power calculated by mRND also proved the robustness of our results (Supplementary Table S13).

This study also has some limitations. First, although we have taken control measures, IVs may still have unmeasurable confounding and affect the outcome. Second, many IVs rely on monotonicity conditions. Estimating the IVs effect under monotonicity usually involves an unrecognized subgroup in the study population, but using the results of subgroups to guide decision-making is not an ideal method. In this case, if more information is provided, the subgroup effects' correlation will significantly increase (69). Our IVs are genetic variants identified from the United Kingdom biobank. We only know the size of the subgroup of IV origins, but we do not know the specific characteristics of this subgroup. Meanwhile, the sensitivity of effect estimation to monotonicity bias is difficult to be quantified. Therefore, monotonicity may be violated in our analysis, which may cause our results to be unsuitable for an extension to a larger population. Third, due to the lack of summary-level data classified by age and sex, this study cannot conduct a stratified analysis of lung cancer based on these factors. Fourth, two-sample MR is usually assumed to be linearly correlated with exposure and outcome. However, a meta-analysis of observational studies showed a non-linear association between some diets and lung cancer (8). Unfortunately, we cannot detect this non-linear correlation based on the current summary-level data. Finally, although the MR method can provide associational estimates, the results reported here cannot automatically be assumed to be causal because there is considerable room for other explanations. Therefore, our results should be interpreted carefully, and well-designed prospective studies are still needed to confirm our findings in the future.

Conclusion

This work characterizes the correlations between genetically predicted dietary intake and lung cancer. Our study preliminarily showed that dried fruit intake could significantly reduce the risk of lung cancer and SqCLC; beer intake was significantly associated with an increased risk of lung cancer; cheese intake may significantly reduce the SqCLC risk. Moreover, a diet characterized by a low intake of beef and a high intake of cereal and non-oily fish was nominally correlated with the low risk of lung cancer or its subtypes. Our results should be interpreted carefully, and well-designed prospective studies are still needed to confirm our findings in the future.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.ebi.ac.uk/gwas/.

Author contributions

HY, XJ, CZhang, XD, and GF conceived the study. HY, XJ, and CZhang and obtained the genetic data. HY, XJ, and CZhang verified all the data in the study. HY, XJ, CZhang, and YH performed the

analyzes and interpreted the results. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1149317/full#supplementary-material

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Clinical significance of the controlling nutritional status (CONUT) score in gastric cancer patients: A meta-analysis of 9,764 participants

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Background: The clinical value of the controlling nutritional status (CONUT) score has been widely reported in multiple malignancies. The aim of this study is to investigate the association between the CONUT score and clinical outcomes in patients with gastric cancer.

Methods: A comprehensive literature search of electronic databases including PubMed, Embase, and Web of Science was performed up to December 2022. The primary endpoints were survival outcomes and postoperative complications. Subgroup analysis and sensitivity analysis were performed during the pooled analysis.

Results: Nineteen studies including 9,764 patients were included. The pooled results indicated that patients in the high CONUT group had a worse overall survival (HR = 1.70 95%CI: 1.54–1.87; $P < 0.0001$; $I^2 = 33\%$) and recurrence-free survival (HR = 1.57; 95%CI: 1.36–1.82; $P < 0.0001$; $I^2 = 30\%$), and a higher risk of complications (OR = 1.96; 95%CI: 1.50–2.57; $P < 0.0001$; $I^2 = 69\%$). In addition, a high CONUT score was significantly associated with larger tumor size, higher percentage of microvascular invasion, later TNM stage and fewer patients receiving adjuvant chemotherapy, but not with tumor differentiation.

Conclusion: Based on existing evidence, the CONUT score could act as a valuable biomarker to predict clinical outcomes in patients with gastric cancer. Clinicians could use this useful indicator to stratify patients and formulate individual treatment plans.

KEYWORDS

controlling nutritional status score, postoperative complications, survival outcomes, meta-analysis, gastric cancer

1. Background

Gastric cancer (GC) remains the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths in the world (1, 2). Despite advances in perioperative therapies and surgical techniques for GC patients, the clinical prognosis for GC has not significantly improved until now, mainly due to early recurrence and metastasis (3, 4). It is important to formulate treatment plans based on the expected survival time of patients to improve the cure rate for GC. Currently, the treatment of GC is mainly based on the AJCC TNM staging system. However, the staging system alone does not support treatment selection and prognosis assessment of GC well (5, 6). Therefore, it is essential to explore novel prognostic biomarkers to guide treatment of GC.

As indicated by growing evidence, host's nutrition status plays a critical role in the progression and survival of cancer patients (7). Based on these insights, several nutritional indicators have been successfully constructed to predict outcomes in cancer patients (8, 9). Among these, the controlling nutritional status (CONUT) score, which is calculated using peripheral albumin level, total cholesterol level and total lymphocyte count, has been developed as a nutritional screening tool (**Table 1**) (10). Recently, the clinical value of the CONUT score for predicting short-term and long-term outcomes has been widely reported in solid tumors and hematologic malignancies (11). The impact of the CONUT score on outcomes in GC patients was first reported in 2017 (12). After that, a growing number of studies have further explored the relationship between the CONUT score and clinical outcomes in GC patients (13–18). In 2019, Takagi et al. (19) preliminarily confirmed the prognostic value of CONUT score in GC by pooling five studies. Nevertheless, the authors acknowledge that the included studies are limited, and the role of the CONUT score in GC patients is actually unclear. Given that additional reports have been published in recent years, we therefore performed a meta-analysis based on available evidence to further investigate the association between the CONUT score and outcomes in patients with GC.

2. Methods

2.1. Search strategy

The current study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify studies that assess the association of the CONUT score with clinical outcomes in GC patients. Relevant studies from PubMed, Embase, and Web of Science were comprehensively examined up to 1 December 2022. The following combination of key words was used to search the potential related studies: ("CONUT") AND ("gastric cancer" OR "stomach cancer" OR "stomach tumor"). Language restriction was not applied during the search process. In addition, the references of the included studies were further scanned for extra reports. The search was independently performed by two investigators (HL and X-CY).

2.2. Study selection

The inclusion criteria were presented as follows: (1) studies examined the relationship between the CONUT score and clinical outcomes of GC patients; (2) the outcomes including survival outcomes and/or complications were available; (3) the cut-off value of the CONUT was clearly reported; and (4) studies were published in any language.

The exclusion criteria were as follows: (1) studies did not report data for GC patients separately; (2) studies were reported as case reports, reviews, conferences and letters; (3) duplicated data; and (4) studies was not peer reviewed.

2.3. Data extraction and quality assessment

Two reviewers (HL and X-CY) conducted the data extraction independently and cross-checked all the results. The extracted data included first author, publication year, study interval, country, study design and sample size, selection method, cut-off value, clinicopathological features like age, sex, tumor size, tumor differentiation, microvascular invasion, tumor stage and adjuvant chemotherapy, and clinical outcomes including postoperative complications, survival data, and follow-up time. When necessary, the authors would be contacted to provide relevant data.

The quality assessment of included studies was performed following the method described by Lin et al. (20) with the following nine items: (1) clear description of purpose/objectives, (2) clear ethical statements, (3) clear description of tumor stage and/or clinical setting, (4) clear description of inclusion criteria, (5) clear description of the cutoff value, (6) predefinition of outcome measurements, (7) whether or not use multivariate analysis and/or univariate analysis, (8) long enough follow-up period, and (9) limitations considered. Finally, a study could get a final score from 0 to –9 after assessment. Quality assessment was not used as exclusion criterion for these 19 included studies.

2.4. Outcomes assessment

In this study, the primary outcomes were postoperative complications and survival outcomes including overall survival

TABLE 1 The scoring criteria for the CONUT score.

Variables	Degree			
	Normal	Mild	Moderate	Severe
Albumin level (g/dl)	≥3.50	3.00–3.49	2.50–2.99	<2.50
Score	0	2	4	6
Cholesterol level (mg/dl)	≥1,600	1,200–1,599	800–1,199	<800
Score	0	1	2	3
Total lymphocyte count (/ml)	≥180	140–179	100–139	<100
Score	0	1	2	3
CONUT score	0–1	2–4	5–8	9–12

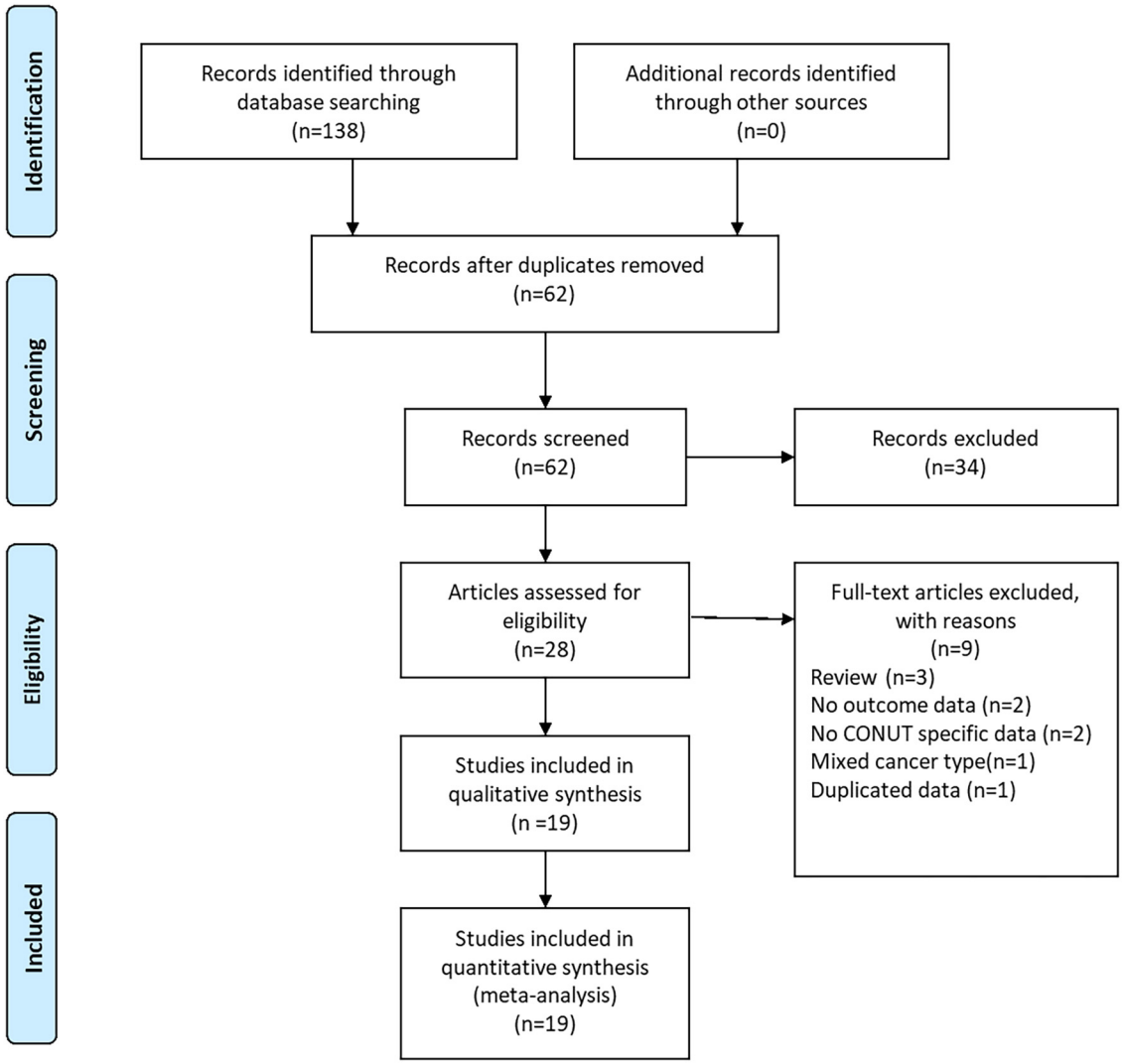

FIGURE 1
The PRISMA flowchart of study selection.

(OS), recurrence-free survival (RFS), progression-free survival (PFS), disease-free survival (DFS), and cancer-specific survival (CSS). The postoperative complications were defined as any morbidities occurred with 30 days after gastrectomy and graded by Clavien-Dindo (CD) (21, 22) system. Since RFS, PFS, DFS, and CSS share similar endpoints, they were analyzed together as one outcome, RFS, as previously suggested (23, 24). The secondary outcomes were other postoperative oncological parameters, including tumor size (<5 cm), tumor differentiation (poor differentiation), and TNM stage (Stage III/IV), microvascular invasion (Yes), and adjuvant chemotherapy (Yes).

2.5. Statistical analysis

The odds ratios (ORs) and hazard ratios (HRs) with their 95% confidence intervals (CIs) were used as the effect size for postoperative complications and survival outcomes, respectively. Statistical heterogeneity among enrolled studies was assessed using I^2 statistic. When I^2 is less than 50%, a fixed-effect model was used to calculate the pooled estimates; otherwise, a random-effects model was performed. Subgroup analysis and sensitivity analysis were utilized to evaluate the credibility of pooled results. Begg's funnel plot was applied to assess the possibility of publication bias. A two-tailed P-value <0.05 was considered statistically significant. All of these statistical analyses were performed by Review Manager Software, version 5.3 (Cochrane, London, UK) and Stata, version 12.0 (Statacorp, College Station, TX, USA).

3. Results

3.1. Study characteristics

As shown in Figure 1, a total of 138 records were yielded after searching the databases. Through careful title, abstract assessment and full text assessment, 19 studies (12–18, 25–36) with 21 cohorts were finally included in the present study. The basic information

TABLE 2 Basic information of included studies.

Author	Publication year	Country	Study design	Study interval	Sample size	Age, years	Sex (male/female)	TNM stage
Akagunduz	2021	Turkey	R; S	2017–2021	161	58.7 (range,32–80)	110/51	I–III
Aoyama	2022	Japan	R; S	2013–2017	331	NA	219/112	I–III
Chen	2022	China	R; S	2016–2020	146	59 (range,34–82)	102/44	I–IV
Hirahara	2019	Japan	R; S	2010–2016	210	NA	146/64	I–III
Huang	2019	China	P; S	2014–2016	357	73.29 ± 5.24	275/82	I–III
Jeon	2020	Korea	R; S	2009–2015	1,307	NA	862/445	I–III
Jin	2021	China	R; S	2004–2015	272	61 (range, 32–80)	201/71	0–III
Kudou	2019	Japan	R; S	2005–2016	144	65 (range,35–91)	104/40	I–III
Kuroda	2018	Japan	R; S	2005–2014	416	67.2 (range 25–94)	276/149	I–III
Lin	2019	China	R; S	2009–2014	2,182	60.8 (IQR, 54–68.3)	1,643/539	I–III
Liu	2018	China	R; S	2000–2012	697	57 (range, 21–86)	457/230	II–III
Mimatsu	2017	Japan	R; S	2006–2016	33	NA	28/6	IV
Qian	2021	China	R; S	2016–2019	309	63.4 ± 0.6	228/81	I–IV
Ryo	2019	Japan	R; M	2010–2014	626	67.9 ± 10.9	435/191	II–III
Sun	2021	China	R; S	2016–2018	1,479	60.4 ± 17.3	1,083/396	I–IV
Suzuki	2021	Japan	R; S	2000–2015	211	≥75	141/70	I–III
Xiao	2022	China	R; S	2014–2019	106	67 (range,43–85)	84/22	I–IV
Zheng	2018	China	R; S	2010–2011	532	61.1 ± 11.5	403/129	I–III
Zhu	2021	China	R; S	2005–2015	245	NA	179/66	I–IV

R, retrospective; S, single center; M, multiple center; NA, not available; IQR, inter-quartile range; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; DFS, disease-free survival.

and clinical characteristics of the included studies were summarized in Tables 2, 3, respectively. A total of 9,764 patients from China, Japan, Korea, and Turkey were included in this study. These studies were published from 2017 to 2022 with a sample size ranging from 33 to 2182. In terms of primary treatment, surgery was performed in 16 studies, neoadjuvant therapy was performed in two studies and mixed treatment including immunotherapy was performed in one study. The quality of the included studies was good with a median score of 9 (range: 6–9, Figure 2 and Supplementary Table 1).

3.2. Relationship between the CONUT and OS

Fifteen studies involving 6,922 patients described the association between the CONUT and OS. The fixed-effect model was applied due to the low heterogeneity (I^2 = 33%; P = 0.10). The pooled HR was 1.70 (95%CI: 1.54–1.87; $P < 0.0001$), which indicated that a high CONUT score was significantly associated with worse OS in patients with gastric cancer (Figure 3). Furthermore, subgroup analyses based on country, sample size, primary treatment, cut-off method, cut-off value and analysis method were performed. As shown in Table 4 and Supplementary Figure 1, the pooled results from all subgroup analyses revealed that patients in the high CONUT group had a substantially reduced OS when compared to these in the low CONUT group. In addition, sensitivity analysis by omitting one study at a time demonstrated that the combined outcome was not significantly changed (Supplementary Figure 3A).

3.3. Relationship between the CONUT and RFS

A total of ten studies consisting of 3,620 patients reported on RFS. The heterogeneity test showed a low heterogeneity among studies (I^2 = 30%; P = 0.17), and the fixed-effect model was performed. The pooled HR was 1.57 (95%CI: 1.36–1.82; $P < 0.0001$), which suggested that patients in the high CONUT group had a significantly poorer RFS when compared with patients in the low CONUT group (Figure 4). Similarly, Stratification by country, sample size, primary treatment, cut-off method, cut-off value, and analysis method showed that the incorporated results were consistent in each subgroup (Table 4 and Supplementary Figure 2). Sensitivity analysis demonstrated that the pooled result remained unchanged (Supplementary Figure 3B).

3.4. Relationship between the CONUT and postoperative complications

Twelve studies, comprising 6,893 patients, investigated postoperative complications in patients with gastric cancer. Following the result of heterogeneity test (I^2 = 69%; P = 0.0002), the random-effect model was applied. The pooled OR was 1.96 (95%CI: 1.50–2.57; $P < 0.0001$), which suggested that a high CONUT score was a risk factor of postoperative complications for gastric cancer patients (Figure 5). Stratification by CD grade showed that the pooled results were almost unchanged in each

TABLE 3 Survival information of included studies.

Author	Publication year	Sample size	Low group	High group	Primary treatment	Selection method	Cut-off value	Multivariate analysis	Survival outcomes	Median follow-up time, months
Akagunduz	2021	161	56	105	Neoadjuvant chemotherapy	ROC	≥4	Yes	OS	11.2 (range:2.3–32.3)
Aoyama	2022	331	221	110	Curative surgery	NA	≥2	Yes/Yes	OS; RFS	NA
Chen	2022	146	75	71	PD-1/PD-L1 inhibitors or chemotherapy	NA	>0	Yes/Yes	OS; PFS	NA
Hirahara	2019	210	105	105	Curative surgery	ROC	≥3	Yes	OS	35.3 (range:4.0–97.0)
Huang	2019	357	153	204	Curative surgery	NA	≥2	NA	NA	NA
Jeon	2020	1,307	Normal: 893	Light:396; Moderate:18; Severe:1	Curative surgery	NA	NA	Yes	OS	59.0 (range: 1–109)
Jin	2021	272	182	85	Neoadjuvant chemotherapy	ROC	≥4	Yes/Yes	OS; PFS	NA
Kudou	2019	144	118	26	Curative surgery	ROC	≥3	No/No	OS; RFS	NA
Kuroda	2018	416	354	62	Curative surgery	ROC	≥4	Yes/No	OS; RFS	61.2 (range: 1–134)
Lin	2019	2,182	1704	478	Curative surgery	X-tile	>2	No	OS	52 (range: 1–118)
Liu	2018	697	480	217	Curative surgery	ROC	≥3	Yes	CSS	36 (range: 3–162)
Mimatsu	2017	33	16	17	Non-curative surgery	NA	>4	No	OS	NA
Qian	2021	309	214	95	Curative surgery	ROC	2.5	NA	NA	NA
Ryo	2019	626	337	289	Curative surgery	ROC	≥2	Yes/No	OS; DFS	49.2
Sun	2021	1,479	627	852	Curative surgery	ROC	≥2	NA	NA	NA
Suzuki	2021	211	175	36	Curative surgery	NA	>4	Yes/Yes	OS; CSS	47 (range: 5–185)
Xiao	2022	106	43	63	Curative surgery	NA	>4	No	OS	30 (range:7–64)
Zheng	2018	532	Normal:291	Light: 183; Moderate or severe: 58	Curative surgery	NA	NA	Yes/Yes	OS; RFS	60 (range: 2- 76)
Zhu	2021	245	104	141	Curative surgery	ROC	≥4	Yes/Yes	OS; DFS	NA

ROC, receiver operating characteristic curve; NA, not available; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; DFS, disease-free survival; CSS, cancer specific survival.

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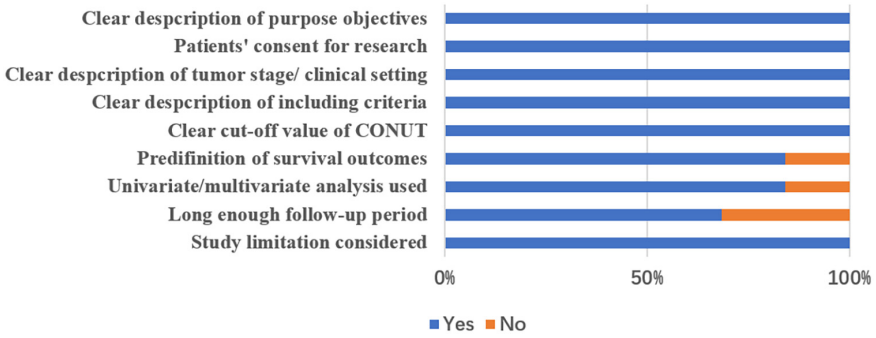

FIGURE 2
Quality assessment of included studies.

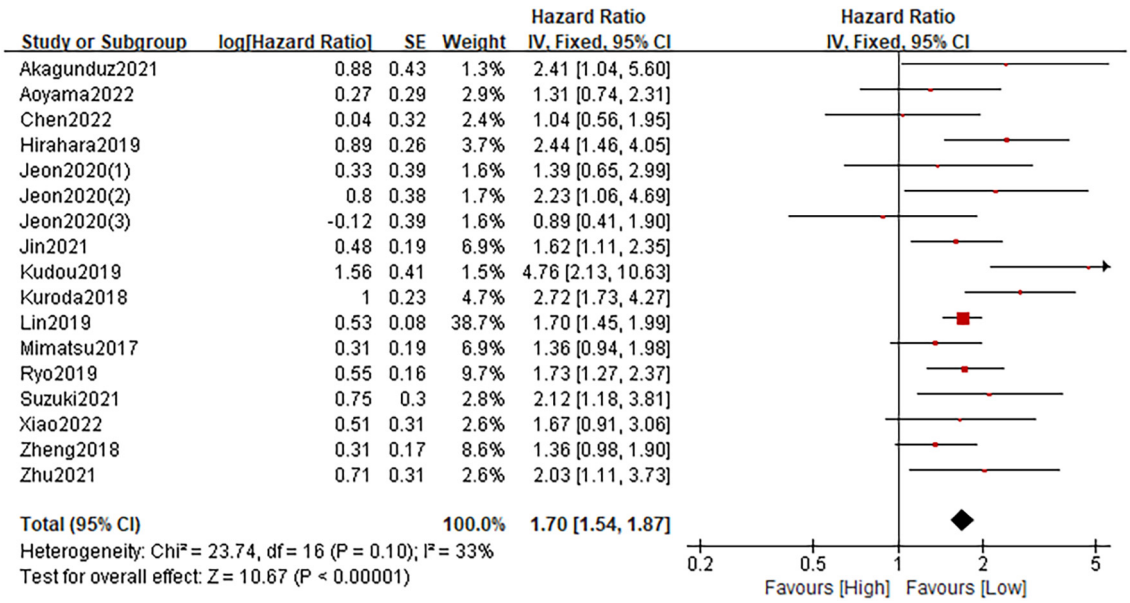

FIGURE 3
Forest plot assessing the relationship between the CONUT and OS.

subgroups. Sensitivity analysis confirmed the credibility of the combined result (Supplementary Figure 3C).

3.5. Relationship between the CONUT and other postoperative oncological parameters

As shown in Table 5 and Supplementary Figure 4, the pooled results revealed that a higher CONUT score was associated with larger tumor size (OR = 0.60; 95%CI:0.49–0.75; $P < 0.0001$; $I^2 = 0\%$), higher percentage of microvascular invasion (OR = 0.67; 95%CI:0.50–0.89; $P = 0.006$; $I^2 = 0\%$), later TNM stage (OR = 0.63; 95%CI:0.55–0.72; $P < 0.0001$; $I^2 = 35\%$) and fewer patients receiving adjuvant chemotherapy (OR = 1.44; 95%CI:0.98–2.12; $P = 0.06$; $I^2 = 68\%$). Nevertheless, no significant association was found in tumor differentiation (OR = 1.03; 95%CI:0.88–1.20; $P = 0.72$; $I^2 = 33\%$).

3.6. Publication bias

The Begg's funnel plots of the primary outcomes were displayed in Supplementary Figure 5. Begg's test revealed that there was no significant publication bias in the present study about CONUT score and OS ($P = 0.680$), RFS ($P = 0.602$), and postoperative complications ($P = 0.304$).

4. Discussion

Malnutrition is common in cancer patients, which is further exacerbated in gastric cancer patients due to additional factors such as malabsorption and obstructive syndrome (37). Numerous pieces of evidence have illustrated that malnutrition can lead to increased length of hospital stays and deteriorate the prognosis of cancer patients (38, 39). Therefore, early screening and proper treatment of malnourished patients is extremely important in clinical practice.

TABLE 4 Subgroup analyses for OS and RFS of CONUT-high patients vs. CONUT-low patients.

		Cohorts, *n*	Patients, *n*	HR (95%CI)	*P*-value	I^2 (%)
Overall survival						
	Total	17	6,922	1.70 (1.54–1.87)	<0.0001	33
Country	China	6	3,483	1.62 (1.43–1.83)	<0.0001	0
	Japan	7	1,971	1.90 (1.60–2.26)	<0.0001	56
	Others	4	1,468	1.58 (1.07–2.33)	0.02	26
Sample size	>200	12	6,332	1.72 (1.54–1.91)	<0.0001	16
	≤200	5	590	1.61 (1.25–2.08)	<0.0001	62
Primary treatment	Surgery	14	6,343	1.72 (1.55–1.91)	<0.0001	37
	Others	3	579	1.54 (1.14–2.07)	0.005	25
Cut-off method	ROC	7	2,074	2.06 (1.72–2.46)	<0.0001	33
	Others	10	4,848	1.57 (1.39–1.76)	<0.0001	0
Cut-off value	≥4	7	1,444	1.82 (1.51–2.19)	<0.0001	10
	<4	10	5,478	1.66 (1.48–1.86)	<0.0001	45
Analysis method	Univariate	4	2,465	1.70 (1.48–1.95)	<0.0001	61
	Multivariate	13	4,457	1.70 (1.49–1.95)	<0.0001	25
Recurrence free survival						
	Total	10	3,620	1.57 (1.36–1.82)	<0.0001	30
Country	China	5	1,892	1.50 (1.25–1.81)	<0.0001	0
	Japan	5	1,728	1.70 (1.34–2.16)	<0.0001	53
Sample size	>200	8	3,330	1.56 (1.34–1.82)	<0.0001	13
	≤200	2	290	1.69 (1.02–2.79)	0.04	79
Primary treatment	Surgery	8	3,202	1.60 (1.36–1.89)	<0.0001	40
	Others	2	418	1.47 (1.07–2.02)	0.02	0
Cut-off method	ROC	6	2,400	1.64 (1.36–1.97)	<0.0001	39
	Others	4	1,220	1.47 (1.16–1.87)	0.002	29
Cut-off value	≥4	4	1,144	1.99 (1.47–2.70)	<0.0001	24
	<4	6	2,476	1.47 (1.24–1.73)	<0.0001	15
Analysis method	Univariate	3	1,186	1.60 (1.22–2.12)	0.0008	67
	Multivariate	7	2,434	1.56 (1.31–1.86)	<0.0001	10

Currently, although several tumor-related nutrition assessment tools like NRS2002 and PG-SGA have been developed (40, 41), the utilization of these tools is controversial due to their complexity and subjectivity. Ideally, the screening tool should be simple, convenient, sensitive and objective.

In this context, the CONUT score was constructed by González-Madroño et al. (42) in 2012 as a potential tool to make clinical undernutrition screening using three peripheral blood parameters (albumin level, total cholesterol level, and total lymphocyte count). Since then, the CONUT has been gradually used to assess the prognosis of various cancers due to its easy availability and convenient calculation (43–45). Niu et al. in a meta-analysis of 12 studies have reported that high CONUT score is associated with worse survival OS and CSS in urological cancers (46). Another meta-analysis by Takagi et al. also confirmed that the CONUT score is a practical prognostic factor associated with the prognosis of colorectal cancer (45). Additionally, the clinical value of the CONUT score has been successfully validated in other malignancies, such as lung cancer (47) and hepatocellular carcinoma (48). However, since each cancer type varies a lot, it is important to explore the applicability of the CONUT score in gastric cancer.

We conducted a comprehensive literature search and identified 19 studies with 9,764 GC patients. Relative to previous studies (19), this update has several strengths. First, by including all patients in our study, the generalizability of the CONUT score as a predictive marker in GC patients is enhanced compared to previous studies that only included patients undergoing radical resection. Second, by including an adequate number of samples, the heterogeneity of the pooled survival outcomes is significantly reduced. Third, due to the full inclusion of all studies, we are able to perform adequate subgroup analyses to fully explore the ability of the CONUT score as a nutritional screening metric to predict clinical outcomes in different kinds of GC patients. Through our pooled analyses, we found that patients in the high CONUT score group had 1.70, 1.57, and 1.96 times increased risk of the poor OS and RFS, as well as higher incidence of postoperative complications, compared to those with low CONUT score. Besides, we noted that high COUNT score was significantly associated with larger tumor size, higher percentage of microvascular invasion, later

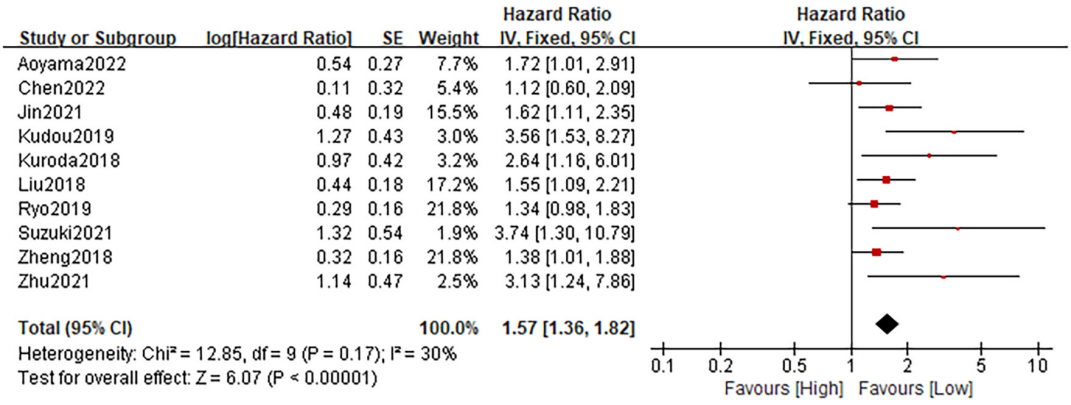

FIGURE 4
Forest plot accessing the relationship between the CONUT and RFS.

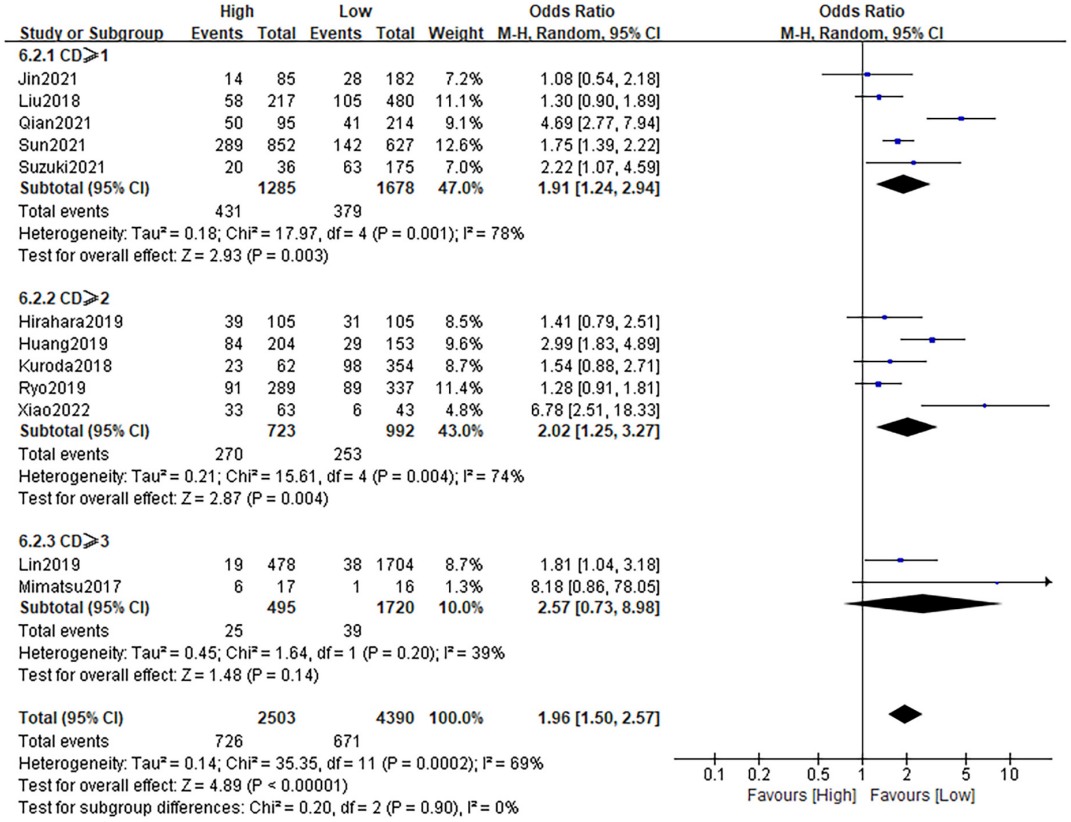

FIGURE 5
Forest plot assessing the relationship between the CONUT and postoperative complications.

TABLE 5 Secondary outcomes in terms of CONUT-high patients vs. CONUT-low patients.

Variables	Cohorts, *n*	Patients, *n*	OR (95%CI)	*P*-value	I^2 (%)
Tumor size (<5 cm)	3	1,469	0.60 (0.49–0.75)	<0.0001	0
Tumor differentiation (Poor)	11	3,544	1.03 (0.88–1.20)	0.72	33
Microvascular invasion (Yes)	3	1,645	0.67 (0.50–0.89)	0.006	0
TNM stage (Stage III/IV)	12	4,122	0.63 (0.55–0.72)	<0.0001	35
Adjuvant chemotherapy (Yes)	6	1,913	1.44 (0.98–2.12)	0.06	68

TNM stage and fewer patients receiving adjuvant chemotherapy. On examination of all subgroup analyses, it can be seen that all of the pooled outcomes supported the efficacy of the CONUT score in the primary outcomes prediction. Meanwhile, the pooled outcomes remained their significance on sensitivity analyses, and no evidence of publication bias was observed through Begg's tests. The results were robust and therefore increase the credibility of our conclusions.

The good discriminatory value of the CONUT score could be explained as follows: Firstly, each of the components of the CONUT score has been demonstrated to be associated with outcomes in cancer patients. Albumin as a recognized indicator has been widely used to reflect a patient's nutritional status. Hypoalbuminemia has been demonstrated to be significantly associated with poor wound healing, increased risk of infections and reduced survival of cancer patients (49, 50). In addition, serum albumin plays an important role in inhibiting the production of pro-inflammatory cytokines and enhancing cell-mediated immunity (51). And low levels of albumin thereby reduce response to adjuvant therapy. Secondly, cholesterol, as an important component of the cell membrane, plays an essential role in maintaining the cellular function. Low levels of cholesterol have been suggested to prompt tumor progression and deteriorate patient prognosis in various cancers (52, 53). The underlying mechanism may be a consequence of the requirement of cholesterol consumption for tumor growth (54). In addition, a recent study based on animal models showed that high serum cholesterol levels can enhance the antitumor effect of natural killer cells in mice (55). Finally, lymphocyte count, an important indicator of immune and nutritional status in cellular immunity, has been confirmed to inhibit tumor progression by inducing its lysis and apoptosis (56). Numerous studies have demonstrated that lymphopenia is strongly associated with early recurrence and poor survival in cancer patients (57). Secondly, our pooled results further revealed that higher COUNT score was significantly related to larger tumor size, higher percentage of microvascular invasion, later TNM stage and fewer patients receiving adjuvant chemotherapy, even though it remains unclear whether the results of the CONUT score were a cause or a consequence of these advanced tumor characteristics.

The present meta-analysis had several limitations. First, all of these studies were retrospective in nature, which may increase the risk of selection bias, and more prospective studies are thereby required to further investigate this issue. Second, most included studies were from Asian countries, which may affect the applicability of the CONUT score in Western populations. Third, the cut-off value of the CONUT score varies greatly among studies, which might affect the clinical utility of these findings.

5. Conclusion

Our results suggested that the CONUT score could be a valuable prognostic biomarker for patients with gastric cancer. Patients in the high CONUT score group have poor OS, RFS, and a higher rate of complications. Clinicians could use this useful indicator to stratify patients and formulate individual treatment plans. However, further research is still required to validate the value of this index in gastric malignancy.

Author contributions

HL wrote the manuscript. HL and X-CY performed the data search and data analysis. HL, X-CY, and D-CL prepared the figures and tables. WW and R-HC approved the final manuscript. All authors reviewed the manuscript.

Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1156006/full#supplementary-material

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Association between dietary approaches to stop hypertension eating pattern and lung cancer risk in 98,459 participants: results from a large prospective study

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Background: Dietary approaches to stop hypertension (DASH) eating pattern is linked to anti-inflammatory responses and antioxidation, which overlap with the pathogenesis of lung cancer. However, there is insufficient epidemiological evidence to link this dietary pattern to lung cancer risk conclusively.

Aim: To determine if adherence to the DASH diet is linked to a lower risk of developing lung cancer in a large prospective study.

Methodology: The data of participants were retrieved from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. A DASH score was calculated based on 8 dietary components to reflect adherence to DASH, with greater scores representing higher adherence. Three Cox proportional hazards models were constructed to analyze the association between DASH scores and lung cancer risk, including an unadjusted model and two adjusted models (model 1 for demographics and model 2 for fully confounding factors). A restricted cubic spline plot was utilized to illustrate the likelihood of developing lung cancer across the entire range of DASH scores. The association between each of the 8 DASH components and the risk of lung cancer was assessed separately. Several subgroup analyses were conducted to identify potential modifiers, and several sensitivity analyses were performed to verify the robustness of the findings.

Results: The study involved 98,459 individuals in total. The mean (standard deviation) DASH score was 24.00 (4.62) points, along with the mean follow-up period of 8.84 (1.94) years. Lung cancer was identified in 1642 cases over 869807.9 person-years of follow-up, and the overall incidence rate was 0.189 cases/100 person-years. Participants in the highest quartile in the fully adjusted model had a relatively decreased risk of developing lung cancer in comparison to those in the lowest quartile ($HR_{quartile\ 4\ versus\ 1}$: 0.647; 95% CI: 0.557, 0.752; $P_{trend}<0.001$). The restricted cubic spline plot demonstrated that DASH score and lung cancer risk were inversely associated and had a linear dose–response relationship ($P_{non\text{-}linear}=0.944$). According to subgroup analyses, those who were current or former smokers had a stronger inverse connection than those who never smoked ($P_{interaction}=0.013$). The results remained robust after several sensitivity analyses.

Conclusion: The risk of lung cancer was inversely associated with DASH scores in the US population. This suggests that following the DASH pattern can help prevent

lung cancer, especially for current or former smokers. More epidemiological evidence from other regions and populations is needed to confirm our findings.

KEYWORDS

DASH diet, lung cancer, PLCO trial, prevention, Cox regression analysis

Introduction

Lung cancer is the second most widely occurring cancer, with about 2.24 million new cases recorded globally in 2020. It has contributed to 18% of all cancer fatalities (1). For a long time, smoking has been considered a key risk factor for lung cancer, however, an increasing number of people who have never smoked are being diagnosed with lung cancer (2). Therefore, the increasing rate of lung cancer cannot be attributed to smoking alone. In addition to smoking status, duration and intensity, other factors may also play a role in the pathogenesis of lung cancer, such as heredity (3), alcohol consumption (4), air pollution (5) and diet (6). Specially, numerous studies have identified various dietary components as a potential modifiable risk factor for lung cancer. For example, a prospective cohort study from the United Kingdom showed that adding fruits, vegetables, and dietary fiber to the diet was related to lower lung cancer risk, but high consumption of processed and red meat elevated the risk of developing the disease (7). Another observational study also showed that high consumption of sodium was associated with an increased risk of developing lung cancer (8).

Nowadays, research on dietary patterns rather than single foods or nutrients is being sought after for its improved science (9). Dietary approaches to stop hypertension (DASH) eating pattern was established from a hypertension control program in the USA (10). It encourages people to consume more fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains and to consume less sodium, beverages with high sugar content, processed and red meat. Obviously, certain dietary components in the DASH dietary pattern, such as fruits, vegetables, sodium, processed and red meat are closely associated with the occurrence of lung cancer. In addition, although the DASH pattern was originally designed for the prevention and control of hypertension, studies have revealed that it is also linked to anti-inflammatory responses and anti-oxidative damage, which overlap with the pathogenesis of lung cancer (11, 12).

Based on the above, a hypothesis was made that there might be a correlation between DASH dietary pattern and the likelihood of developing lung cancer. In order to provide epidemiological evidence for the possible association, we performed this prospective designed analysis in a large US population.

Methodology

Study design and population

All data used in our study was obtained from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a randomized, controlled study funded by the National Cancer Institute (NCI) aimed at assessing whether specific screening tests could reduce mortality resulting from PLCO cancers. Study design of the PLCO trial has been provided in the initial literature (13). The trial enrolled 154,887 participants between November 1993 and July 2001, aged 55–74 years from ten different centers, after obtaining written informed consent from each participant and meeting the eligibility inclusion criteria (Figure 1). Participants were each randomly assigned to the control or the intervention group in equal proportions. Regular care was provided to participants assigned to the control group, whereas those assigned to the intervention group received predefined screening exams for PLCO cancers. In PLCO trial, each participant was asked to complete several questionnaires, including the baseline questionnaire (BQ) and diet history questionnaire (DHQ), based on his or her real-life condition. BQ was utilized to gather data such as demographic features that participants could actively report as baseline information. The DHQ was a food frequency questionnaire that asked about the quantity and frequency of diet intake during the previous year (14, 15). The raw responses collected from participants were processed into analysis-ready variables. Simply put, the frequency of receiving a particular item was multiplied by the number of servings taken each day to estimate the daily consumption with the aid of the DietCalc software (16). DHQ is a frequently used nutritional assessment scale, and its validity has been confirmed elsewhere (17). The information on cancer diagnoses until 2009 and the patients' mortality until 2018 were also collected. In our present study, as we aimed to investigate the association between DASH and lung cancer risk, the follow-up time was defined as the interval between the date of completion of the DHQ and the occurrence of lung cancer, death, loss during follow-up, or the end of the follow-up period (i.e., December 31, 2009), whichever event occurred first (Figure 2).

According to our study design, participants who met the following criteria were further excluded (Figure 1): (i) participants who failed to complete the BQ (n = 4,918); (ii) participants who failed to complete the DHQ (n = 33,241); (iii) participants who completed the invalid DHQ, such as missing ≥8 frequency responses (n = 5,221); (iv) participants who had any cancer diagnosis in their history before DHQ entry (n = 9,684); (v) participants who had lung cancer between DHQ entry and DHQ completion (n = 68); (vi) individuals who had potentially unlikely extreme energy intake (n = 3,296). Extreme energy intake in our study was classified as <800 kcal/day or > 4,200 kcal/day for men and < 600 kcal/day or > 3,500 kcal/day for women (18). Specially, our present study was conducted based on the data obtained with permission from the NCI (approval number: PLCO-1137).

Assessment of DASH score

A DASH score was employed to describe the adherence of participants to the DASH pattern. The calculation of DASH score was proposed by Dr. Fung et al. in 2008 (19). For each participant, the intake of each DASH component was collected from the DHQ

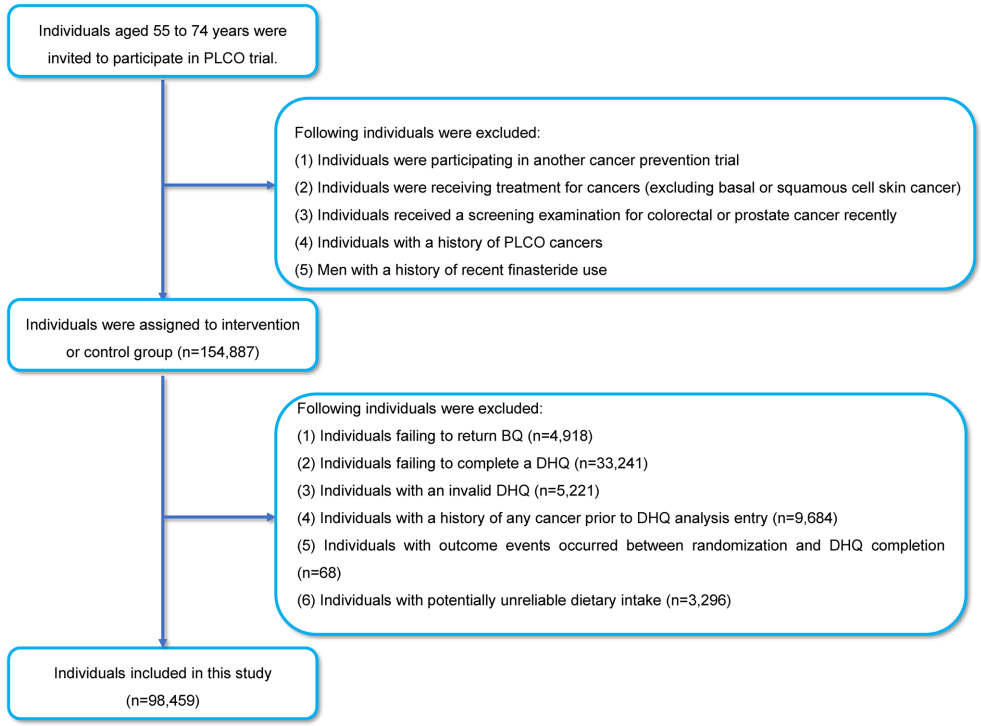

FIGURE 1
The flow chart of identifying participants included in our study.

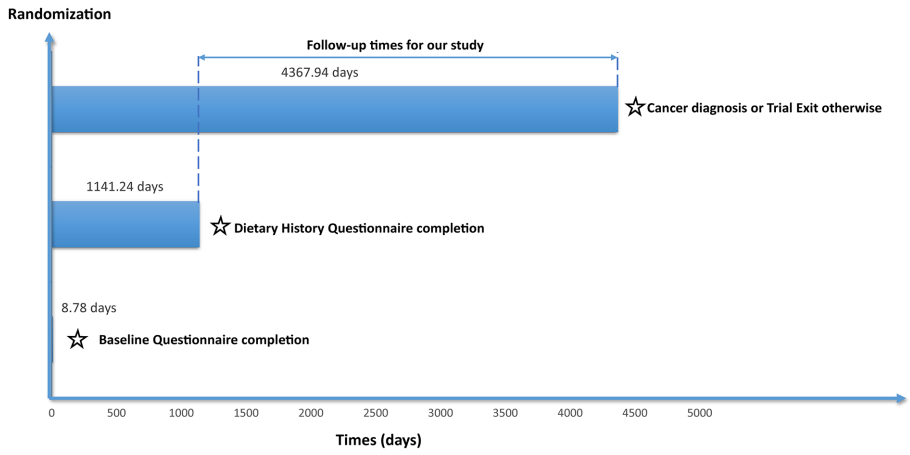

FIGURE 2
The timeline and follow-up scheme of our study.

mentioned above. Based on the consumption data of each component, participants were divided into quintiles. In the case of vegetables, fruits, low-fat dairy products, nuts and legumes, and whole grains, participants in the lowest quintile scored 1 point, whereas those in the highest quintile scored 5 points. However, in the case of sodium, beverages with high sugar content, red and processed meat, participants in the lowest quintile scored 5 points, and those in the highest quintile scored 1 point. Criteria for determining scores are shown in Supplementary Table 1. The final DASH score was recorded by summing the scores of each component with a range of 8–40. As a result, the participants were more adherent to the DASH diet, as indicated by a higher score.

Determination of lung cancer

Each participant in the study received an annual report *via* mail that included a form that asked them to indicate if they were diagnosed with cancer, the date of that diagnosis, and the location of the malignancy. Participants were contacted again by phone or email if

they did not respond to the form. Death certificates and family reports were also viewed as sources of information. In addition, for participants who were diagnosed with lung cancer, their medical records were reviewed for confirmation of the lung cancer diagnosis and more details about this cancer.

Assessment of covariates

The BQ was used in this research to gather data on gender, randomization group, smoking status, numbers of cigarettes smoked per day during smoking, number of packs smoked per day multiplied by years smoked (pack-years), race, hypertension history, and family history of lung cancer. Body mass index (BMI) was measured as weight (kg)/height square (m^2). The DHQ was used to determine age, daily calorie intake from diet (kcal), and alcohol consumption profile.

Statistical analysis

Missing data for categorical (family history of lung cancer, race, smoking status, cigarettes smoked per day, history of hypertension) and continuous variables (BMI, pack-years) with missing values <5% were imputed by the modal value and median, respectively, (20). The data characteristics before and after imputation are demonstrated in Supplementary Table 2. Subsequent analysis was carried out based on the complete data set after imputation.

To describe the link between DASH scores and lung cancer risk, the Cox proportional risk model was used, with follow-up time as the time metric. In order to illustrate this relationship, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. In this model, all individuals were classified into quartiles as per their DASH scores, and the person-years of each quartile were determined independently. The reference group served as the first quartile with the lowest score. HRs and 95% CIs for the other quartiles were calculated and compared with the first quartile. Model 1 was adjusted for age, gender, and race, whereas model 2 was additionally adjusted for drinking status, smoking status, cigarettes smoked per day, pack-years, BMI, randomization group, hypertension history, family history of lung cancer, and dietary energy intake in multivariate analysis. The adjusted covariates in the above two models were selected based on existing literature rather than our subjective tendency to make conclusions statistically significant (6). Small cell carcinoma and non-small cell carcinoma risk were investigated separately to further investigate the relationship between the risk of subtypes of lung cancer and DASH scores. The median score for individual quartiles was allocated to all participants in the group and used as a continuous variable to understand the overall trend in lung cancer risk between groups. The p_{value} for the trend test was calculated to roughly describe the convergent relationship between DASH scores and risk for developing lung cancer. A restricted cubic spline plot with three knots at the 10th, 50th, and 90th percentiles was utilized to demonstrate the likelihood of developing lung cancer over the full range of DASH scores. $P_{non\text{-}linear}$ was calculated to elucidate whether lung cancer risk and DASH scores have a non-linear dose–response relationship. In addition, by treating the intake of individual components as continuous variables, the link between the consumption of each component and the likelihood of lung cancer was investigated separately to help us identify the potential contributors to the association between DASH pattern and the risk of developing lung cancer.

After classification for age (≤65 vs. >65 years), gender (male vs. female), race (white vs. colored), randomization group (intervention group vs. control group), BMI (≤25 vs. >25 kg/m^2), smoking status (never-smokers vs. current/former smokers), drinking status (no vs. yes), family history of lung cancer (no vs. yes/possible), history of hypertension (no vs. yes) and energy intake from diet (≤ median vs. > median), a series of prespecified subgroup analyses were carried out. p_{value} for likelihood ratio tests were computed to find out the significance of the interaction. Several sensitivity analyses were conducted to verify the robustness of the findings: (i) excluded participants with missing information to avoid the effect of data imputation on the final outcomes; (ii) eliminated individuals having a family history of lung cancer, as they might be more susceptible to developing lung cancer; (iii) excluded individuals who had a history of hypertension, since they might follow DASH-like dietary patterns to manage their condition; (iv) eliminated cases identified within the first two and four years of follow-up for ruling out any reverse causality.

R software 4.2.1 was utilized for statistical analyses. A two-tailed p_{value} of 0.05 was utilized to assess if the outcomes were statistically significant.

Results

Baseline characteristics

The mean value (standard deviation) of the DASH score for the 98,459 individuals in the current study was 24.00 (4.62) points. All individuals were classified into quartiles according to DASH scores as follows: quartile 1, DASH score 8–21, n = 29,523; quartile 2, DASH score 22–24, n = 23,433; quartile 3, DASH score 25–27, n = 22,564; quartile 4, DASH score 28–40, n = 22,939. The baseline features of the individuals are displayed in Table 1 by quartile. Subjects in the top quartile were more likely to be female, never-smokers, never-drinkers and had less tobacco exposure, a lower BMI and a history of hypertension in contrast with those in the lowest quartile. Individuals in the highest quartile of the DASH score consumed more fruits, nuts and legumes, vegetables, whole grains, low-fat dairy products and less sodium, sugared beverages, red and processed meats than those in the lowest quartile.

Association between DASH scores and lung cancer risk

In this study, the mean (standard deviation) of the follow-up period was 8.84 (1.94 years) years. In total, 1,642 cases of lung cancer, comprising 234 small cell carcinoma and 1,408 non-small cell carcinoma cases, were recorded during 869807.9 person-years. The overall incidence was 0.189 cases per 100 person-years. In the unadjusted model, individuals in the highest quartile had a

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TABLE 1 Baseline characteristics of study population according to quartiles of DASH scores. Values are means (standard deviation) for continuous variables and percentages for categorical variables.

		Quartiles of DASH scores			
Characteristics	Overall	Quartile 1 (8–21)	Quartile 2 (22–24)	Quartile 3 (25–27)	Quartile 4 (28–40)
Number of participants	98,459	29,523	23,433	22,564	22,939
DASH score	24.00 ± 4.62	18.56 ± 2.28	23.03 ± 0.81	25.95 ± 0.82	30.08 ± 1.96
Age	65.52 ± 5.73	64.51 ± 5.57	65.51 ± 5.71	65.98 ± 5.69	66.38 ± 5.79
Gender					
Male	47,218 (47.96%)	18,320 (62.05%)	11,607 (49.53%)	9,574 (42.43%)	7,717 (33.64%)
Female	51,241 (52.04%)	11,203 (37.95%)	11,826 (50.47%)	12,990 (57.57%)	15,222 (66.36%)
Race					
White	91,221 (92.65%)	27,219 (92.20%)	21,774 (92.92%)	21,069 (93.37%)	21,159 (92.24%)
Non-white	7,238 (7.35%)	2,304 (7.80%)	1,659 (7.08%)	1,495 (6.63%)	1780 (7.76%)
Body mass index (kg/m^2)	27.20 ± 4.79	27.95 ± 4.81	27.45 ± 4.78	27.05 ± 4.73	26.14 ± 4.61
Family history of lung cancer					
No	85,845 (87.19%)	25,429 (86.13%)	20,523 (87.58%)	19,733 (87.45%)	20,160 (87.89%)
Yes/ Possible	12,614 (12.81%)	4,094 (13.87%)	2,910 (12.42%)	2,831 (12.55%)	2,779 (12.11%)
Smoker					
Never	47,233 (47.97%)	11,561 (39.16%)	10,937 (46.67%)	11,708 (51.89%)	13,027 (56.79%)
Current/ Former	51,226 (52.03%)	17,962 (60.84%)	12,496 (53.33%)	10,856 (48.11%)	9,912 (43.21%)
Pack-years[a]	17.49 ± 26.40	23.99 ± 30.46	17.89 ± 26.33	14.57 ± 23.66	11.60 ± 20.99
Cigarettes smoked per day					
0	47,233 (47.97%)	11,561 (39.16%)	10,937 (46.67%)	11,708 (51.89%)	13,027 (56.79%)
1–20	32,197 (32.70%)	10,098 (34.20%)	7,919 (33.80%)	7,211 (31.96%)	6,969 (30.38%)
>20	19,029 (19.33%)	7,864 (26.64%)	4,577 (19.53%)	3,645 (16.15%)	2,943 (12.83%)
Randomization group					
Intervention group	50,151 (50.94%)	15,024 (50.89%)	11,828 (50.48%)	11,575 (51.30%)	11,724 (51.11%)
Control group	48,308 (49.06%)	14,499 (49.11%)	11,605 (49.52%)	10,989 (48.70%)	11,215 (48.89%)
Drinker					
No	26,681 (27.10%)	7,457 (25.26%)	6,114 (26.09%)	6,130 (27.17%)	6,980 (30.43%)
Yes	71,778 (72.90%)	22,066 (74.74%)	17,319 (73.91%)	16,434 (72.83%)	15,959 (69.57%)
History of hypertension					
No	66,641 (67.68%)	19,587 (66.34%)	15,651 (66.79%)	15,250 (67.59%)	16,153 (70.42%)
Yes	31,818 (32.32%)	9,936 (33.66%)	7,782 (33.21%)	7,314 (32.41%)	6,786 (29.58%)
Energy intake from diet (kcal/day)	1728.71 ± 658.04	1792.50 ± 685.67	1709.94 ± 679.96	1704.04 ± 658.02	1690.05 ± 589.63
DASH components intake					
Fruits (g/day)	275.24 ± 213.29	172.80 ± 161.71	254.35 ± 194.61	310.29 ± 207.58	393.94 ± 226.47
Nuts and legumes (g/day)	20.57 ± 26.06	12.08 ± 15.84	17.42 ± 20.40	21.89 ± 24.46	33.40 ± 36.18
Vegetables (g/day)	284.83 ± 181.87	210.68 ± 138.99	261.72 ± 159.58	304.33 ± 176.62	384.70 ± 206.03
Grains (g/day)	61.53 ± 59.68	33.96 ± 38.55	54.11 ± 50.11	70.08 ± 59.14	97.17 ± 71.17
Low-fat dairy (g/day)	137.18 ± 222.00	47.98 ± 131.73	108.89 ± 198.87	170.04 ± 235.35	248.57 ± 264.19
Sodium from diet (mg/day)	2728.47 ± 1126.48	2788.05 ± 1135.77	2708.86 ± 1166.99	2712.09 ± 1148.16	2687.92 ± 1044.88
Sugared beverages (g/day)	398.08 ± 463.51	535.76 ± 578.37	401.38 ± 442.44	344.63 ± 389.73	270.07 ± 314.11
Red/processed meats (g/day)	12.26 ± 14.62	19.59 ± 18.49	12.86 ± 13.24	9.48 ± 11.18	4.96 ± 6.72

[a]The product of the daily cigarette pack consumption and the number of years of smoking.

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TABLE 2 Association of DASH scores with the risk of lung cancer and its subtypes.

Quartiles of DASH score	No. of participants	No. of cases	person-years	Hazard ratio (95% confidence interval)		
				Unadjusted	Model 1[a]	Model 2[b]
Overall						
Quartile 1 (8–21)	29,523	669	256327.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2 (22–24)	23,433	387	206820.1	0.715 (0.631,0.811)	0.687 (0.606,0.779)	0.826 (0.728,0.937)
Quartile 3 (25–27)	22,564	331	199987.0	0.632 (0.554,0.721)	0.599 (0.524,0.685)	0.805 (0.704,0.921)
Quartile 4 (28–40)	22,939	255	206673.4	0.470 (0.407,0.543)	0.445 (0.384,0.516)	0.647 (0.557,0.752)
P for trend				<0.001	<0.001	<0.001
Small cell carcinoma						
Quartile 1 (8–21)	29,078	104	254480.7	1.00 (reference)	1.000 (reference)	1.00 (reference)
Quartile 2 (22–24)	23,138	63	205412.8	0.749 (0.548,1.024)	0.711 (0.518,0.974)	0.876 (0.638,1.202)
Quartile 3 (25–27)	22,230	46	198154.7	0.566 (0.400,0.801)	0.526 (0.370,0.749)	0.736 (0.516,1.049)
Quartile 4 (28–40)	22,605	21	204617.8	0.250 (0.156,0.399)	0.231 (0.143,0.372)	0.363 (0.224,0.588)
P for trend				<0.001	<0.001	<0.001
Non-small cell carcinoma						
Quartile 1 (8–21)	29,449	567	256066.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2 (22–24)	23,380	323	206596.1	0.704 (0.614,0.807)	0.678 (0.591,0.778)	0.811 (0.707,0.932)
Quartile 3 (25–27)	22,517	284	199745.2	0.640 (0.555,0.738)	0.609 (0.527,0.704)	0.811 (0.701,0.938)
Quartile 4 (28–40)	22,879	234	206254.2	0.510 (0.438,0.594)	0.484 (0.414,0.567)	0.693 (0.591,0.812)
P for trend				<0.001	<0.001	<0.001

[a]Adjusted for age (years), gender (male, female) and race (white, non-white).

[b]Adjusted for model 1 plus drinking status (no, yes), smoking status (never, current/former), cigarettes smoked per day (0, 1–20, >20), pack-years (continuous), body mass index (continuous), randomization group (intervention group/control group), history of hypertension (no, yes), family history of lung cancer (no, yes/possible) and energy intake from diet (continuous).

considerably decreased risk of lung cancer than the ones in the lowest quartile, as shown in Table 2 ($HR_{quartile\ 4\ versus\ 1}$: 0.470; 95% CI: 0.407, 0.543; $P_{trend} < 0.001$), the inverse relationship was still noted in the fully adjusted model ($HR_{quartile\ 4\ versus\ 1}$: 0.647; 95% CI: 0.557, 0.752; $P_{trend} < 0.001$). Moreover, when the observed lung cancer cases were analyzed separately for small cell and non-small cell carcinoma, the inverse relationship persisted after adjustment for possible confounders (For small cell carcinoma, $HR_{quartile\ 4\ versus\ 1}$: 0.363; 95% CI: 0.224, 0.588; $P_{trend} < 0.001$; For non-small cell carcinoma, $HR_{quartile\ 4\ versus\ 1}$: 0.693; 95% CI: 0.591, 0.812; $P_{trend} < 0.001$).

Additional analyses

In order to represent the risk of lung cancer across the complete range of DASH scores, a restricted cubic spline plot was used. As can be seen in Figure 3, the DASH score and the risk of lung cancer were inversely correlated and had a linear dose–response relationship ($P_{non\text{-}linear} = 0.944$). According to subgroup analyses, factors like age, gender, race, randomization group, BMI, drinking habits, family history of lung cancer, hypertension history, and dietary energy intake had no effect on the relationship between the DASH score and risk of developing lung cancer ($P_{interaction} > 0.05$). However, the inverse relationship was significantly stronger for participants who were current or former smokers than for never-smokers ($P_{interaction} = 0.013$) (Table 3). The inverse relationship between DASH score and lung cancer risk did not change significantly in sensitivity analysis after the individuals with missing data, those with a history of hypertension and a family history of lung cancer, and lung cancer cases assessed within the first two or four years of follow-up were eliminated, showing that the findings of this research have good stability (Table 4).

Individual components and lung cancer risk

The link between the intake of all eight components of the DASH pattern and lung cancer risk was investigated. Higher fruit consumption was linked to a lower risk of lung cancer, according to Supplementary Table 3 ($HR_{quartile\ 4\ versus\ 1}$: 0.758; 95% CI: 0.657,0.873; $P_{trend} < 0.001$), this inverse relationship was also found for vegetables, nuts and legumes, whole grains, and low-fat dairy products. For red and processed meats, increased intake indicated the increased possibility of developing lung cancer ($HR_{quartile\ 4\ versus\ 1}$: 1.409; 95% CI: 1.203,1.650; $P_{trend} < 0.001$). However, for sodium and sweetened beverages, higher consumption was linked to a decreased risk. (For sodium, $HR_{quartiles\ 4\ versus\ 1}$: 0.694; 95% CI: 0.553,0.870; $P_{trend} = 0.002$; For sweetened beverages, $HR_{quartile\ 4\ versus\ 1}$: 0.795; 95% CI: 0.691,0.914; $P_{trend} = 0.007$).

TABLE 3 Subgroup analyses on the association of DASH score with the risk of lung cancer.

Subgroup variable	No. of subjects	No. of cases	HR $_{\text{Quartile 4 vs. Quartile 1}}$ (95% CI)[a]	$P_{\text{-interaction}}$
Age (years)				0.140
≤65	28,099	370	0.764 (0.574, 1.018)	
>65	24,363	554	0.916 (0.754, 1.113)	
Gender				0.735
Male	26,037	566	0.902 (0.720, 1.128)	
Female	26,425	358	0.751 (0.597, 0.944)	
Race				0.098
White	48,378	865	0.808 (0.684, 0.954)	
Non-white	4,084	59	1.265 (0.709, 2.258)	
Body mass index (kg/m^2)				0.914
≤25	18,172	366	0.839 (0.654, 1.078)	
>25	34,290	558	0.833 (0.676, 1.027)	
Smoking status				0.013
Never	24,588	61	1.202 (0.690, 2.093)	
Current/ Former	27,874	863	0.612 (0.520, 0.721)	
Randomization group				0.706
Intervention group	26,748	473	0.791 (0.630, 0.992)	
Control group	25,714	451	0.875 (0.698, 1.097)	
Drinking status				0.506
No	14,437	245	0.851 (0.631, 1.148)	
Yes	38,025	679	0.823 (0.681, 0.995)	
Family history of lung cancer				0.415
No	45,589	715	0.871 (0.727, 1.044)	
Yes/ Possible	6,873	209	0.707 (0.499, 1.001)	
History of hypertension				0.553
No	35,740	621	0.802 (0.658, 0.978)	
Yes	16,722	303	0.901 (0.687, 1.182)	
Energy intake from diet (kcal/day)				0.443
≤medium	26,233	442	0.803 (0.642, 1.004)	
>medium	26,229	482	0.861 (0.685, 1.081)	

[a]Adjusted for age (years), gender (male, female), race (white, non-white), drinking status (no, yes), smoking status (never, current/former), cigarettes smoked per day (0, 1–20, >20), pack-years (continuous), body mass index (continuous), randomization group (intervention group/control group), history of hypertension (no, yes), family history of lung cancer (no, yes/possible) and energy intake from diet (continuous).

TABLE 4 Sensitivity analyses on the association of DASH score with the risk of lung cancer.

Categories	HR $_{\text{Quartile 4 vs. Quartile 1}}$ (95% confidence interval)[a]	$P_{\text{-trend}}$
Repeated analysis in subjects with non-missing data	0.651 (0.558, 0.758)	<0.001
Excluded subjects with a family history of lung cancer[b]	0.671 (0.566, 0.794)	<0.001
Excluded subjects with a history of hypertension[c]	0.614 (0.510, 0.739)	<0.001
Excluded cases observed within the first 2 years of follow-up	0.613 (0.519, 0.725)	<0.001
Excluded cases observed within the first 4 years of follow-up	0.586 (0.483, 0.711)	<0.001

[a]Adjusted for age (years), gender (male, female), race (white, non-white), drinking status (no, yes), smoking status (never, current/former), cigarettes smoked per day (0, 1–20, >20), pack-years (continuous), body mass index (continuous), randomization group (intervention group/control group), history of hypertension (no, yes), family history of lung cancer (no, yes/possible) and energy intake from diet (continuous).
[b]HRs was not adjusted for history of lung cancer.
[c]HRs was not adjusted for history of hypertension.

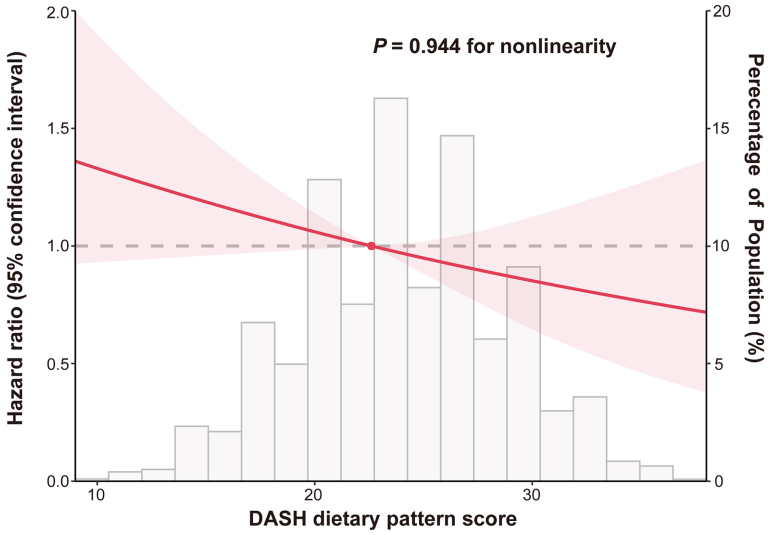

FIGURE 3
Dose–response association between DASH score and lung cancer risk. Hazard ratios were adjusted for age (years), gender (male, female), race (white, non-white), drinking status (no, yes), smoking status (never, current/former), cigarettes smoked per day (0, 1–20, >20), pack-years (continuous), body mass index (continuous), randomization group (intervention group/control group), history of hypertension (no, yes), family history of lung cancer (no, yes/possible) and energy intake from diet (continuous).

Discussion

It was discovered in the current study that adherence to the DASH eating pattern was linked to a lower risk of lung cancer (small cell carcinoma as well as non-small cell carcinoma) in accordance with the prospective data from the PLCO trial. The restricted cubic spline plot showed that the inverse relationship between lung cancer risk and DASH score followed a linear dose–response relationship. Subgroup analyses revealed that DASH eating pattern was more protective against lung cancer among current or former smokers. Furthermore, the results remained stable after excluding participants who might have influenced the results, which strengthens the conclusions.

DASH dietary pattern was originally proposed as a dietary model for preventing and controlling hypertension and has shown significant advantages in blood pressure control and metabolic diseases (21). However, as this dietary pattern becomes better understood, it has been linked to a number of cancers. For instance, participants in case–control research with 1,050 Iranian women revealed that those with the highest quartile of the DASH score had 85% reduced risk of developing breast cancer than those with the lowest quartile (22). According to another hospital-based case–control study that included 454 participants (178 histo-pathologically confirmed gastric cancer patients and 276 matched healthy controls), the highest adherence to the DASH dietary pattern was linked to a 54% lower risk of gastric cancer after adjusting for relevant confounders (23). Additionally, a meta-analysis conducted in 2020 revealed that following the DASH dietary pattern was related to a lowered risk of colorectal cancer (24). To our knowledge, Myneni et al. has investigated the association between DASH dietary pattern and lung cancer risk in a population of 86,090 perimenopausal women (25), and their results showed that adherence to the DASH diet was not linked to an overall risk of developing lung cancer but reduced the risk of squamous cell carcinoma by up to 13%. In addition, Anic et al. investigated the correlation between four diet quality indices and lung cancer risk, and found that the DASH diet pattern had a 16% reduced risk of lung cancer (26). Compared with the previous studies, our results suggest DASH was protective against lung cancer and its subtypes. One potential explanation for the inconsistent results mentioned above is that Myneni et al.'s study only included female participants, whereas our research involved a population with a nearly equal distribution of both males and females. Additionally, there were differences in the covariates included in previous and our studies. Although smoking factors were comprehensively adjusted in previous studies, family history of lung cancer and hypertension history were not considered. Individuals with a higher score of DASH diet would be less likely to have a history of hypertension (27), and individuals with a family history of lung cancer may be at an increased risk of developing lung cancer (28). However, we adequately accounted for these crucial factors in our multivariable model.

Based on our findings of the relationship between the consumption of all eight components and lung cancer risk, it was found that adding adequate amounts of fruits, vegetables, nuts and legumes, whole grains, and low-fat dairy products was linked to reduced lung cancer risk, higher intake of red and processed meat increased the risk of developing lung cancer. The association of these dietary components with lung cancer risk was largely supported by former studies (7, 29), and further supporting the potential rationale for the inverse association between the DASH diet and the risk of developing lung cancer. Interestingly, dietary sodium and sugar-sweetened beverages, which are advocated to reduce consumption in the DASH diet, may have potential protective effects against lung cancer as presented in our study. These results were inconsistent with previous evidence that higher intake of sugar-sweetened beverages and dietary sodium were associated with an increased risk of various cancers (8, 30). Although direct evidence linking sugar-sweetened beverages to

lung cancer risk is currently lacking, they are believed to be closely associated with risk factors for lung cancer, such as insulin resistance, inflammation, obesity, and type 2 diabetes (31). Further basic research and comprehensive epidemiological studies are needed to clarify the relationship between sugar-sweetened beverages and lung cancer. In addition, our study found no significant association between dietary sodium intake and lung cancer risk in both the unadjusted model and adjusted model 1. However, in the fully adjusted model 2, higher dietary sodium intake was associated with a lower risk of lung cancer. It is possible that this finding was incidental due to interactions between dietary sodium intake and the covariates considered in our study. On the other hand, research focused solely on individual nutrients or foods has not adequately explored the complex interplay between dietary components (32).

The benefits of the DASH diet in lowering the risk of developing lung cancer might be attributed to multiple underlying mechanisms. Firstly, fruits, vegetables, and grains are rich in phytochemicals with antioxidant activity, such as β-carotene and vitamin C (33). Evidence shows that oxidative stress can cause intracellular DNA base changes, strand breaks, overexpression of proto-oncogenes, and inactivation of oncogenes, resulting in the growth of certain malignancies, including lung cancer (34–36). Adherence to the DASH diet may lower the risk of lung cancer by increasing antioxidant capacity. Secondly, the DASH diet requires a limited consumption of red and processed meats, which are rich in many carcinogens such as aromatic amines and nitrites, and these substances can promote cancer development by causing DNA damage (37, 38). Thirdly, persistent inflammation-induced generation of reactive oxygen/nitrogen species in the lungs may increase the risk of lung cancer (39, 40). Animal studies have demonstrated that eating large amounts of fiber, which is abundant in fruits, vegetables and grains, can change the composition of lung microbiota, which in turn remodels the immune environment of the lungs (41). Moreover, previous studies have shown the benefits of adhering to the DASH diet in improving circulating serum inflammatory biomarkers such as highly sensitive C-reactive protein, which suggested that DASH diet might be able to reduce the inflammatory response of the body (42). Fourthly, some components, such as low-fat dairy products, may reduce the insulin resistance (43), which was demonstrated to be closely related to increased risk of lung cancer (44, 45). To sum up, adherence to DASH diet may potentially reduce lung cancer risk through mechanisms that involve increased antioxidant capacity, anti-inflammatory responses, and improved insulin resistance. Nevertheless, more research is necessary to confirm these mechanisms.

In subgroup analyses, it was found that for current or former smokers, there were more benefits from adherence to the DASH diet in terms of lung cancer prevention compared to those who never smoked. One possible explanation is that only a few cases of lung cancer were observed in individuals who never smoked, causing the loss of sufficient statistical efficiency. Another possible rationale is that oxidative stress and inflammation in the lung are alleviated by the DASH diet, while a vital mechanism of smoking-induced lung cancer is that smoking-related oxidative stress causes inflammation and potentially increased oxidative damage to lung tissue (46). Regardless, it was suggested in the findings of this research that adherence to the DASH diet may be more meaningful for current or former smokers. The underlying mechanisms need to be confirmed by further studies.

This study has distinct advantages. (i) This study was a well-designed prospective study in a large population and up to 8.84 years follow-up period ensured that the outcome events could occur; (ii) Consistent findings were obtained by analyzing the association between the DASH dietary pattern and each component and lung cancer risk, which increased the credibility of the conclusion. (iii) Our study provided dietary guidance to the US population in terms of lung cancer prevention, especially for current or former smokers.

However, there are several limitations to our study. (i) Participants included were the US population aged 55–74 years, the findings cannot be extended to other regions or ages; (ii) Although food frequency questionnaire is a well-designed dietary evaluation tool (17), the fact that participants self-report dietary history information still introduced bias into our study. The bias was non-differential and often unavoidable in epidemiological investigations. (iii) Collecting dietary information at once without considering possible changes in the dietary habits of individuals during the follow-up period might lead to non-differential bias. However, current nutritional epidemiology research suggests that the eating habits of individuals do not usually alter dramatically (20). Secondly, using one-time baseline data for cancer risk analysis tends to yield a weaker association than using cumulative average food consumption over a period of time (47); (iv) Although most potential confounders were adjusted in model 2, there are still some possible risk factors for lung cancer that were not excluded, such as passive smoking (48, 49) and air pollution (5), these factors cannot be further adjusted due to the unavailability of the data. However, participants included in our study were derived from ten centers across the United States, which could partially eliminate the effect of air pollution on the incidence rate of lung cancer.

Conclusion

In the US population, DASH scores were inversely linked to the risk of developing lung cancer. This suggests that adherence to the DASH dietary pattern can be beneficial in lung cancer prevention, especially for current or former smokers. More epidemiological evidence from other regions and populations is needed to confirm and strengthen the findings of this research.

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 Institutional Review Board of the National Cancer Institute. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZZ, LX, and YW designed the study. LP and LX collected the raw data. ZZ, HG, and YX analyzed the data. YT, MY, and HH assisted in the interpretation of the results. ZZ and LX drafted the manuscript, YW reviewed the manuscript and finalized it. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1142067/full#supplementary-material

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Food groups and urologic cancers risk: a systematic review and meta-analysis of prospective studies

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Background: To assess the association between 12 food groups intake and the risk of urologic cancers.

Methods: We scanned PubMed and Web of Science databases up to April 1st, 2023, and 73 publications met the inclusion criteria in the meta-analysis. We used a random effects model to estimate the summary risk ratios (RRs) and 95% confidence intervals (95% CI).

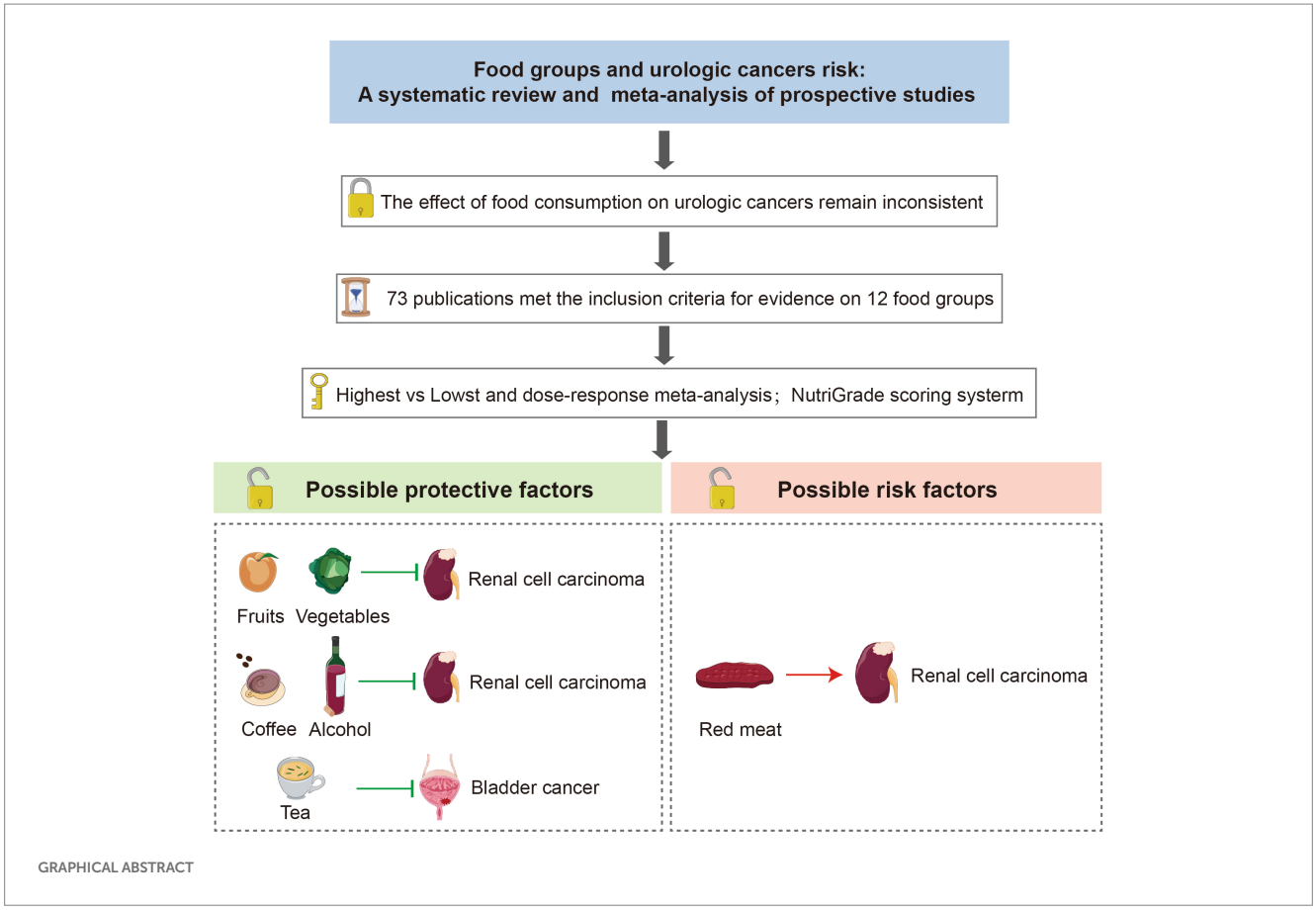
Results: In the linear dose–response meta-analysis, an inverse association was found between each additional daily 100g of fruits [RR: 0.89, 95%CI=(0.83, 0.97)], 100g of vegetables [RR: 0.92, 95%CI=(0.85, 0.99)], 12g of alcohol [RR: 0.91, 95%CI=(0.88, 0.94)] and 1 cup of coffee [RR: 0.95, 95%CI=(0.83, 0.97)] intake and the risk of renal cell carcinoma. Conversely, each additional daily 100g of red meat intake was positively associated with renal cell carcinoma [RR: 1.41, 95%CI=(1.03, 2.10)]. Inverse associations were observed between each additional daily 50g of egg [RR: 0.73, 95%CI=(0.62, 0.87)] and each additional daily 1 cup of tea consumption and bladder cancer risk [RR: 0.97, 95%CI=(0.94, 0.99)]. There were no significant associations for nonlinear dose–response relationships between 12 food groups and urological cancers.

Conclusion: Our meta-analysis strengthens the evidence that appropriate intake of specific food groups, such as fruits, vegetables, alcohol, tea, and coffee, is associated with the risk of renal cell carcinoma or bladder cancer. More studies are required to fill the knowledge gap on the links between various food groups and urologic cancers because the evidence was less credible in this meta-analysis.

Systematic Review Registration: This study was registered on PROSPERO (CRD42022340336).

KEYWORDS

urologic cancers, foods, prospective cohort, meta-analysis, dose–response



1. Introduction

Urologic cancers can occur anywhere in the kidney, bladder, renal pelvis, ureter, and urethra. Notably, renal cell carcinoma (RCC) and bladder cancer (BC) are the most common urinary system tumors in both men and women. RCC and BC incidence have been steadily increasing worldwide over the past decades (1). According to GLOBOCAN data, more than 431,000 new cases of RCC were diagnosed and more than 573,000 new cases of BC were recorded worldwide in 2020 (2). Despite the identification of several modifiable lifestyle risk factors, including excess body weight (3), hypertension (4), smoking (5), and physical inactivity (6), there has been little progress in understanding the origin of urologic cancers.

Efforts to find a connection between diet and urologic cancers have a long history in cancer research. Currently, several studies have demonstrated a strong connection between food and the risk of urologic cancers (7–10). Many dietary factors, such as total fruits, total vegetables, processed meat, and alcohol consumption, are thought to influence urologic cancers risk (11–14). However, insights from epidemical studies on the modifying effects of food consumption on urologic cancers are still controversial (15–18). Therefore, more updated and sufficient evidence is needed to address these long-controversial issues. In this meta-analysis, we aim to investigate the associations of 12 food groups with the risk of urologic cancers, evaluate the food groups' credibility of meta-evidence on their association with urologic cancers risk, and propose optimally effective strategies for the prevention of urologic cancers.

2. Methods

The PROSPERO International Prospective Register of Systematic Reviews has acknowledged the protocol for this meta-analysis (CRD42022340336). This systematic review was developed based on the guidelines of the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) (19).

2.1. Search strategy and study selection

To investigate the association between specific food group intake and urologic cancer risk, articles published in PubMed and Web of Science before April 1st, 2023 were searched. The search was restricted to the English language. The keywords used in the search strategy are presented as search terms (Supplementary Appendix S1). To discover pertinent research more comprehensively, the electronic search method also looked through all related earlier reviews. The study inclusion criteria were as follows: (1) prospective cohort studies, case cohorts, nested case–control studies; (2) studies reported the association for at least one of the 12 food groups (fruits, vegetables, legumes, egg, dairy, fish, red meat, processed meat, sugar-sweetened beverages (SSB), alcoholic drinks, coffee, and tea) and risk of urologic cancers; (3) the authors reported the risk ratio (RR) estimates or hazard ratios (HRs) with 95% confidence intervals (CIs) or the number of urologic cancers events. Exclusion criteria were (1) studies did not report relevant exposure; (2) studies did not contain cases of

urinary system cancer; (3) reviews, meta-analyses, retrospective studies, non-human studies, studies without sufficient data, case–control studies, cross-sectional designs, and interventional studies.

After screening the titles and abstracts, duplicate papers and those that did not fit the criteria for inclusion had been removed. The full-texts of the remaining records were then assessed for eligibility.

2.2. Data extraction

Our 2 reviewers (S.W. and X.Z.) independently extracted the information as follows: first author's name, year of publication, country, cohort name, study duration (years of follow-up), sex, age, cases, sample size, exposure assessment method, outcome, type of food groups, quantity of food intake, risk estimate (most adjusted RRs or HRs with 95% CI), and covariates used for adjustment. When the same study appeared to have multiple publications, we selected the version which contains the largest sample and longest follow-up.

2.3. Risk of bias assessment

The Newcastle-Ottawa scale (NOS) was used to assess the methodological quality of prospective cohort studies included (20). It contains 8 categories relating to methodological quality: representativeness of the exposed cohort, selection of non-exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the start of the study, comparability of the cohorts on the basis of the design or analysis, assessment of outcome, follow-up duration, and adequacy of follow up of cohorts. This scoring system suggests classifying the meta-evidence into three categories: low (0–3 points), moderate (4–6 points), and high (7–9 points).

2.4. Statistical analysis

We used the random effects model to calculate the pooled RR and 95% CI, and linear or non-linear dose–response analysis. The HRs reported in the included studies were considered equal to RRs. We carried out the dose–response meta-analysis using the approach suggested by Greenland and Longnecker et al. (21). The distribution of cases, person-years or non-cases, as well as the RRs with 95% CIs, were required for at least three quantitative exposure categories when we applied this method. In dose–response meta-analysis, the lowest intake category from each study was used as the reference, and the other intake categories were compared to the reference. When the exposure category was reported in the closed interval, consumption was considered as the midpoint of the interval. When the exposure category was open-ended, we assumed that its length was the same as the adjacent category.

Restricted cubic splines for each study with more than 3 quantiles of exposure were calculated to explore possible nonlinear associations. We used three fixed knots through the total range of the reported intake at 10, 50, and 90% (22, 23). Units of exposure were defined as follows: total fruits (100 g/day), total vegetables (100 g/day), legumes (100 g/day), egg (50 g/day), dairy (200 g/day), fish (100 g/day), red meat (100 g/day), processed meat (50 g/day), alcohol (12 g/day), coffee (1 cup/day), tea (1 cup/day) and SSB (1 drink/day). When the studies did not specify the quantitative amount or reported food intake as serving size only, we adopted the WCRF 2017 suggested conversions (Supplementary Table S1).

We performed subgroup analyses of potential influencing factors to discern the source of heterogeneity. If there were an adequate number of studies ($n \geq 5$) available for a particular food group in the meta-analysis, subgroup analyses by geography (US, UK, Asia), sex (Male, Female, Male and female), follow-up duration (mean ≥ 10 years vs. <10 years), no of participants (≥100,000 vs. <100,000). Egger's linear regression tests and visual inspection of funnel plots were used to evaluate publication bias (24, 25). Furthermore, we conducted sensitivity analysis by omitting one study at a time when significant publication bias ($p > 0.05$) or heterogeneity ($I^2 \geq 50\%$) was detected in the results. All statistical analyses in this systemic review were performed with Stata (version 14; Stata Corp). Two-tailed was used in all tests and value of p of less than 0.05 was considered to indicate statistical significance.

2.5. Quality of meta-evidence

Two independent researchers (J.Q. and D.J.) evaluated the overall quality of the evidence using the NutriGrade scoring system (max 10 points). This tool comprises the following items: (1) risk of bias, study quality, and study limitations; (2) precision; (3) heterogeneity; (4) directness; (5) publication bias; (6) funding bias; (7) effect size; and (8) dose–response (26). Scores between 0 and 3.99, 4–5.99, 6–7.99 were categorized as very low, low, and moderate, and score between 8–10 represents good quality meta-evidence, respectively. Disagreements were settled by conversation until an agreement was achieved.

3. Results

3.1. Study characteristics

The selection of the studies and the outcomes of the literature search were reported in Figure 1. In total, the original search turned up 5,788 articles. Duplicate papers and those that did not fit the criteria for inclusion have been removed. 113 full-text articles from potentially relevant studies were further evaluated. After a full-text review, additional 41 articles were excluded (Supplementary Appendix S2). And one additional record was added through systematic review. At last, 73 publications were included in the meta-analysis. During a mean of 13.6 years of follow-up, 4,903,674 participants were documented, of which 15,666 cases were ascertained (Supplementary Table S2). We evaluated the quality of the studies and yielded an average score of 8.38. Details of quality scores for all included studies are presented in Supplementary Table S3.

3.2. Foods associated with increased urologic cancers risk

3.2.1. Red meat

Comparing extreme intake categories (0 g/d vs. 43 g/d), a positive association was observed between red meat consumption

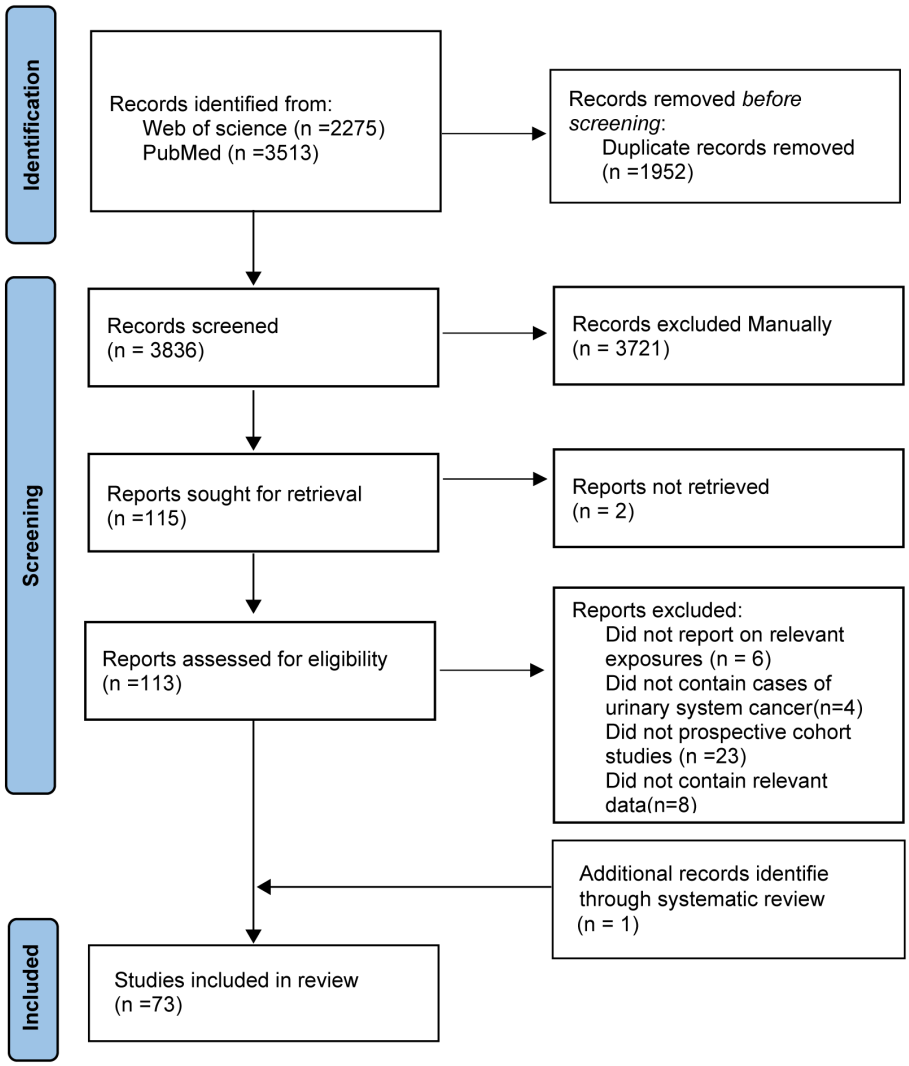


FIGURE 1
Flowchart of study selection.

and risk of RCC [RR: 1.24, 95%CI = (1.07, 1.43)] (Figure 2; Supplementary Figure S1). A positive association was found for each additional 100 g/d of red meat consumption and risk of RCC [RR: 1.41, 95%CI = (1.03, 2.10)], but not for BC [RR: 1.09, 95%CI = (0.94, 1.27)] (Figure 3). No nonlinear dose–response relationship was found between red meat consumption and RCC ($p = 0.42$) (Figure 4E) or BC ($p = 0.12$) (Figure 5E).

3.3. Foods associated with decreased urologic cancers risk

3.3.1. Fruits

An inverse association was observed between fruits consumption and RCC risk when extreme intake categories were compared [RR: 0.86, 95%CI = (0.77, 0.97)] (Figure 2; Supplementary Figure S2). However, we found that fruit intake did not reduce the risk of BC when comparing the highest and lowest intake categories [RR: 0.89, 95%CI = (0.76, 1.04)] (Figure 2; Supplementary Figure S4).

Each additional 100 g/d of fruits was inversely associated with RCC risk [RR: 0.89, 95%CI = (0.83, 0.97)] (Figure 3), but not for BC risk [RR: 0.98, 95%CI = (0.95, 1.01)]. Nonetheless, fruits intake and RCC risk did not appear to have a nonlinear dose–response relationship ($p = 0.55$) (Figure 4A). Although fruit intake and risk of RCC did appear to be associated in a non-linear dose–response manner ($p = 0.001$) (Figure 5A), the CI overlaps with RR = 1, so it is not a statistically significant association.

In a stratified analysis of high-category versus low-category fruit intake and BC risk, there was no indication of heterogeneity between subgroups ($I^2 < 50\%$). These differences between the subgroups were not statistically significant ($p > 0.05$) (Supplementary Table S6).

3.3.2. Vegetables

Comparing the highest to the lowest categories of vegetable intake, increased vegetable consumption was linked to a lower RCC risk [RR: 0.88, 95%CI = (0.79, 0.98)], but not for BC risk [RR: 0.97, 95%CI = (0.84, 1.11)] (Figure 2; Supplementary Figure S3). Additionally, vegetable intake was inversely correlated with the risk of

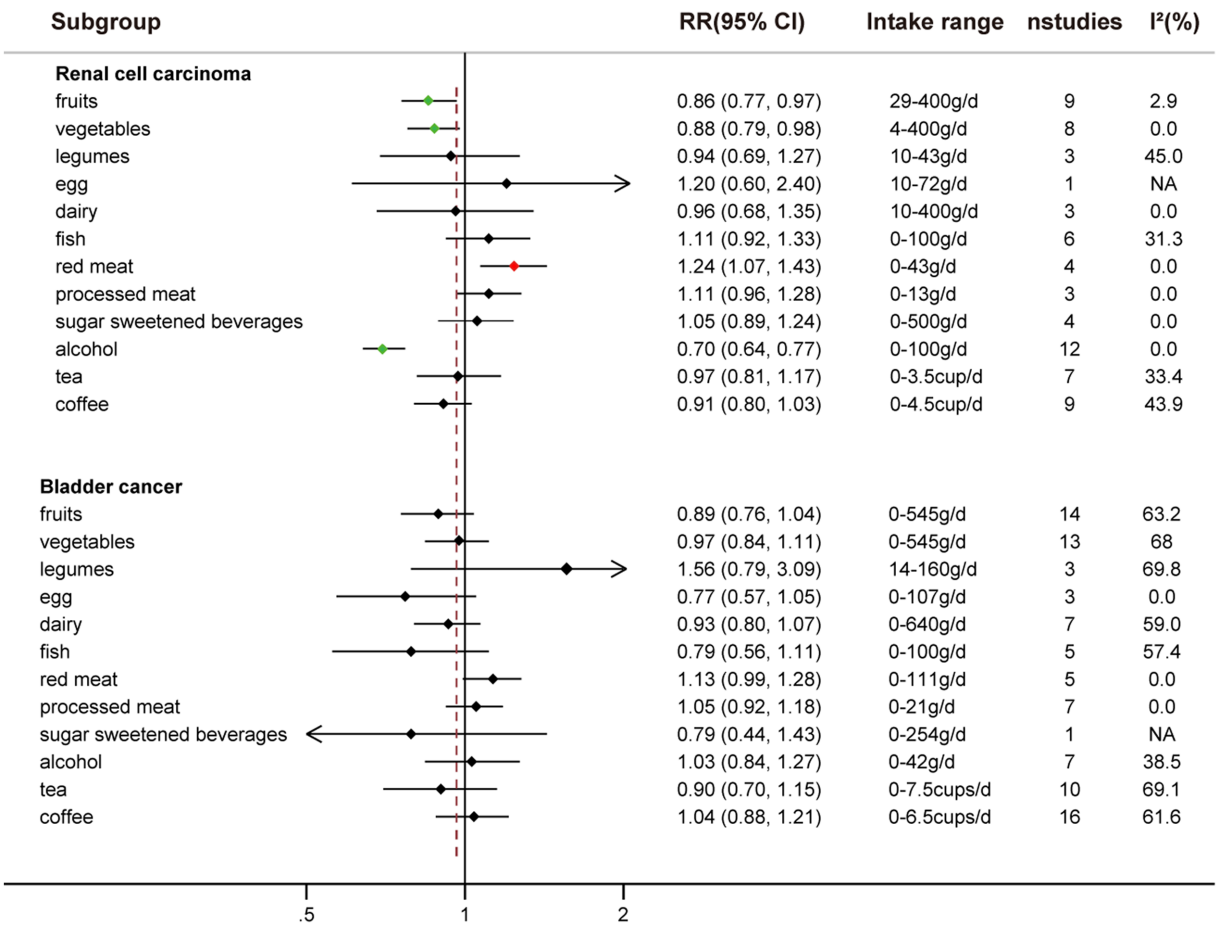


FIGURE 2
The highest versus lowest meta-analysis of food groups and the risk of RCC and BC.

RCC for each additional 100 g consumed daily [RR: 0.92, 95%CI = (0.85, 0.99)] (Figure 3). But each additional 100 g/d vegetable intake [RR: 0.98, 95%CI = (0.96, 1.00)] was not associated with the risk of BC (Figure 3). In stratified studies of vegetable intake and BC risk, there was no indication of heterogeneity between subgroups (Supplementary Table S7).

In the nonlinear dose–response meta-analysis, no association was observed between vegetable intake and RCC risk ($p = 0.59$) (Figure 4B) or BC risk ($p = 0.05$) (Figure 5B).

3.3.3. Alcohol

An inverse association between alcohol consumption and risk of RCC was found when comparing the highest to lowest categories [RR: 0.70, 95%CI = (0.64, 0.77)] (Figure 2; Supplemental Figure S4). No correlation between alcohol consumption and the risk of BC was seen when the highest to lowest categories are compared [RR: 1.03, 95%CI = (0.84, 1.27)] (Figure 2; Supplementary Figure S4).

The risk of RCC was inversely correlated with the additional daily 12 g of alcohol intake [RR: 0.91, 95%CI = (0.88, 0.94)] (Figure 3). But no association was found between the additional daily 12 g of alcohol intake [RR: 1.01, 95%CI = (0.97, 1.05)] and the risk of BC (Figure 4). No non-linear dose–response association between alcohol consumption and RCC risk ($p = 0.22$) or BC risk was found ($p = 0.37$) (Figure 5).

3.3.4. Tea

Comparing the highest to the lowest categories, no associations between tea intake and risk of RCC [RR: 0.97, 95%CI = (0.91, 1.17)] and BC [RR: 0.90, 95%CI = (0.70, 1.15)] were observed (Figure 2; Supplementary Figure S5).

An inverse association was observed for each additional daily 1 cup of tea and risk of BC [RR: 0.97, 95% CI = (0.94, 0.99)], but not for RCC [RR: 0.98, 95%CI = (0.92 to 1.04)] (Figure 3). There was no evidence of a non-linear dose–response association between tea and RCC risk ($p = 0.15$) (Figure 4H) or BC risk ($p = 0.84$) (Figure 5H).

No evidence of heterogeneity was detected between subgroups in stratified analyses on tea and bladder cancer (Supplementary Table S8).

3.3.5. Coffee

While comparing the highest to lowest categories, there was no association between coffee consumption and RCC risk [RR: 0.91, 95%CI = (0.80, 1.03)] or BC risk [RR: 1.04, 95%CI = (0.88, 1.21)] (Figure 2; Supplementary Figure S6). The risk of RCC decreased with each additional daily cup of coffee [RR: 0.95, 95%CI = (0.93, 0.97)] (Figure 3). There was no correlation between the risk of BC and the additional daily cup of coffee [RR: 1.00, 95%CI = (0.99, 1.01)] (Figure 3). No non-linear dose–response association between coffee consumption and BC risk was found ($p = 0.009$) (Figure 5I). After stratification by Geographic location, heterogeneity was observed,

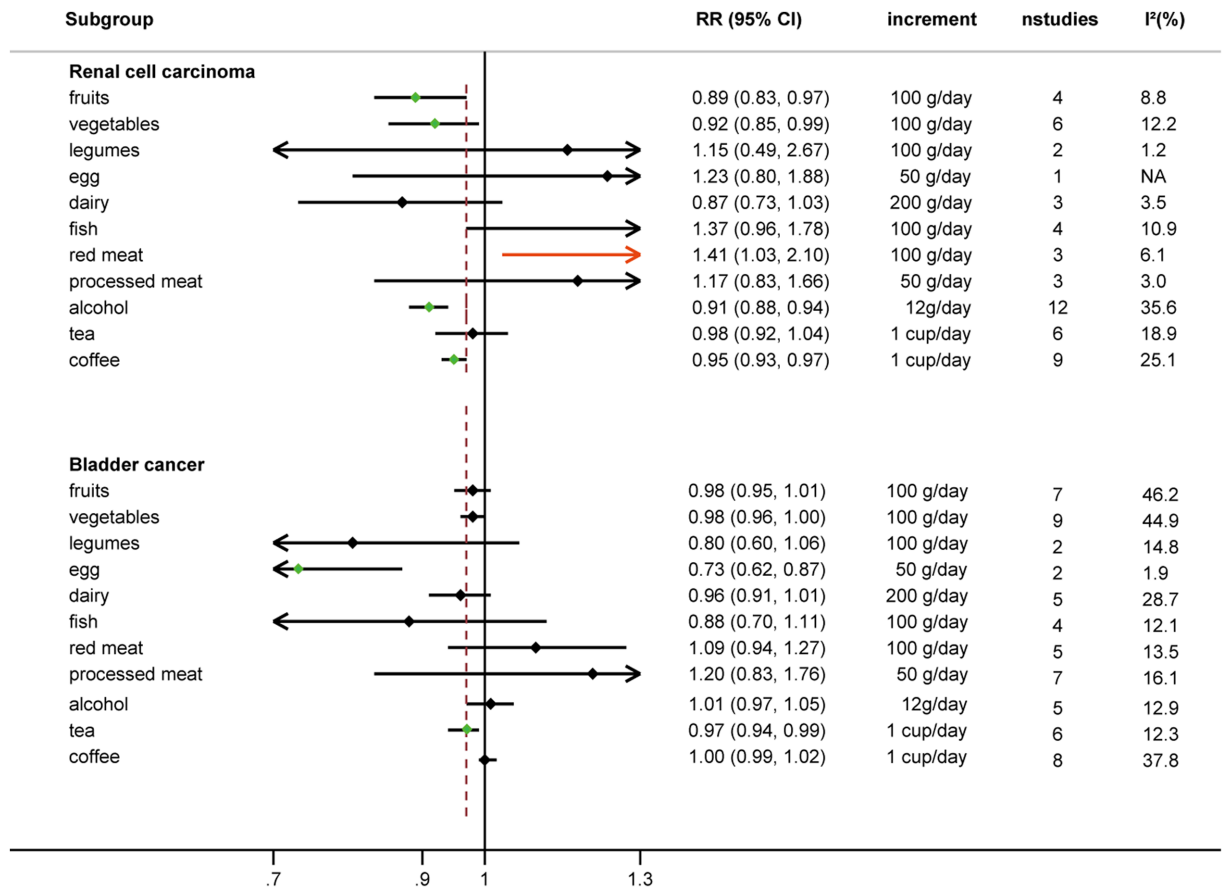


FIGURE 3
Linear dose–response of food groups and the risk of RCC and BC.

demonstrating a positive association between coffee consumption and incidence of BC only in research conducted in Europe [RR: 1.19, 95%CI = (1.01, 1.39)] (Supplementary Table S5).

3.4. Foods not associated with urologic cancers risk

3.4.1. Legumes

There was no association between legumes intake and risk of RCC [RR: 0.94, 95%CI = (0.69, 1.27)] or risk of BC [RR: 1.56, 95%CI = (0.79, 3.09)] when the highest and lowest categories of legumes intake were compared (Figure 2; Supplementary Figure S7). There was no correlation between each additional daily intake of 100 g of legumes and the risk of RCC [RR: 1.15, 95%CI = (0.49, 2.67)] or BC [RR: 0.80, 95%CI = (0.60, 1.06)] (Figure 3). Due to the limited availability of the data, non-linear dose–response meta-analysis was not applicable.

3.4.2. Egg

No correlation between egg intake and risk of RCC [RR: 1.20, 95%CI = (0.60, 2.40)] or risk of BC [RR: 0.77, 95%CI = (0.57, 1.05)] was observed when comparing the highest to lowest categories of egg consumption (Figure 2; Supplementary Figure S8). An inverse association was found between each additional daily 50 g of egg consumption and the risk of BC [RR: 0.73, 95%CI = (0.62, 0.87)] (Figure 3). Due to the scarcity of data in prospective cohort studies, it was not possible to analyze the non-linear dose–response relationship between egg intake and urological cancers.

3.4.3. Dairy

There was no association between dairy intake and the risk of RCC [RR: 0.96, 95%CI = (0.68, 1.35)], or BC [RR: 0.93, 95%CI = (0.80, 1.07)] when the highest and lowest categories of dairy intake were compared (Figure 2; Supplementary Figure S9). Each additional 200 g of dairy consumption daily did not affect the risk of RCC [RR: 0.87, 95%CI = (0.73, 1.03)] or BC [RR: 0.96, 95%CI = (0.91, 1.01)] (Figure 3). There was also no evidence of a non-linear dose–response relationship between dairy consumption and RCC risk ($p = 0.74$) (Figure 4C) or BC risk ($p = 0.37$) (Figure 5C). In stratified analyses of dairy consumption and BC risk, no significant evidence of heterogeneity was found between subgroups (Supplementary Table S9).

3.4.4. Fish

Comparing the highest to the lowest categories, no association between fish intake and RCC risk [RR: 1.11, 95%CI = (0.92, 1.33)] or BC risk [RR: 0.79, 95% CI = (0.56, 1.11)] was observed (Figure 2; Supplementary Figure S10). Each additional daily 100 g of fish intake was not associated with the risk of RCC [RR: 1.37, 95% CI = (0.96, 1.78)] or BC [RR: 0.88, 95% CI = (0.70, 1.11)] (Figure 3).

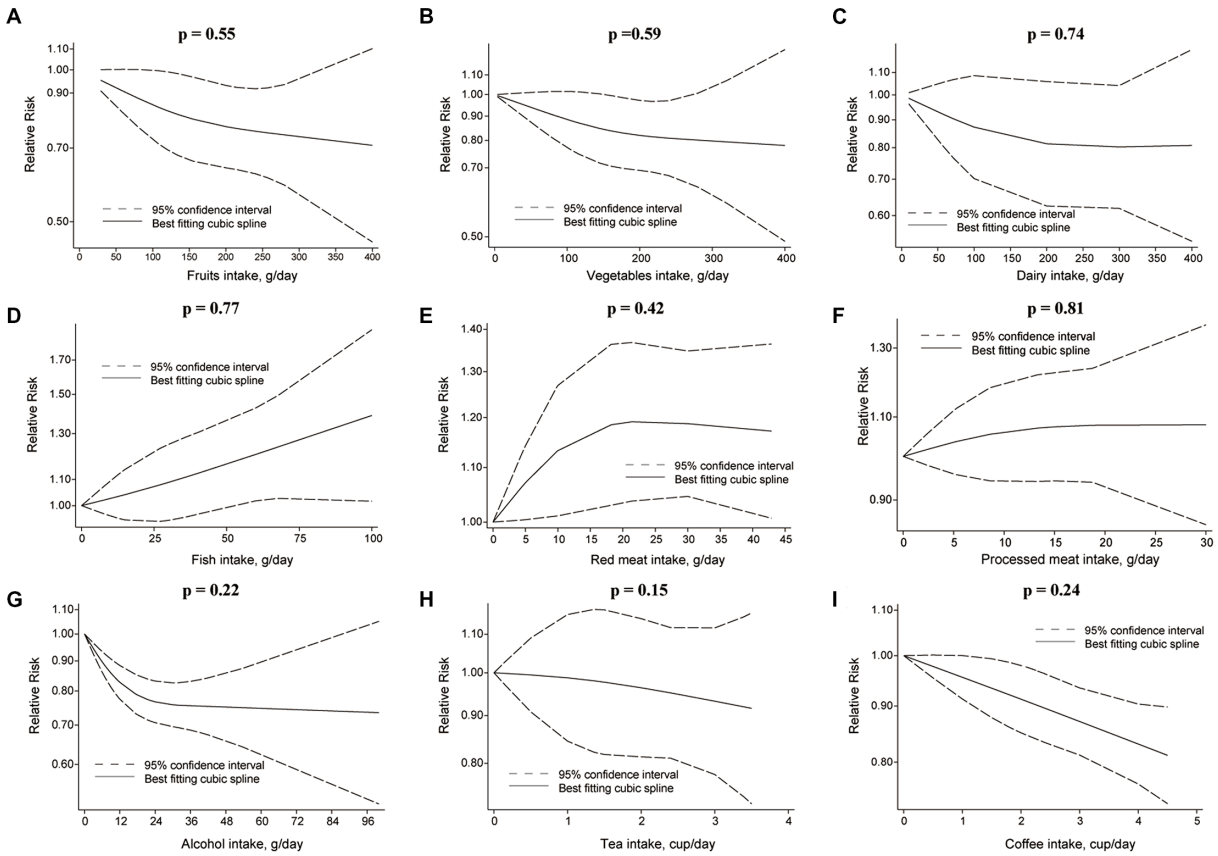


FIGURE 4
Non-linear dose–response relationship between food groups and risk of RCC. **(A)** Fruits, **(B)** vegetables, **(C)** dairy, **(D)** fish, **(E)** red meat, **(F)** processed meat, **(G)** alcohol, **(H)** tea, and **(I)** coffee.

There was no evidence of a non-linear dose–response association between fish intake and RCC risk ($p = 0.77$) (Figure 4D), or BC risk ($p = 0.21$) (Figure 5D). Subgroup analyses showed evidence of heterogeneity, for the prospective cohort studies in America and studies with ≥100,000 participants, a high intake of fish has been linked to a significantly lower risk of BC (Supplementary Table S4).

3.4.5. Processed meat

There was no significant association between processed meat consumption and the risk of RCC [RR: 1.11, 95%CI = (0.96, 1.28)], or BC [RR: 1.05, 95%CI = (0.92, 1.18)] (Figure 2; Supplementary Figure S11). Each additional 50 g of processed meat consumed daily was not associated with a higher risk of RCC [RR: 1.17, 95%CI = (0.83, 1.66)], or BC [RR: 1.20, 95%CI = (0.83, 1.76)] (Figure 3). There was no nonlinear dose–response relationship between processed meat intake and RCC risk ($p = 0.81$) (Figure 4F), or BC risk ($p = 0.39$) (Figure 5F).

3.4.6. Sugar-sweetened beverages

There was no association between SSB intake and the risk of RCC [RR: 1.05, 95%CI = (0.89, 1.24)] or BC [RR: 0.79, 95%CI = (0.44, 1.43)] when the highest and lowest categories were compared (Figure 2; Supplementary Figure S12). In addition, dose–response meta-analysis was not possible due to a lack of data availability.

3.5. Publication bias and sensitivity analysis

Based on the funnel plot (Supplementary Figures S13–S17) and Egger's test, there was no publication bias for alcohol intake and risk of RCC ($p = 0.848$, $n = 12$ studies), fruit ($p = 0.402$, $n = 14$ studies), vegetables ($p = 0.469$, $n = 13$ studies), tea ($p = 0.186$, $n = 10$ studies), coffee ($p = 0.748$, $n = 16$ studies) intake for BC. In the influence analysis in which we excluded one study from high versus low meta-analysis with high heterogeneity ($I^2 \geq 50\%$), in turn, the summary estimates were not substantially altered for all of the exposures (fruits, vegetables, legumes, dairy, fish, tea, and coffee) (Supplementary Figures S18–S24).

3.6. Quality of evidence

We graded and assessed the quality of meta-evidence regarding the association between food groups and the risk of RCC and BC. In our results, the classification of RCC's NutriGrade meta-evidence was given as follows: "high" for alcohol, "moderate" for fruits, vegetables, red meat,

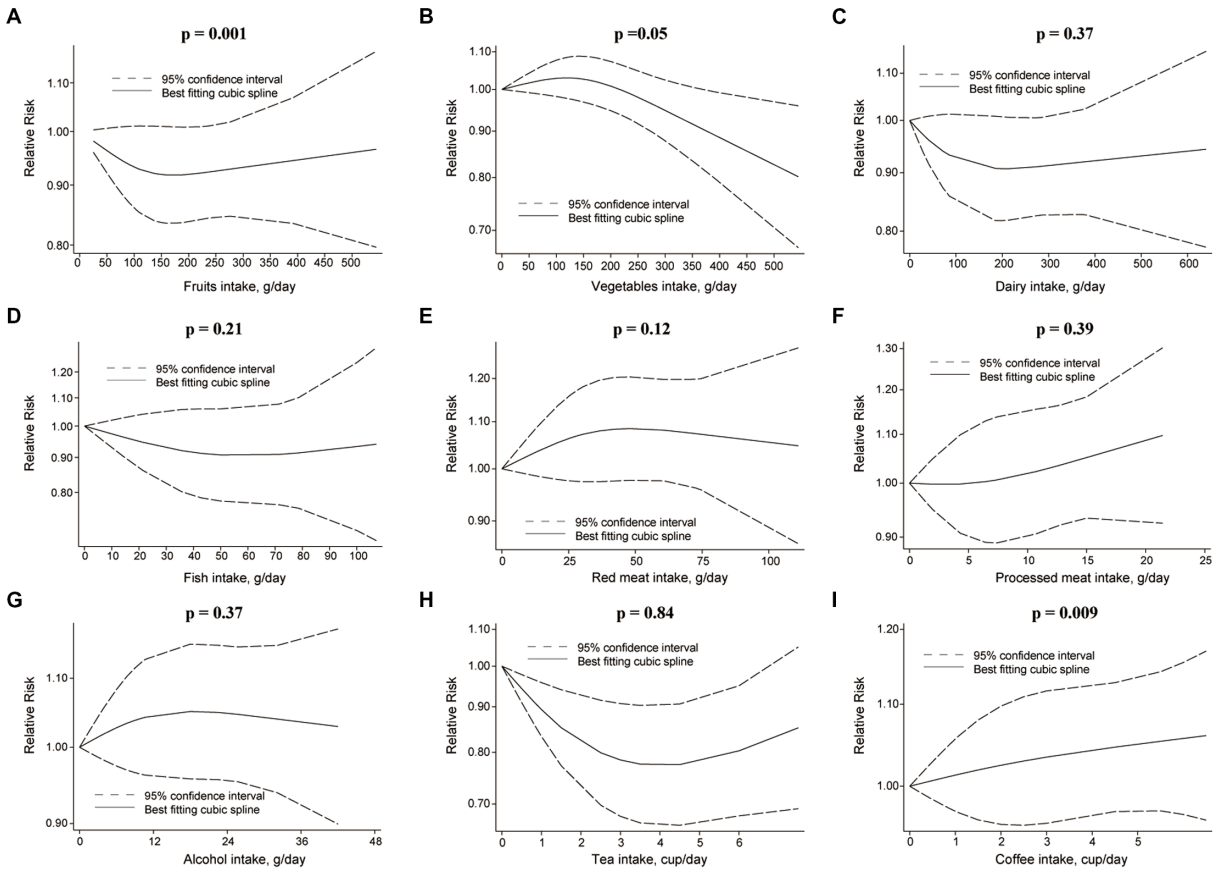


FIGURE 5
Non-linear dose–response relationship between food groups and risk of BC. **(A)** Fruits, **(B)** vegetables, **(C)** dairy, **(D)** fish, **(E)** red meat, **(F)** processed meat, **(G)** alcohol, **(H)** tea, and **(I)** coffee.

and coffee, and "low" for the other seven food groups (Table 1). The NutriGrade grading on BC was rated "moderate" for fruits, vegetables, tea, and coffee, and "low" for the 8 other food groups (Table 2).

4. Discussion

4.1. Principal findings

In this study, we evaluated the associations of targeted food groups—fruits, vegetables, legumes, egg, dairy, fish, red meat, processed meat, SSB, alcohol, tea, and coffee—and the risk of RCC and BC. First, we found that fruits, vegetables, and alcohol were associated with a decreased risk of RCC in the high versus low meta-analysis, while red meat was associated with an increased risk of RCC. Second, in the linear dose–response meta-analysis, an inverse association was found between fruits, vegetables, alcohol, coffee intake and risk of RCC, and a positive association was found between red meat intake and RCC. Differently, tea consumption was negatively associated with the risk of BC. At last, there were no indications for nonlinear dose–response relationships between preselected food groups intake and risk of RCC and BC.

The NutriGrade tool suggested a high confidence in the estimate of the alcohol intake and risk of RCC, and moderate confidence in the estimate of the effect of fruits, vegetables, tea, and coffee intake for the risk of RCC. The NutriGrade tool for BC was classified as "moderate" for fruits, vegetables, tea, and coffee, and the confidence for other food groups was lower.

4.2. Strengths of the study

The study has some advantages. First, the article is the first meta-analysis that includes all the available prospective cohort studies to estimate the connection between food groups and the risk of urologic cancers.

Of note, we only included urologic cancers that occur in both men and women, which minimizes gender differences. Furthermore, we performed various types of analyses that enable us to thoroughly identify the associations between food groups and urological cancers and found an ideal intake with the lowest risk. This meta-analysis included prospective studies only, the recall bias was successfully avoided, and the likelihood of selection bias was decreased (27). Additionally, the overall quality of evidence is further ensured by the Newcastle-Ottawa scale assessment (8.38 on average).

4.3. Comparison with other studies

Our findings are consistent with earlier meta-analyses that showed an inverse association between fruits and vegetable intake and RCC

TABLE 1 NutriGrade assessment of confidence in estimate effect of studies evaluated the association between various food groups and risk of RCC.

Food groups	Risk of bias[1]	Precision[2]	Indirectness	Heterogeneity[3]	Publication bias	Effect size	Dose response	Funding bias	Total score	Confidence evidence[4]
Fruits	2	1	1	0.5	0.5	0	1	1	7	Moderate
Vegetables	2	1	1	0.5	0.5	0	1	1	7	Moderate
Legumes	2	0	1	0	0	0	0	1	4	Low
Egg	2	0	1	0	0	0	0	1	4	Low
Dairy	2	0	1	0	0	0	0	1	4	Low
Fish	2	0	1	0.5	0.5	0	0	1	5	Low
Red meat	2	1	1	1	0	0	1	1	7	Moderate
Processed meat	2	0	1	0	0	0	0	1	4	Low
Sugar-sweetened drinks	2	0	1	0	0	0	0	1	4	Low
Alcohol	2	1	1	1	1	1	1	1	9	High
Tea	2	0	1	0.5	0.5	0	0	1	5	Low
Coffee	2	0	1	0.5	0.5	0	1	1	6	Moderate

NutriGrade, Nutrition Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio.[1]Risk of bias was based on the Newcastle-Ottawa Scale, where ≥ 7 = 2 points; 4–6.9 = 1 point; and 0–3.9 = 0 points.

[2]Precision is 1 point if the number of events ≥500 and the 95% CI excludes the null value; precision is 0 points if the number of events <500 or number of events ≥500, but 95% CI includes the null value and 95% CI fails to exclude an important benefit (RR of 0.8) or harm (RR of 1.2).

[3]Based on the funnel plots, Egger or Begg's test. For the outcomes with small number of studies ($n < 10$), the risk of publication bias was not formally assessed.

[4]High quality indicates that there is high confidence in the effect estimate, and further research probably will not change the confidence in the effect estimate. Moderate quality indicates that we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality indicates that our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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TABLE 2 NutriGrade assessment of confidence in estimate effect of studies evaluated the association between various food groups and risk of BC.

Food groups	Risk of bias[1]	Precision[2]	Indirectness	Heterogeneity	Publication bias[3]	Effect size	Dose response	Funding bias	Total score	Confidence evidence[4]
Fruits	2	0	1	1	1	0	0	1	6	Moderate
Vegetables	2	0	1	1	1	0	0	1	6	Moderate
Legumes	2	0	1	0	0	0	0	1	4	Low
Egg	2	0	1	0	0	0	1	1	5	Low
Dairy	2	0	1	0	0	0	0	1	4	Low
Fish	2	0	1	0	0	0	0	1	4	Low
Red meat	2	0	1	0	0	0	0	1	4	Low
Processed meat	2	0	1	0.5	0.5	0	0	1	5	Low
Sugar-sweetened drinks	2	0	1	0	0	0	0	1	4	Low
Alcohol	2	0	1	0	0	0	0	1	4	Low
Tea	2	0	1	1	1	0	1	1	7	Moderate
Coffee	2	0	1	1	1	0	0	1	6	Moderate

NutriGrade, Nutrition Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio.

[1]Risk of bias was based on the Newcastle-Ottawa Scale, where ≥7 = 2 points; 4–6.9 = 1 point; and 0–3.9 = 0 points.

[2]Precision is 1 point if the number of events ≥500 and the 95% CI excludes the null value; precision is 0 points if the number of events <500 or number of events ≥500, but 95% CI includes the null value and 95% CI fails to exclude an important benefit (RR of 0.8) or harm (RR of 1.2).

[3]Based on the funnel plots, Egger or Begg's test. For the outcomes with small number of studies ($n < 10$), the risk of publication bias was not formally assessed.

[4]High quality indicates that there is high confidence in the effect estimate, and further research probably will not change the confidence in the effect estimate. Moderate quality indicates that we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality indicates that our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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risk (28–32). While other research indicates that the incidence of urologic cancers is not associated with overall fruit and vegetable consumption (11–13, 33–37). The base of the dietary pyramid, fruits and vegetables, contain many compounds that may prevent cancers, yet it is challenging to determine the proportional value of each component. Any preventative impact could most likely be attributed to a confluence of actions on many carcinogenesis-related pathways. Numerous antioxidant elements (including carotenoids and vitamin C), minerals, dietary fiber, phenols, flavonoids, and phytochemicals are present in many fruits and vegetables, which may influence the processes governing cell proliferation and death (38). These processes are assumed to be primarily responsible for the association between consuming fruits and vegetables and a decreased risk of urological cancers. For example, cruciferous vegetables have high levels of glucosinolates, which are converted into isothiocyanates by the enzyme myrosinase during food preparation and change the way carcinogens are metabolized, which could decrease the risk of cancers (39).

No association was found in our meta-analysis between dairy consumption and RCC and BC risk. Similarly, previous studies found no association between BC risk and milk consumption (40, 41), whereas some previous meta-analyses suggested dairy (such as milk) consumption is positively associated with the risk of BC (42–44). Calcium, vitamins, and protein are the elements found in dairy, which may benefit human health (45). Suggestions on dairy consumption to urologic cancers cannot yet be made due to conflicting results.

In this meta-analysis, we found a statistically significant positive association between red meat intake and RCC. A positive association has previously been reported between red meat consumption and the risk of RCC (46, 47), while some meta-analyses found no associations between red meat intake and the risk of RCC (48). The difference could be explained by the inclusion of prospective studies only. However, we observed no associations between red meat and processed meat intake and the risk of BC. Meat plays a significant role in human nutrition because it offers high-quality protein as well many vital minerals, including iron, zinc, and vitamin B12 (49). Nevertheless, a high intake of red and processed meat is associated with an increased risk for diseases. A recent study has found the consumption of Neu5Gc (N-Glycolylneuraminic acid) from red meat increases the risk of cancers (50). On the cell surface of the majority of mammals, Neu5Gc exists naturally. Due to the inactivation of the gene encoding CMP-N-acetylneuraminic acid hydroxylase, it is not present in human tissues. Whenever people eat too much red meat, Neu5Gc enters cells, where the immune system recognizes it as a foreign threat and produces antibodies to destroy it. Repeated consumption of these meats will trigger this immune response, leading to long-term chronic inflammation and an increased risk of tumor formation (51, 52).

The association between alcohol intake and the risk of BC is not consistent. A meta-analysis reported that in males, alcohol may increase the risk of BC in a dose-independent manner (53), whereas another study reported that there is no material relationship between high levels of alcohol consumption and BC risk (17). No significant association was found between alcohol consumption and BC risk in our results, which is consistent with previous meta-analyses (54). However, there was a statistically significant and persuasive relationship between alcohol and RCC. The findings from our meta-analysis support the previous hypothesis that alcoholic beverage intake is inversely associated with risk of RCC (17, 55, 56).

There are various theories as to how alcohol may lower the risk of kidney cancer, but the exact processes remain elusive: (1) Moderate alcohol consumption is linked to lower rates of type 2 diabetes and hyperinsulinemia, which may be risk factors for kidney cancer; (2) Antioxidant phenolic substances that can prevent cell cycle progression and reduce oxidative stress may be present in alcoholic beverages (57, 58); (3) The diuretic impact of alcohol, which increases urine volume and shortens exposure times, is another theory that might apply (59). (4) It is worth noting that the relationship between alcohol intake and RCC risk would seem to be influenced by inter-individual germline variation in alcohol-metabolizing genes (60). Taken together, to corroborate our findings, further investigate other particular demographic groups, and identify possible regulator genes or biomarkers based on molecular epidemiology, additional high-quality studies should be carried out.

Our findings did not support the conclusion that tea consumption is related to a decreased risk of RCC, which is consistent with previous studies (61, 62). Our findings of an inverse correlation between tea consumption and BC were indeed consistent with the findings of several previous studies (63, 64). Studies in animals have demonstrated that some tea constituents may have a restraining effect on BC development (65). This inhibitory activity is believed to be primarily due to the antioxidative and possibly antiproliferative effects of polyphenol compounds (such as epigallocatechin gallate), through inhibition of metabolic or signal-transduction pathways (66, 67).

In our meta-analysis, there was no significant statistical association between coffee drinking and BC risk, and no correlation was detected in earlier cohort studies (68–70). Our results support that the consumption of coffee is associated with a reduced risk of RCC. Results from previous analyses provide evidence of the benefit of caffeinated coffee (71), while other studies demonstrate no significant association between coffee consumption and RCC (72). According to epidemiological research, coffee consumption was inversely associated with the risk of several cancers (73). Many studies have suggested mechanisms by which coffee intake reduces RCC risk. For example, the presence of phytochemicals, such as caffeine, chlorogenic acid, and caffeic acid, may be responsible for enhanced insulin sensitivity (74). Furthermore, convincing evidence showed that being overweight may increase the risk of developing RCC (75). However, caffeine may enhance energy balance by suppressing appetites, raising basal metabolic rate, and stimulating food-induced thermogenesis to regulate weight (76). The exact mechanism by which obesity raises the risk of RCC is uncertain, but the accumulation of body fat directly affects insulin levels in the body, thereby elevating the probability of hypertension, both of which are strongly associated with the development of RCC (77, 78).

The high versus low meta-analysis and dose–response analysis revealed no association between legumes and the risk of RCC or BC. To support our findings, additional well-designed prospective studies will be required, taking into account the limitations of the included research (69). In addition to being an excellent source of fiber, legumes also contain certain bioactive substances, which are peptides formed from proteins that have been shown in *in vitro* experiments to have antioxidant effects (79). We observed an inverse association between egg consumption and BC risk, which is different from previous meta-analyses (80, 81). This inconsistency could be explained by the inclusion of new studies. Egg yolks contain accessible xanthophyll carotenoids, which have anti-inflammatory and

antioxidant properties and may be able to prevent cancers (82). Taking into account the limitations of the included studies and the low credibility of meta-evidence confidence, this result should be considered with caution. In our meta-analysis, no association was found between fish consumption and RCC risk or BC risk. Similarly, a previous cohort study has found no association between BC risk and fish consumption (83). On the contrary, an investigation reported a beneficial effect (84). Multiple studies have suggested that ω-3 fatty acids which is abundant in fatty fish may have a reducing influence on the chance of developing cancer (84–86). Further well-designed prospective studies are required to further investigate the impact of fish on RCC and BC due to the dearth of studies in this area.

4.4. Limitations of the study

Unfortunately, this study has some technical and biological limitations. First, substantial heterogeneity exists in some analyses, which could not be further explored due to the limited number of studies. The heterogeneity between studies was not completely omitted after subgroup analysis, and the interpretation of the findings should be done with caution. Second, food frequency questionnaires, which rely on recall are a common source for estimates of food category intake. Therefore, measurement errors seemed inevitable and can lead to the misclassification of exposures. In addition, since the food categories in each food questionnaire were not fully standardized, the food items in our meta-analysis were only counted according to broad categories, and the completeness and credibility of this analysis would be higher if more detailed and standardized food categories were available in the future. Of note, sex is a significant factor in epidemiological studies, but the data were not sufficient to support analyses by sex of the meta-analysis. As a result, some of these results need to be evaluated carefully. Therefore, it is meaningful to design more effective and comprehensive prospective cohort studies to investigate associations between food groups and urological cancers risk.

5. Conclusion

Overall, our meta-analysis collectively tends to show some correlation between food group intake and urological cancers. We found that a high intake of red meat increases the risk of RCC. High fruit, vegetable, alcohol, and coffee intake may play a protective role against RCC. A high intake of tea may decrease the risk of BC. For urethral cancer and renal pelvis carcinoma, the number of related studies is too small to support meta-analysis. In summary, these findings may contribute to developing food-based dietary recommendations for preventing urologic cancers.

Author contributions

JQ: conceptualization, investigation, data curation, software, and writing–original draft. PA: conceptualization and methodology. DJ: data curation and writing–original draft preparation. YJ: visualization and investigation. SW and XZ: software and validation. YL: writing-reviewing and funding acquisition. JL: writing–reviewing and editing. CZ: supervision and project administration. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1154996/full#supplementary-material

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Association between ultra-processed foods and risk of cancer: a systematic review and meta-analysis

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Background: Despite increasing evidence that has shown the association of ultra-processed foods (UPFs) with cancer risk, the results remain inconclusive. We, therefore, conducted the meta-analysis to clarify the association by including recently published studies.

Methods: A comprehensive search was conducted in PubMed, Embase, and Web of Science to identify all relevant studies from inception to January 2023. To pool data, fixed-effects or random-effects models were used where appropriate. Subgroup analyses, sensitivity analyses, and publication bias tests were performed.

Results: A total of 13 studies (4 cohort studies and 9 case–control studies) were included in the analysis, with a total of 625,738 participants. The highest UPFs consumption was associated with increased risk of colorectal cancer (OR = 1.23, 95% CI: 1.10–1.38), colon cancer (OR = 1.25, 95% CI: 1.14–1.36), and breast cancer (OR = 1.10, 95% CI: 1.00–1.20) but not rectal cancer (OR = 1.18, 95% CI: 0.97–1.43) and prostate cancer (OR = 1.03, 95% CI: 0.93–1.12). In addition, the subgroup analyses showed that a positive association between UPFs consumption and colorectal cancer was observed among men (OR = 1.31, 95% CI: 1.15–1.50), whereas no significant association was observed among women (OR = 1.10, 95% CI: 0.94–1.29).

Conclusion: The present meta-analysis suggests that high UPFs consumption is associated with a significantly increased risk of certain site-specific cancers, especially the digestive tract and some hormone-related cancers. However, further rigorously designed prospective and experimental studies are needed to better understand causal pathways.

KEYWORDS

ultra-processed foods (UPFs), colorectal cancer, breast cancer, systematic review, meta-analysis

1. Introduction

Cancer is one of the leading causes of death worldwide (1). According to a report from the World Health Organization, cancer is responsible for almost 10 million deaths per year, and every sixth death in the world is attributed to cancer (2, 3). It is expected that new cases of cancer will increase to 28.4 million by 2040, and the burden of cancer will double in the

next 20 years. Therefore, there is a need for more research on exploring and intervening in potential risk factors for cancer. It is reported that a substantial proportion of cancer cases could be prevented by eliminating risk factors (4). In addition to genetic predisposition, numerous modifiable factors have also been implicated in regulating tumorigenesis and cancer development, such as a sedentary lifestyle (5) and unhealthy dietary patterns (6). Thus, further study on lifestyle modification is warranted to better identify targets for the intervention of cancer.

Evidence of the link between the degree of food processing and increased cancer risk is emerging (7). Recent global estimates demonstrate dramatical changes in the processing of foodstuffs, which have witnessed a marked increase in processed food availability, especially during the historically unprecedented SARS-CoV-2 pandemic lockdown setting (8), with ultra-processed foods (UPFs) accounting for more than half of total energy intake (9). Indeed, UPFs are usually characterized by their poor nutritional composition, high energy density, and the presence of components derived from food processing or packaging, with potential carcinogenic properties. Previous studies have investigated the possible linkage between UPFs consumption and chronic non-communicable diseases (10, 11) and related morbidity (12) and mortality (13), including three systematic reviews on cancer (14–16). Nevertheless, existing systematic reviews evaluating the associations of UPFs consumption with cancer did not get quantitative synthesis results limited by the number of studies available for inclusion (14). In addition, although there is evidence suggesting the potential carcinogenic pathways underlying the association between UPFs and cancer risk, previous studies have only focused on the most common cancer sites, such as breast cancer, and no previous study has assessed the effect of UPFs on a comprehensive range of cancers. Furthermore, several additional studies have been published on the effect of UPFs consumption on various types of cancer (17); however, these results are conflicting, leading to insufficient generalizability of the findings.

To bridge the knowledge gap, in the present study, we conducted the current comprehensive and updated systematic review and further explored the association between UPFs consumption and different types of cancer.

2. Methods

The present systematic review and meta-analysis were carried out in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18).

2.1. Search strategy

The electronic databases of PubMed, Embase, and Web of Science were comprehensively searched for relevant studies from inception to January 2023. The following search terms were used: (ultra-processed OR processed food OR ultraprocessed) and (neoplasm OR tumor* OR cancer* OR malignant* OR carcinoma OR adenocarcinoma OR neoplasia). There were no restrictions on language. Further studies and relevant gray literature were manually searched by checking the references of the potentially eligible articles.

2.2. Inclusion and exclusion criteria

This review included observational studies (cross-sectional, cohort, and case–control) that investigated the association between UPFs consumption and cancer risk and reported the results as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs). The UPFs were defined by the NOVA food classification system. The outcome of interest is specific cancer type, and non-malignant abnormalities (e.g., adenomas) were not considered. We excluded experimental studies, review articles, letters, editorials, and abstracts without full texts.

2.3. Data extraction and quality assessment

Data extraction was carried out from eligible articles using a predefined checklist. The following information was extracted: the first author's name, year of publication, country, design, follow-up time (for cohort studies), total subjects, the number of cases, type of cancer, age, gender, exposure, methods of exposure assessment, ORs, or RRs (95% CIs), and adjusted (confounding) variables. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the included studies (19). Scores ranged from 0 to 9 with a score of $\geq$7 being considered as of high quality. Data collection and quality assessment processes were independently performed by YL and G-PW. Any discrepancies in data extraction and quality assessment were resolved by discussion with the third author.

2.4. Statistical analysis

All data were analyzed using STATA version 14.0 (StataCorp, College Station, TX, USA). The ORs with 95%CIs for UPF consumption and cancer risk were pooled using fixed-effects or random-effects models where appropriate. Heterogeneity was assessed using the I^2 value and Q-test (P-heterogeneity). If the P-heterogeneity of the Q-test $\leq$ 0.10 or $I^2 \geq$ 50% indicated a high degree of heterogeneity among studies, then a random-effects model was used. UPFs consumption was analyzed as a continuous variable (per 10% increment) and as a categorical variable. Subgroup analyses were conducted according to a series of key variables that might influence the association between UPFs and cancer, including tumor subtype, sex (for colorectal), and menopausal status (for breast cancer). Sensitivity analyses were carried out by removing each study and recalculating the pooled effect estimates (i.e., one study removed analysis). Publication bias was assessed by formal testing by Egger's test and Begg's test.

3. Results

3.1. Study characteristics

The flow chart of the literature screening and selection process is presented in Figure 1. A total of 13 studies met our inclusion criteria and were included in the present systemic review (17, 20–31). All the studies with a total sample size of 625,738 participants were published from 2018. Of these studies, four were cohort

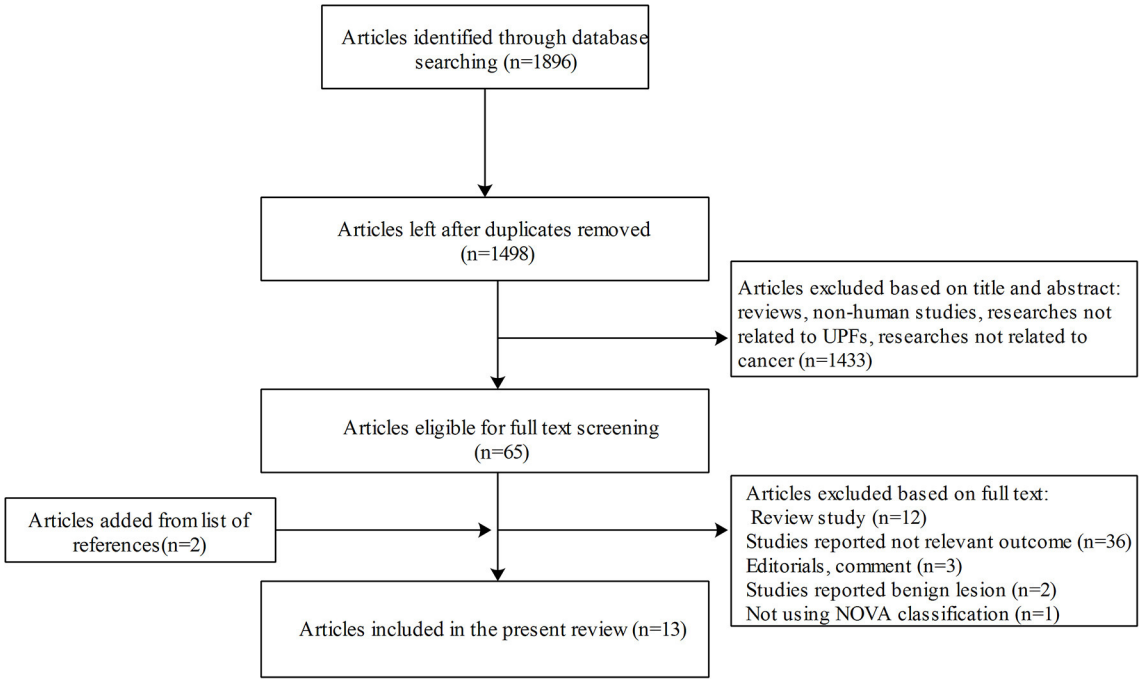

FIGURE 1
Flow diagram of study selection.

studies and nine were case–control designs. In total, five studies were conducted in America, five in Europe, two in Africa, and one in Asia. Of the 13 eligible studies, six focused on colorectal cancer, six on breast cancer, four on prostate cancer, and two on pancreatic cancer, chronic lymphocytic leukemia, and central nervous system tumors. The degree of processing of foods was classified according to the NOVA classification system. The general characteristics of included studies are described in Table 1.

3.2. Meta-analysis

3.2.1. UPFs consumption and colorectal cancer risk

In total, three prospective cohort studies with a total of 508,654 participants and three case–control studies with a total of 8,424 participants reported the association between UPFs consumption and the risk of colorectal cancer. The highest consumption of UPFs was found to be associated with an increased risk of colorectal cancer. The pooled OR was 1.23 (95% CI: 1.10–1.38), with moderate evidence of heterogeneity (I^2 = 67.2%, P = 0.01, Figure 2A). There was no evidence of significant publication bias with Begg's test (P = 0.54) and Egger's test (P = 0.27). Sensitivity analyses suggested that the pooled estimate of colorectal cancer risk did not apparently modify any one study, confirming the stability of the present results. Each 10% increase in UPFs consumption was associated with a 4% higher risk of colorectal cancer (OR = 1.04, 95% CI: 1.01–1.07; I^2= 55.9%, P=0.06, Figure 2B). Subgroup analyses showed that a positive association between UPF consumption and colorectal cancer was observed among men (OR = 1.31, 95% CI: 1.15–1.50), whereas no significant association was observed among women (OR = 1.10, 95% CI: 0.94–1.29). The subgroup analyses are presented in Table 2.

3.2.2. UPFs consumption and breast cancer risk

In total, two cohort studies with a total of 279,585 participants and four case–control studies with a total of 5,059 participants assessed the link between UPFs consumption and breast cancer risk. This meta-analysis showed that greater UPFs consumption was associated with higher odds of breast cancer (OR: 1.10, 95%CI: 1.00–1.20). Heterogeneity between studies was not significant (I^2 = 45.4%, P = 0.10, Figure 3A). Publication bias was tested by Egger's test (P = 0.03) and Begg's test (P = 0.19). Each 10% increase in UPFs consumption was not associated with the risk of breast cancer (OR = 1.03, 95% CI: 0.98–1.09, I^2= 58.8%, P = 0.09, Figure 3B).

3.2.3. UPFs consumption and prostate cancer risk

In total, two cohort studies with a total of 220,247 participants and two case–control studies with a total of 6,123 participants reported the association between UPFs consumption and prostate cancer risk. There was no significant association between UPFs consumption and prostate cancer. The pooled OR (95%CI) for the highest UPFs consumption was 1.03 (0.93–1.12), with no significant heterogeneity between studies (I^2 = 0%, P = 0.75, Figure 4).

3.2.4. UPFs consumption and other types of cancer

In total, two studies were available regarding three other types of cancer including pancreatic cancer, chronic lymphocytic

TABLE 1 Characteristics of included studies.

Author	Location	Sample size	Sex: female, %	Age	Design of study	Type of cancer	UPFs assessment	Comparison	NOS score
Romaguera et al. (20)	Spanish	7,834	49.9	62.9 ± 11.9	CCS	Colorectal, breast, and prostate cancer	FFQ	Tertile 3 vs. Tertile 1. Each 10% increase of UPFs	7
Fiolet et al. (21)	French	104,980	78.26	42.8 ± 14.8	CS	Colorectal, breast, and prostate cancer	24 h dietary records	Quartile4 vs. Quartile 1. Each 10% increase of UPFs	8
Jafari et al. (29)	Iran	213	NR	40–75	CCS	Colorectal cancer	FFQ	Tertile 3 vs. Tertile 1	8
Wang et al. (17)	America	206,248	77.53	25–75	CS	Colorectal cancer	FFQ	Quintile 5 vs. Quintile 1. Each 10% increase of UPFs	8
Trudeau et al. (22)	Canada	3,910	0	64 ± 7	CCS	Prostate cancer	FFQ	Quartile4 vs. Quartile 1	7
Jacobs et al. (23)	African	792	100	54.6 ± 12.9	CCS	Breast cancer	QFFQ	Tertile 3 vs. Tertile 1	8
El Kinany et al. (24)	Morocco	2,906	50.7	56.0 ± 13.9	CCS	Colorectal cancer	FFQ	Tertile 3 vs. Tertile 1	8
Solans et al. (25)	Spanish	1,864	41.4	63.9 ± 10.8	CCS	Chronic lymphocytic leukemia	FFQ	Tertile 3 vs. Tertile 1. Each 10% increase of UPFs	7
Zhong et al. (26)	America	98,265	52.53	65.6 ± 5.7	CS	Pancreatic cancer	DHQ	Quartile4 vs. Quartile 1	8
Romieu et al. (27)	Latin American	1,050	100	40 (31–45)	CCS	Breast cancer	FFQ	Tertile 3 vs. Tertile 1	8
Queiroz et al. (30)	Brazil	118	100	53.1 ± 13.8	CCS	Breast cancer	FFQ	Categories of UPFs	8
Chang et al. (31)	UK	197426	54.6	58.0 ± 8.0	CS	Various site-specific cancers	24 h dietary records	Quintile 5 vs. Quintile 1. Each 10% increase of UPFs	8
Esposito et al. (28)	Italy	132	40.9	54.3 ± 13.5	CCS	Central nervous system tumors	FFQ	Quartile4 vs. Quartile 1	8

UPFs, ultra-processed foods; NR, no report; FFQ, food frequency questionnaire; DHQ, a diet history questionnaire; CCS, case–control study; CS, cohort study; NOS, Newcastle–Ottawa Quality Assessment Scale.

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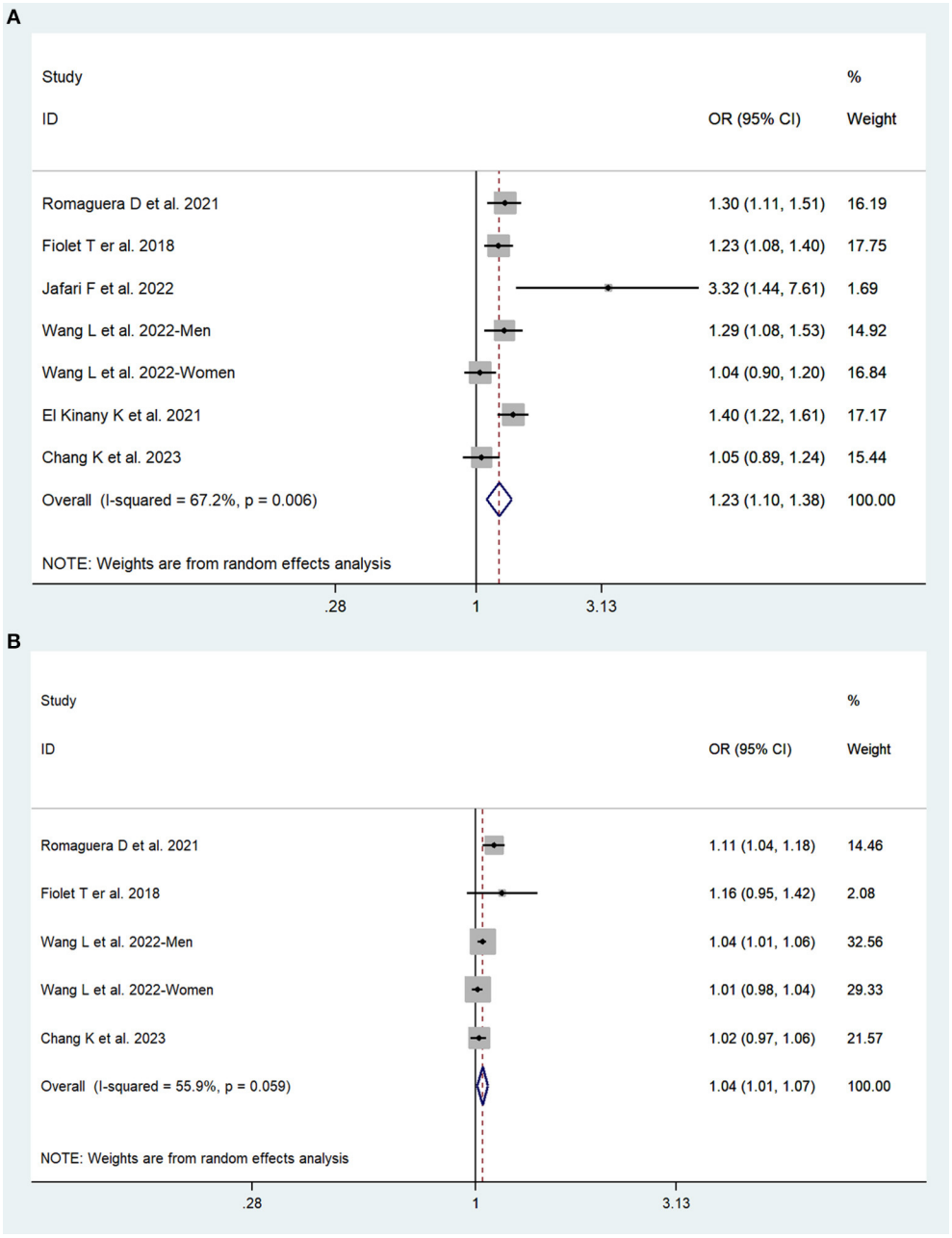

FIGURE 2
Forest plots of pooled ORs for UPFs and colorectal cancer. **(A)** The highest category UPFs compared with the lowest category UPFs. **(B)** 10% increase in UPFs consumption.

leukemia, and central nervous system tumors. One study investigated the link between UPFs consumption and other multiple cancer sites with the findings shown in Figure 4.

4. Discussion

The present systematic review comprehensively quantified the association between UPFs consumption and various types of cancer risk integrating four prospective cohort studies and nine case–control studies. Our findings indicated that greater intake of UPFs was associated with increased odds of colorectal and breast cancer. Every 10% increase in the proportion of UPFs in the diet was associated with a 4% higher risk of colorectal cancer. In addition, the results of subgroup analyses proposed that a significant association of UPFs consumption with an increased risk of colorectal cancer was noted in men but not among women.

Our findings provided robust evidence that a high intake of processed foods increases the risk of colorectal cancer, which has been previously reported in recent systematic reviews (32). For example, a meta-analysis of prospective cohort studies showed that compared with the lowest category of processed meat intake,

TABLE 2 Subgroup analyses for UPFs consumption and cancer risk.

Type of cancer	Number of studies	OR (95% CI)	I^2(%)	*P*
Colorectal cancer	6			
Categorical variable	6	1.23 (1.10–1.38)	67.2	0.01
Continuous variable 10% increase in UPFs	4	1.04 (1.01–1.07)	55.9	0.06
Anatomic subsites				
Colon cancer	4	1.25 (1.14–1.36)	19.3	0.28
Rectal cancer	4	1.18 (0.97–1.43)	62.0	0.03
Gender				
Men	2	1.31 (1.15–1.50)	0	0.78
Women	2	1.10 (0.94–1.29)	29.0	0.24
Breast cancer	6			
Categorical variable	6	1.10 (1.00–1.20)	45.4	0.10
Continuous variable 10% increase in UPFs	3	1.03 (0.98–1.09)	58.8	0.09
Menopausal status				
Premenopausal breast cancer	5	1.24 (0.95–1.60)	50.2	0.09
Postmenopausal breast cancer	4	1.08 (0.96–1.20)	40.2	0.17
Prostate cancer	4			
Categorical variable	4	1.03 (0.93–1.12)	0	0.75
Continuous variable 10% increase in UPFs	3	0.99 (0.96–1.02)	0	0.83
Tumor aggressiveness				
Low-grade prostate cancers	2	0.93 (0.76–1.14)	0	0.60
High-grade prostate cancers	2	1.05 (0.84–1.32)	0	0.56
Pancreatic cancer	2	1.24 (0.98–1.57)	59.8	0.12
Chronic lymphocytic leukemia	2	1.08 (0.80–1.44)	0	0.93
Central nervous system tumors	2	1.20 (0.87–1.66)	69.2	0.07

the highest category was associated with higher overall colorectal cancer risk (33). Similarly, significant positive associations were also observed for colon cancer. In addition, our results are also consistent with previous meta-analyses and broaden whole of dietary pattern analyses. The systematic reviews found that the dietary inflammatory index characterized by excess consumption of processed foods, including processed meats, sweets, fried foods, and refined grains appears to be associated with cancer risk (34), while Mediterranean-style diets, which are rich in fruits, vegetables, extra virgin olive oil, whole grains, and other unprocessed or minimally processed foods, reduce the risk of colorectal cancer by 17% (35). However, these dietary patterns are often unable to determine the industrial processing level of foods. The objective and standardized criteria of the NOVA classification system were used in all the included studies to distinguish UPFs from other foods based on the nature, extent, and purpose of food processing (36–38), which can provide novel insights into understanding the role of food processing level in the development of cancer (39). Of note, the stratified analyses showed a positive association between UPFs consumption and increased risk of colorectal cancer in men but not among women. The findings are somewhat concordant with another previous ultra-processed food inflammation study, which suggests that men are more predisposed to the carcinogenic effects of diet (40). Potential explanations for such different sex patterns may involve the effect of sex hormones or genetics (41). Further studies are required to clarify these findings.

In the analysis of breast cancer, a positive association was found between higher UPFs consumption and breast cancer risk, which is consistent with those from the prior meta-analyses. Previously, a meta-analysis combining data from 15 studies showed that the highest processed meat intake was related to a 9% increased risk of breast cancer compared with the lowest intake (32). In another previous analysis, a similar magnitude positive association was found between processed meat intake and breast cancer risk by comparing the highest with the lowest category (42). It seems that menopausal status may influence the association between UPFs consumption and breast cancer risk. It was found that higher processed meat consumption was associated with a 9% greater risk of postmenopausal breast cancer; however, such a positive association was not observed for premenopausal breast cancer (42). The present study examining the association by menopausal status suggested no significant associations with the intake of

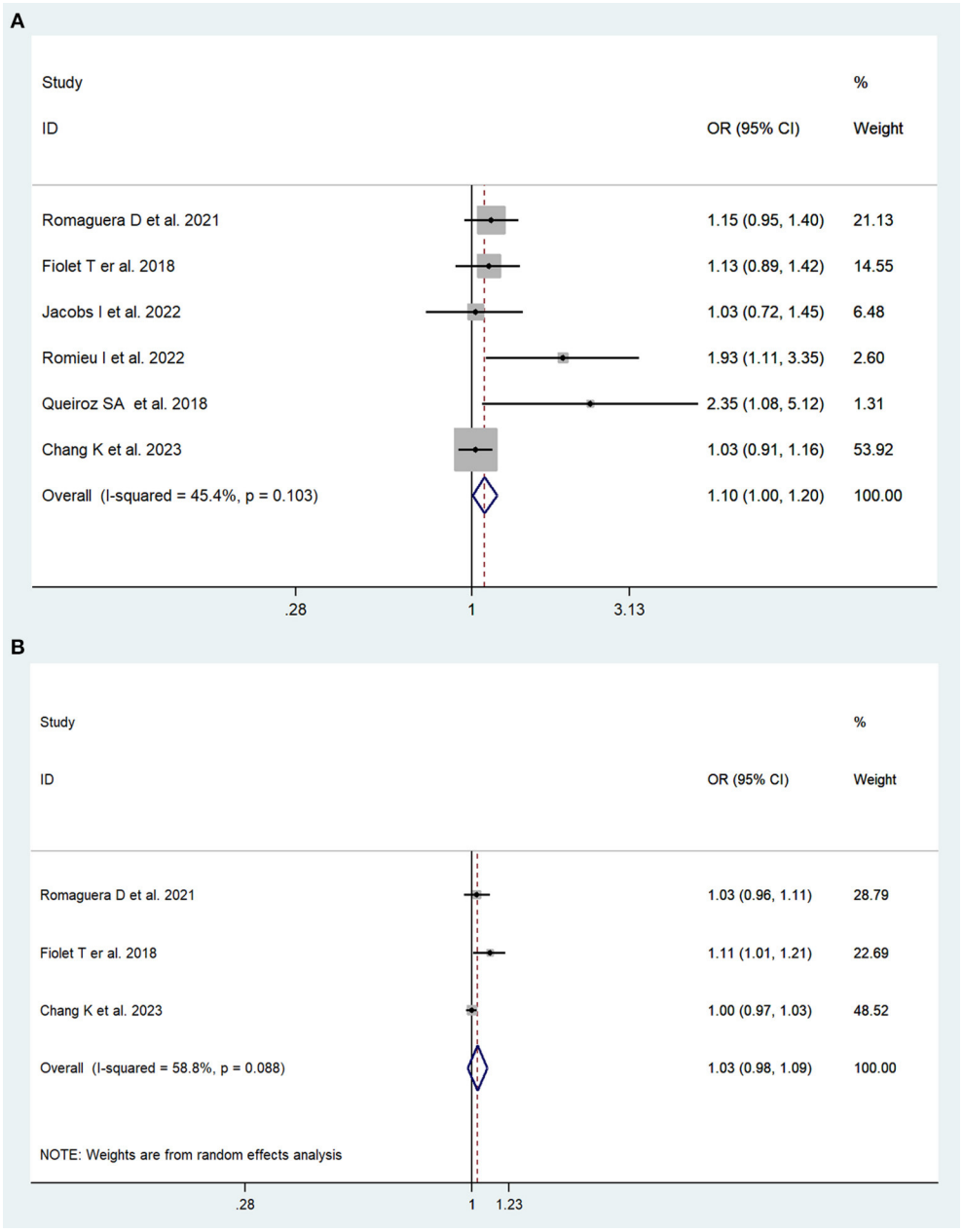

FIGURE 3
Forest plots of pooled ORs for UPFs and breast cancer. **(A)** The highest category UPFs compared with the lowest category UPFs. **(B)** 10% increase in UPFs consumption.

UPFs for breast cancer in premenopausal and postmenopausal women. In addition, breast cancer is a heterogeneous disease, with potentially distinct etiology for different hormone receptor statuses, and it has been suggested that estrogen receptor-positive breast tumors (ER+) are more strongly associated with hormone-related factors than estrogen receptor-negative tumors (ER-) (43); therefore, assessing risk factors for breast cancer incorporating molecular pathological information may confer even greater insights (44). ER status was reported in one included study; it shows a significant association for UPFs among ER + breast cancer, while no association was observed in ER-tumor risk (27). Thus, further studies are required to understand the heterogeneity of this relationship by molecular subtypes according to the menopausal status of breast cancer.

The present meta-analysis has some strengths. This is the first meta-analysis comprehensively quantitatively summarizing the evidence on the association between UPFs consumption and various types of cancer, providing strong implications for dietary policies and guidelines. In addition, the present meta-analysis included large sample size and high-quality epidemiological data, with the standardized assessment of processed diet intake using the NOVA system, along with sensitivity analyses and

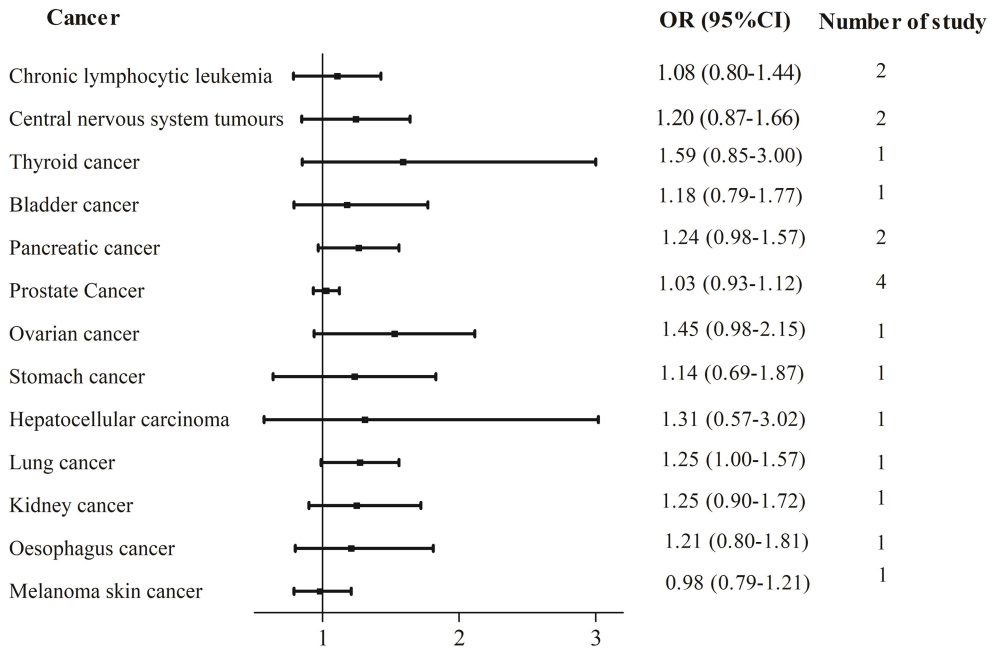

FIGURE 4
Forest plots of pooled ORs for UPFs and other types of cancer.

detailed subgroup analyses, ensuring greater precision and reliability of the results. Despite the interesting results of the present meta-analysis, some limitations should be considered. First, although we include several prospective cohorts with large sample sizes, some of the included studies are case–control designs, which does not allow for the identification of a causal link between the exposure and outcome. Second, cancer is often described as the result of complex interactions between biological, social, and psychological factors, although most included studies have adjusted for a wide range of potential confounders, other unmeasured or inadequately measured factors, for example, genetic and environmental factors, may result in residual confounding. Third, of the articles included, UPFs intake was generally evaluated through food frequency questionnaires or food records that were not specifically designed to identify UPFs, which can result in some degree of misclassification error, thus leading to bias associations. Further well-designed studies that address such limitations are warranted to confirm the associations.

Although the underlying pathways of our findings have not yet been fully elucidated, several mechanisms have been proposed to account for the potential carcinogenicity of UPFs. First, UPFs often have a poorer nutritional quality compared to minimally processed foods, which tend to be rich in unfavorable nutritional components, such as saturated fat, added sugar, energy density, and salt, along with lower fiber and vitamins. Meanwhile, a randomized controlled trial conducted in inpatients found that more ultra-processed diet intake could lead to excess calorie intake and substantial weight gain (45). Poor diet quality together with obesogenic properties are all important factors in driving their detrimental impact on cancer. Second, food additives in the processing or packaging of UPFs, such as emulsifiers, preservatives, colors, and flavors, have also been suggested as potential mechanisms linking UPFs to higher cancer risk. Some contaminants in UPFs have been linked to proinflammation potential (46), endocrine-disrupting effects (47), and dysbiosis (48), which have been proven to promote carcinogenesis in epidemiological, clinical, and experimental studies. For example, it is notably suggested that consumption of UPFs was associated with an elevated level of inflammatory biomarkers, such as IL-6 concentration, which are involved in tumor progression at almost every step including initiation, progression, and metastasis (49). Moreover, consumption of UPFs may increase exposure to endocrine-disrupting chemicals, including bisphenol A and phthalates, leading to a persistent epigenetic change in genes and subsequently stimulating the proliferation of hormone-sensitive tissues in a tumor sense. In addition, UPFs could also alter gut microbiota composition and function unfavorably (50), which, in turn, increase cancer risk through multiple molecular signals, including inhibiting T-cell activity and promoting DNA damage (51). Further investigation into the mechanistic pathways is warranted to better identify targets for intervention.

5. Conclusion

The present systematic review showed that the high consumption of UPFs was associated with an increased risk of certain site-specific cancers, especially the digestive tract and some hormone-related cancers including colorectal and breast, providing a more comprehensive understanding of the potential implications in the development of cancer associated with processed diet. The findings support the importance of public

health by boosting prevention policies to limit UPFs consumption and promoting healthier nutritional status for primary cancer prevention. Furthermore, well-designed studies are needed to better strengthen the evidence of the association between UPFs and cancer risk.

Author contributions

G-YZ conceived and designed the study. G-PW, H-NC, G-QC, and YL analyzed the data. G-PW and YL wrote the manuscript. All authors provided critical revisions of the manuscript and approved the final manuscript.

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Conflict of interest

The 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 sulfur microbial diet and the risk of colorectal cancer precursors in older adults

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Background: Sulfur microbial diet (SMD), related to the enrichment of sulfur-metabolizing gut bacteria, has been confirmed to be linked to an elevated risk of early-onset colorectal adenoma in young females. However, it remains unclear whether SMD is associated with the risk of colorectal adenoma in older people, who are at greater risk for colorectal cancer.

Methods: All data on participants in this study were retrieved from the intervention arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening test. Participants' adherence to this dietary pattern was assessed using SMD score. Hazard ratios (HR) and 95% confidence intervals (CI) were adopted in Cox proportional hazards regression models to assess the link between SMD score and the incidence of colorectal adenoma in participants included in the study. Specific stratified analyses were constructed to assess whether this association changed in different conditions, whereas the robustness of the association was examined through sensitivity analyses.

Results: The mean baseline age of participants was 62.1 (SD 5.2) years (range 54.0–75.0 years). During 19,468,589 person-years of follow-up, 992 colorectal adenoma cases were documented in a total of 17,627 included participants. In a fully adjusted model, an increased risk of colorectal adenoma was determined in participants in the highest quartile of SMD score in comparison with those in the lowest quartile ($HR_{quartile4}$ vs. $HR_{quartile1}$ = 1.23; 95% CI: 1.02, 1.47; p = 0.017 for trend). This positive association between SMD score and adenoma risk was more evident in participants who were current or former smokers (p = 0.029 for interaction).

Conclusion: In this study, our results support a role for the SMD in the carcinogenicity of colorectal cancer precursors among older adults. Nevertheless, these results require validation through more research.

KEYWORDS

sulfur microbial diet, colorectal cancer precursors, cancer prevention, epidemiology, dietary pattern

Introduction

The second most prevalent cause of cancer mortality in the United States is colorectal cancer (CRC), which is considered to be the fourth most frequently diagnosed malignancy (1). Around 41,000 fatalities and 147,000 new cases of colorectal cancer are expected to be diagnosed by 2040 in the United States (2). Recently, research has increasingly indicated that the incidence of early-onset colorectal cancer is increasing rapidly, while the incidence of colorectal cancer after 50 years is gradually decreasing (3). However, it is undeniable that colorectal cancer diagnosed after the age of 50 years still constitutes the majority of newly diagnosed colorectal cancer. Approximately 90% of all colorectal cancer patients are diagnosed after 50 years of age (4). Identifying the high-risk factors for colorectal cancer in the elderly is still the focus of attention.

Colorectal traditional adenoma, as one of the recognized precursors of colorectal cancer, accounts for about 60–80% of sporadic CRC cases (5, 6). Although the majority of traditional adenomas can be removed by colonoscopy, recurrence is observed in nearly 50% of patients at 1 year of follow-up (7). Therefore, early identification of possible risk factors for traditional adenoma is of great significance to reduce the incidence of colorectal cancer. Recently, research has focused on the effects of diet, gut microbiota, and bacterial metabolites on the risk of colorectal cancer (8, 9). A sulfur microbial diet (SMD), which is related to the enrichment of sulfur-metabolizing gut microbiota, was constructed by Nguyen et al. through a large prospective study involving 51,529 U.S. males to investigate its effect on CRC risk (10). Specifically, SMD consists primarily of foods associated with CRC risk (such as decreased legumes and vegetables and an increase in processed meats), and long-term compliance to this diet was linked to a 43% greater risk of distal colon and rectum in this cohort (10). In a study involving a cohort of young female nurses aged 25–42, it was demonstrated that SMD is associated with a 58% increased risk of early-onset colorectal adenoma (11). Given the sex and occupational limitations of the populations included in the above studies, it remains unclear whether SMD is associated with the risk of colorectal adenoma in older individuals, who are at greater risk for colorectal cancer.

Hence, to determine the link between the SMD with the incidence of colorectal adenoma in the population older than 50, a prospective investigation in a large cohort of older adults was executed in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Materials and methods

Study design

Details of the protocol and statistical analysis plan of the PLCO trial are available on this website,[1] the recruitment plan for the study population and the objectives of the study had been thoroughly described in previous literatures (12–14). In brief, the PLCO trial recruited almost 155,000 men and women 55–74 years of age through competitively selected screening centers across the United States during the period of 1993–2001. In subsequent studies, the recruited population was assigned to the intervention or control arms in a 1:1 ratio by a reliable, secure randomized algorithm. The follow-up period continued until 2009–2018 to evaluate the effectiveness of early cancer screening (13). Each participant was required to submit a baseline questionnaire (BQ) covering self-administered risk factors. Additionally, the intervention arm participants were guided to fill in a dietary questionnaire (DQX) documenting daily dietary intake within 1 year and undergo screening programs including 60 cm flexible sigmoidoscopy (15). This trial was approved by the NCI Division of Cancer Prevention and Control, and written informed consent was obtained from the included participants.

Definition of study cohort

The association between SMD and the incidence of colorectal adenoma was determined by executing a detailed nested case–control investigation limited to the intervention arm. Considering the purpose of this study, participants with the following conditions were excluded: (1) did not return complete baseline information; (2) did not return a valid DQX (including the completion date was either missing, or was later to the date of death; at least eight missing frequency responses were available; extreme calorie intake for each gender); (3) confirmed cancer before DQX entry; (4) out of the incident adenoma cohort (the identification: a negative screen at baseline and either a negative screen at T3/T5 or a positive screen at T3/T5 with a left-sided adenoma found on follow-up to the screen); (5) with an inadequate flexible sigmoidoscopy (insertion ≥50 cm with ≥90% of mucosa visualized); (6) received diagnosis of cancer before colorectal adenoma; (7) received a diagnosis of colorectal adenoma before returning a valid DQX; (8) had a history of colon-linked comorbidity (such as Gardner's syndrome, ulcerative colitis, Crohn's disease or familial polyposis); (9) had a history of colorectal polyps (Figure 1). Ultimately, the included participants of the study reached 17,627 in total (992 incident colorectal adenoma cases [655 males; 337 females] and 16,635 controls [9,213 males; 7,422 females]). This study was carried out with the permission of the United States NCI (CDAS project "PLCO-1070").

Data collection and SMD score calculation

This research involved data concerning demographics, lifestyle, and medical history, including age, sex, race, body mass index (BMI), smoking status, smoking pack-years, as well as the history of aspirin consumption, diabetes, hypertension, diverticulitis or diverticulosis, polyps and colonoscopy in the past 3 years retrieved through BQ. Dietary information, including total energy intake, and dietary food or nutrient intake, can be obtained through DQX. The DQX, which counted information on the intake frequency of 137 food items and consisted primarily of 61 Willett FFQ items, has been shown to provide effective, adequate information about the dietary intake of participants over a 1-year period (16–18). The supplemental questionnaire (SQX) was employed to investigate some items not reported in BQ, such as physical activity level, defined as the summarized weekly minutes of self-reported moderate to vigorous activity.

1 https://cdas.cancer.gov/plco/

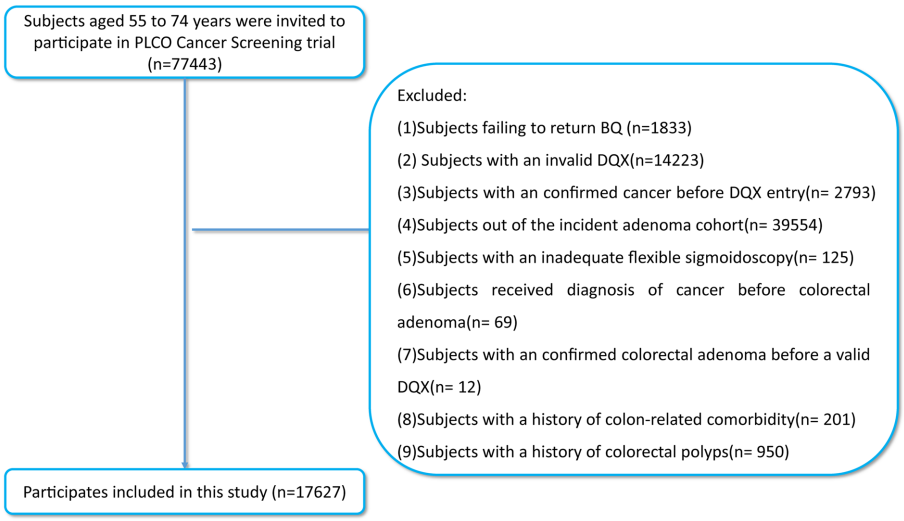

FIGURE 1
The flow chart of identifying subjects included in our study. PLCO, prostate, lung, colorectal, and ovarian; BQ, baseline questionnaire; DQX, dietary questionnaire.

In an initial prospective study of 51,529 male from medical specialties, researchers developed the SMD score by assessing the correlation coefficient of sulfur-metabolizing bacteria abundance in the stools to food groups (10). The detailed components of SMD followed: (1) the positive correlation group included processed meats, liquor and low-calorie drinks; (2) the negative correlation group included beer, fruit juice, legumes, other vegetables and sweets. However, the specific components of SMD developed in another prospective study of 214,797 male and female from medical specialties by the same way were different, compared with the original study (11). In detail, the positive correlation group included low-calorie beverages, French fries, red meats, and processed meats, while negative correlation group included fruits, yellow vegetables, whole grains, legumes, leafy vegetables, and cruciferous vegetables. Considering the contribution of whole grains and sweets to colorectal cancer risk (19–21), we adjusted the specific components of SMD based on previous prospective studies (10, 11, 22). The adjusted SMD score was the sum of the quartile values from 1 to 4 of 8 components, consisting of processed meats, liquor and low-calorie drinks (higher quartiles of intake indicate higher scores); and beer, fruit drinks, legumes, whole grain, other vegetables (higher quartiles of intake indicate lower scores). Thus, the SMD score with a total score ranging from 8 to 32 could be used to assess adherence to this pattern of intake, with higher score indicating greater adherence. Specific food intake and corresponding distribution scores can be found in Supplementary Table S1. In subsequent studies, SMD score were categorized into quartiles.

Assessment of conventional colorectal adenoma

As required in the PLCO trial, participants in the incident adenoma cohort are required to complete a screening colonoscopy at baseline. Subjects with negative results are allowed to enter a follow-up study and must complete at least one additional screening colonoscopy at T3 or T5. It means that none of the participants in this study had a diagnosis of colorectal adenoma at baseline, and all adenoma identifications during screening colonoscopy were confirmed by biopsied and further histological type. According to the current US guidelines for colonoscopy, conventional adenomas were categorized hierarchically: (1) any adenoma ≥1 cm, with high-grade dysplasia, or with tubulovillous or villous histology should be considered as advanced adenoma; (2) while only for the adenoma <1 cm and lacking advanced histology the diagnosis of non-advanced adenoma is considered (23).

Statistical analysis

In this study, the data of some covariates were observed to be missing to varying degrees. Hence, for categorical and continuous variables with missing values reported at <5%, namely smoking status, pack-years, as well as the history of colonoscopy, aspirin usage, hypertension, diabetes, family history of colorectal cancer, and BMI, the missing data was imputed utilizing the modal value and the median, respectively (24). As for the variable "physical activity level" with 22.8% missing data, which were assumed to be randomly distributed, multiple imputations were done to complete them (25). The details of imputation values can be found in Supplementary Table S2.

The Cox proportional hazards regression model was constructed with follow-up time as the time variable for estimation of the 95% confidence interval (CIs) and hazard ratios (HRs) of the relationship between SMD score and the risk of colorectal adenoma. It should be emphasized that the main outcome event in this research was the confirmation of adenoma. In this research, the follow-up time was defined as the data from DQX completion to the diagnosis of adenoma, cancer, fatality, loss of follow-up, or end of follow-up (December 31, 2009), whichever came first (Figure 2).

To investigate the existence of a linear trend between quartiles of SMD score and the risk of colorectal adenoma, each participant in the quartile was assigned the median value of the quartile. This was then considered as a continuous variable in cox regression to order to get its *p*-value, with the reference group considered to be the lowest quartile. As per prior literature review and clinical judgment, sex, race, age, and education levels, total energy intake, BMI, aspirin usage, smoking status, smoking pack-years, as well as the history of hypertension, diverticulitis or diverticulosis, diabetes, colonoscopy, family history of colorectal cancer in past 3 years and physical activity level were adjusted as covariates in multiple regression analyses (11, 22, 26). Meanwhile, 12,916 participants with complete data were selected to test whether the analysis result was influenced by missing data imputation by repeating the same multiple regression analyses. To present colorectal adenoma risk across the full range of SMD score, a restricted cubic spline model with three knots at the 10th, 50th, and 90th was constructed in this study (27).

The influence of various factors on the observed association of SMD score with risk of colorectal adenoma was assessed by means of a series of pre-selected subgroup analyses including age (>65 vs. ≤65 years old), sex (male vs. female), BMI (≤30 vs. >30 kg/m^2), smoking status (non-smokers vs. current/former smokers), smoking pack-years (≤median vs. >median years), family history of colorectal cancer (no vs. yes/possible), and history of aspirin consumption (no vs. yes). To verify the robustness of these findings, several sensitivity analyses were carried out: (1) exclusion of participants with a history of diverticulitis or diverticulosis; (2) exclusion of participants with a history of diabetes (more likely to have colorectal adenoma) (28); (3) exclusion of participants with a family history of colorectal cancer; (4) exclusion of colorectal adenoma cases observed within the first two and four years of follow-up to examine the likelihood of the observed association being caused by reverse causation; (5) Further adjusting model 2 for the Healthy Eating Index-2015 (HEI-2015) to determine if the observed link was diet quality-mediated.

All statistical analyses were completed through the software R 4.2.1. Furthermore, a two-tailed *p*-value less than 0.05 indicated the significance level.

Results

Population characteristic

A total of 17,627 participants [9,868 (55.08%) males and 7,759 (44.02%) females] were involved in the current analysis. The mean (standard deviation) baseline age of participants was 62.1 (5.2) years (range 54.0–75.0 years). The primary baseline features of participants per the quarters of the SMD score were depicted in tabular form (Table 1). In contrast with the lowest quartile (Q1), participants in the highest quartile (Q4) of SMD score tended to be younger, with more smoking pack-years, a higher BMI, a history of hypertension and diabetes, lower energy intake from diet, decreased physical activity level, and were less likely to be non-smokers, were regular users of aspirin, and had a family history of colorectal cancer. Additionally, in contrast to Q1, the participants of the Q4 of SMD score had increased intakes of processed meat, liquor, and low-calorie drinks but lower intakes of beer, fruit drinks, legumes, whole grains, and other vegetables.

Association between SMD score and conventional colorectal adenoma risk

In this study, a total of 992 newly diagnosed conventional colorectal adenomas were documented during 19,468,589 person-years of follow-up, with an overall incidence rate of 0.51 cases per 1,000 person-years. The mean (standard deviation) follow-up length was 11.04 (3.50) years. In univariable analysis, in contrast with Q1, the

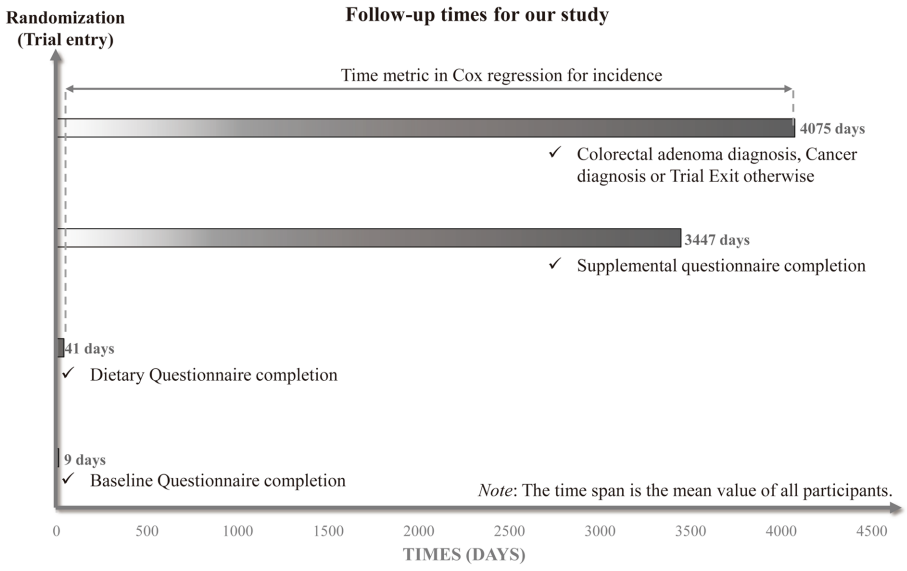

FIGURE 2
The timeline and follow-up scheme of our study.

TABLE 1 Baseline characteristics of study population according to overall sulfur microbial diet score.

Characteristics	Overall	Quartiles of overall sulfur microbial diet score			
		Quartile 1 (8–18)	Quartile 2 (19–20)	Quartile 3 (21–22)	Quartile 4 (23–32)
Number of participants	17,627	5,731	4,030	4,066	4,160
Sulfur microbial diet score	20.17 ± 3.18	16.45 ± 1.54	19.51 ± 0.50	21.47 ± 0.50	24.32 ± 1.40
Age	62.12 ± 5.17	62.50 ± 5.24	62.27 ± 5.16	62.03 ± 5.14	61.59 ± 5.06
Sex					
Male	9,868 (55.98%)	3,184 (59.28%)	2,279 (56.55%)	2,121 (52.16%)	2,284 (54.90%)
Female	7,759 (44.02%)	2,187 (40.72%)	1,751 (43.45%)	1,945 (47.84%)	1,876 (45.10%)
Race					
White	15,955 (90.51%)	4,758 (88.59%)	3,664 (90.92%)	3,710 (91.24%)	3,823 (91.90%)
Non-white	1,672 (9.49%)	613 (11.41%)	366 (9.08%)	356 (8.76%)	337 (8.10%)
Body mass index (kg/m^2)	27.09 ± 4.55	26.66 ± 4.45	27.12 ± 4.50	27.22 ± 4.56	27.49 ± 4.67
Smoking status					
Never	9,379 (53.21%)	2,960 (55.11%)	2,184 (54.19%)	2,189 (53.84%)	2,046 (49.18%)
Current	970 (5.50%)	170 (3.17%)	199 (4.94%)	221 (5.44%)	380 (9.13%)
Former	7,278 (41.29%)	2,241 (41.72%)	1,647 (40.87%)	1,656 (40.73%)	1,734 (41.68%)
Smoking pack-years	13.93 ± 23.50	12.42 ± 21.47	13.60 ± 23.81	13.59 ± 23.44	16.54 ± 25.47
Drinking status					
No	3,704 (21.01%)	1,095 (20.39%)	859 (21.32%)	864 (21.25%)	886 (21.30%)
Yes	13,923 (78.99%)	4,276 (79.61%)	3,171 (78.68%)	3,202 (78.75%)	3,274 (78.70%)
Aspirin use					
No	9,418 (53.43%)	2,738 (50.98%)	2,166 (53.75%)	2,220 (54.60%)	2,294 (55.14%)
Yes	8,209 (46.57%)	2,633 (49.02%)	1,864 (46.25%)	1,846 (45.40%)	1,866 (44.86%)
Family history of colorectal cancer					
No	15,655 (88.81%)	4,818 (89.70%)	3,588 (89.03%)	3,610 (88.79%)	3,639 (87.48%)
Yes	1,521 (8.63%)	429 (7.99%)	348 (8.64%)	361 (8.88%)	383 (9.21%)
possibly	451 (2.56%)	124 (2.31%)	94 (2.33%)	95 (2.34%)	138 (3.32%)
History of diabetes					
No	16,563 (93.96%)	4,972 (92.57%)	3,780 (93.80%)	3,856 (94.84%)	3,955 (95.07%)
Yes	1,064 (6.04%)	399 (7.43%)	250 (6.20%)	210 (5.16%)	205 (4.93%)
History of hypertension					
No	12,236 (69.42%)	3,753 (69.88%)	2,807 (69.65%)	2,824 (69.45%)	2,852 (68.56%)
Yes	5,391 (30.58%)	1,618 (30.12%)	1,223 (30.35%)	1,242 (30.55%)	1,308 (31.44%)
History of colonoscopy or test for blood in stool					
No	9,963 (56.52%)	2,772 (51.61%)	2,241 (55.61%)	2,354 (57.89%)	2,596 (62.40%)
Yes	7,664 (43.48%)	2,599 (48.39%)	1789 (44.39%)	1712 (42.11%)	1,564 (37.60%)
Energy intake from diet (kcal/day)	2087.90 ± 798.59	2368.11 ± 811.86	2148.95 ± 784.18	1957.31 ± 744.88	1794.64 ± 711.34
Physical activity level (min/week)	129.78 ± 111.27	147.55 ± 116.04	133.63 ± 110.61	124.26 ± 108.82	108.50 ± 103.68
Healthy Eating Index-2015	66.54 ± 9.69	57.51 ± 7.93	65.19 ± 7.04	69.90 ± 6.49	75.46 ± 6.24
Components of SMD intakes					
Processed meat (g/day)	12.84 ± 16.49	9.71 ± 14.05	13.21 ± 17.53	13.48 ± 17.09	15.90 ± 17.10
Liquor (g/day)	15.35 ± 57.51	8.90 ± 42.78	13.99 ± 54.02	16.47 ± 50.98	23.89 ± 78.48
Low-calorie drinks (g/day)	86.89 ± 210.11	41.73 ± 127.35	73.99 ± 183.73	92.54 ± 213.41	152.18 ± 286.08

(Continued)

TABLE 1 (Continued)

Characteristics	Overall	Quartiles of overall sulfur microbial diet score			
		Quartile 1 (8–18)	Quartile 2 (19–20)	Quartile 3 (21–22)	Quartile 4 (23–32)
Beer (g/day)	117.05 ± 403.21	136.04 ± 450.09	123.59 ± 376.37	105.69 ± 405.64	97.31 ± 358.30
Fruit drinks (g/day)	17.62 ± 99.17	22.19 ± 99.42	20.00 ± 106.69	15.12 ± 99.87	11.87 ± 89.82
Legumes (cups/day)	0.10 ± 0.10	0.16 ± 0.14	0.10 ± 0.09	0.07 ± 0.06	0.05 ± 0.04
Whole grain (servings/day)	1.49 ± 1.04	2.10 ± 1.13	1.57 ± 0.96	1.23 ± 0.82	0.88 ± 0.65
Other vegetables (servings/day)	1.96 ± 1.08	2.69 ± 1.14	2.03 ± 0.96	1.67 ± 0.83	1.25 ± 0.62

Descriptive statistics are presented as (mean ± standard deviation) and number (percentage) for continuous and categorical.

TABLE 2 Hazard ratios of the association of SMD score with the risk of colorectal cancer precursors.

Quartiles of SMD core	Number of cases	Person-years	Incidence rate per 100 person-years (95% confidence interval)	Hazard ratio (95% confidence interval)		
				Unadjusted	Model 1[a]	Model 2[b]
Quartile 1 (8–18)	271	59980.23	0.452 (0.401, 0.509)	1.000 (reference)	1.000 (reference)	1.000 (reference)
Quartile 2 (19–20)	208	44620.56	0.466 (0.407, 0.534)	1.02 (0.85, 1.22)	1.01 (0.85, 1.22)	1.00 (0.83, 1.20)
Quartile 3 (21–22)	246	45063.23	0.546 (0.482, 0.618)	1.20 (1.00, 1.41)	1.21 (1.01, 1.43)	1.20 (1.00, 1.43)
Quartile 4 (23–32)	267	45021.86	0.593 (0.526, 0.668)	1.28 (1.08, 1.51)	1.27 (1.07, 1.50)	1.23 (1.02, 1.47)
P-trend				0.003	0.004	0.017

[a]Model 1: model 1 was controlled with age (continuous), sex (male, female), race (white, no-white) and education levels (college below, college graduate, postgraduate).
[b]Model 2: model 2 was additionally controlled with smoking status (never, current, former), pack-years of smoking (continuous), BMI (continuous), aspirin use (no, yes), history of hypertension (no, yes), history of diabetes (no, yes), family history of colorectal cancer (no, yes), total energy intake (continuous), history of diverticulitis or diverticulosis (no, yes), history of colonoscopy in past 3 years (no, yes), and physical activity level (continuous).

participants of Q4 of SMD score were found to be at increased risk of colorectal conventional adenoma ($HR_{quartile4}$: $HR_{quartile1}$ = 1.28; 95% CI: 1.08, 1.51; p = 0.003 for trend Table 2). Subsequent to thorough adjustment for all possible confounders, the association of SMD score with the risk of conventional adenoma remained a positive one ($HR_{quartile4}$: $HR_{quartile1}$ = 1.23; 95% CI: 1.02, 1.47; p = 0.017 for trend Table 2). Notably, the repetition of the aforementioned analysis in a cohort of 12,916 participants with complete data resulted in similar data ($HR_{quartile4}$: $HR_{quartile1}$ = 1.24; 95% CI: 1.00, 1.54; p = 0.029 for trend; Supplementary Table S3).

Additional analyses

In the whole study population, the linearity assumptions between SMD score and risk of colorectal conventional adenomas were validated by the restricted cubic spline (p = 0.100 for nonlinearity; Figure 3). The result of subgroup analysis in this study suggested that the status of smoking significantly modified the association between SMD score and incidence of conventional adenoma (p = 0.029 for interaction; Table 3). When compared with the lowest quartile of SMD score, HRs (95%CI) of incidence for the highest quartile of SMD score in the subsets of current or former smoker factors was 1.43 (1.12, 1.83). In addition, the positive association between SMD score and colorectal adenoma risk was depicted as more pronounced in males ($HR_{quartile4}$: $HR_{quartile1}$ = 1.28; 95% CI: 1.02, 1.62; Table 3) than in females ($HR_{quartile4}$: $HR_{quartile1}$ = 1.07; 95% CI: 0.77, 1.51; Table 3), though the interaction test was not statistically significant (concerning interaction p = 0.192). No other interactions were statistically significant (concerning interaction all $p > 0.05$; Table 3). The sensitivity analysis showed the initial associations of SMD score with risks of conventional adenoma were not impacted considerably through the exclusion of participants with specific preset conditions or further adjusting Healthy Eating Index-2015 (all $p < 0.05$ for trend; Table 4), which fully supports the stability of our findings.

Discussion

Based on a prospective large cohort study with adequate colonoscopy, the link between the SMD score and colorectal adenoma risk in the older population was assessed. According to the findings, following the SMD for a prolonged period of time was linked to an elevated risk of developing colorectal adenoma. The dose–response analysis also showed a linear trend of increasing the risk of colorectal adenoma with SMD score, suggesting that the risk of adenoma may increase in parallel with the increase in SMD score. The robustness of these findings was confirmed by subsequent sensitivity analysis. Our subgroup analysis showed that the positive association of SMD score with colorectal adenoma risk was only predominantly found in males, but not in females.

To develop a specific dietary pattern related to sulfur-metabolizing bacteria, Nguyen et al. analyzed the correlation of sulfur-metabolizing bacteria in stool samples with respective dietary components from 307 males (10). In his research, two main sulfur-metabolizing bacteria, *Erysipelotrichaceae bacterium 21_3* and *Bilophila wadsworthia* were identified to be associated with dietary (10), which has been previously confirmed to notably increase in the gut of patients with colorectal cancer or adenoma (29–31). Increasingly, research has shown that diet has a substantial influence on gut microbes, leading to an elevated risk

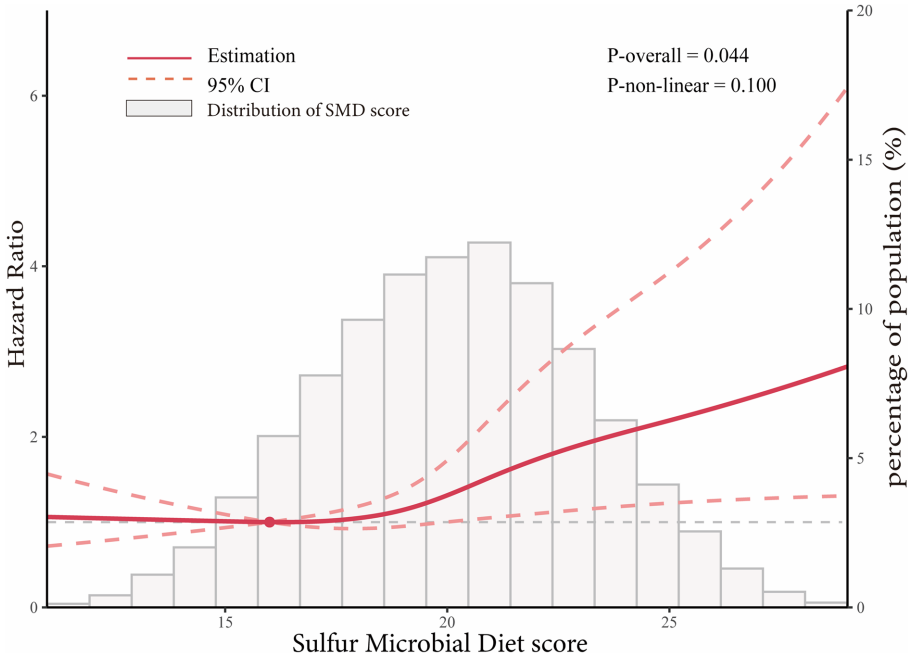

FIGURE 3
Dose–response analysis on the association of SMD score with the risk of colorectal adenoma (including total adenoma, advanced adenoma and non-advanced adenoma). Hazard ratios was adjusted for age, sex, race, education levels, smoking status, pack-years of smoking, BMI, aspirin use, history of hypertension, history of diabetes, family history of colorectal cancer, total energy intake, history of diverticulitis or diverticulosis, history of colonoscopy in past 3 years, and physical activity level.

of developing colorectal tumors via the colorectal adenoma-carcinoma sequence (32–34). It is well-recognized that sulfur-metabolizing microbes are involved in the conversion of dietary sulfur into hydrogen sulfide (H_2S) in the gut, which contributes to the increased prevalence of colorectal tumors (35–38). Specifically, high concentrations of hydrogen sulfide in the intestine may raise the risk of colorectal tumors by damaging DNA in epithelial cells (39), promoting immune cell alterations associated with colorectal cancer (36), and damaging the bilayer of the intestinal mucosa (40, 41).

Notably, SMD score and smoking status depicted a significant interaction concerning the increased colorectal adenoma risk in the subgroup analysis ($p = 0.029$ for interaction). This means that participants who were former or current smokers would have an elevated risk of colorectal adenoma in comparison to participants who never smoked with the same SMD score, which was consistent with the previous study (22). One of the major risk factors for colorectal adenoma or colorectal cancer is considered to be smoking (42–44). Previous studies have shown that smoking leads to a significant shift in the gut microbiome of humans (45–47), which may be responsible for the increased risk of colorectal adenoma or colorectal cancer. However, microbial species changed by smoking mainly consisted of *Prevotella*, *Veillonella*, *Bacteroides*, and *Acidaminococcus* (46–48), which were different from those changed by the SMD. This may suggest that smoking may increase colorectal adenoma risk through different mechanisms, compared with a sulfur microbial diet. Recently, Bai et al. explored the mechanism of smoking and gut microbial-mediated colorectal tumorigenesis in mice, the result demonstrating that smoking can promote colonic tumorigenesis by modulating the components of the gut microbiota and inducing dysbiosis of the gut microbiota (49). Smoking may promote colorectal tumorigenesis which results in impairing the gut barrier function, promoting inflammation in colon tumorigenesis, and enhancing oncogenic *MAPK/ERK* signaling in colonic epithelium (49), which is partially similar to the mechanism of H_2S promoting colorectal tumors (36, 40, 41). Smoking may modulate the abundance of microbiota other than sulfur-metabolizing microorganisms in the gut to have some synergistic effect on the increased colorectal adenoma risk induced by the SMD, which may provide a possible explanation for these results. However, this explanation needs to be confirmed by further investigating the interactions between the different microbiota mentioned above.

Intriguingly, our subgroup analysis revealed a more pronounced positive association between adherence to SMD and the risk of colorectal adenomas in males. Several potential explanations can shed light on this observation. Firstly, in our study cohort, males constituted a higher proportion of smokers, comprising approximately 66% of all current or former smokers. Moreover, our subgroup analysis indicated a significant interaction between smoking and SMD adherence in increasing the risk of colorectal adenomas. Given that smoking is a known contributor to colorectal adenoma risk (50), this difference in smoking prevalence between genders may contribute to the sex-specific association observed in colorectal adenoma incidence. On another note, Liu et al. demonstrated that adherence to SMD was linked to an increase risk of obesity (51). Their gender-specific stratified analysis further suggested a more substantial positive association between SMD adherence and obesity risk in males compared to females (51). Considering that obesity is a significant risk factor for colorectal

TABLE 3 Subgroup analyses on the association of SMD score with the risk of colorectal cancer precursor.

Subgroup variable	Number of participates	Number of cases	HR $_{\text{Quartile 4 vs. Quartile 1}}$ (95% CI)[a]	$P_{\text{-interaction}}$
Age (years)				0.058
≤65	6,970	410	1.09 (0.86, 1.35)	
>65	2,561	128	1.65 (1.11, 2.45)	
Sex				0.192
Male	5,468	364	1.28 (1.02, 1.62)	
Female	4,063	174	1.07 (0.77, 1.51)	
Body mass index (kg/m^2)				0.079
≤30	7,551	401	1.30 (1.04, 1.62)	
>30	1,980	137	1.01 (0.69, 1.47)	
Smoking status				**0.029**
Never	5,006	222	0.99 (0.74, 1.34)	
Current/former	4,525	316	1.43 (1.12, 1.83)	
Smoking pack-years				0.053
≤Medium	5,085	226	1.01 (0.75, 1.35)	
>Medium	4,446	312	1.40 (1.09, 1.80)	
Family history of colorectal cancer				0.989
No	8,457	482	1.18 (0.97, 1.45)	
Yes/possibly	1,074	56	1.37 (0.75, 2.51)	
History of aspirin consumption				0.071
No	5,032	280	1.02 (0.78, 1.33)	
Yes	4,499	258	1.47 (1.10, 1,91)	

[a]HRs were adjusted for age (years), sex (male, female), race (white, non-white), education levels (college below, college graduate, postgraduate), smoking status (never, current, former), pack-years of smoking (continuous), BMI (continuous), aspirin use (no, yes), history of hypertension (no, yes), history of diabetes (no, yes), family history of colorectal cancer (no, yes), total energy intake (continuous), history of diverticulitis or diverticulosis (no, yes), history of colonoscopy in past 3 years (no, yes), and physical activity level (continuous).
The bold values in Table 3 simply indicate statistical significance, with *p*-values less than 0.05.

TABLE 4 Sensitivity analyses on the association of SMD score with the risk of colorectal cancer precursors.

Categories	HR $_{\text{Quartile 4 vs. Quartile 1}}$ (95% CI)[a]	$P_{\text{-trend}}$
Primary analysis	1.23 (1.02, 1.47)	0.017
Excluded participants with history of diverticulitis or diverticulosis[b]	1.23 (1.02, 1.48)	0.016
Excluded participants with a history of diabetes[c]	1.23 (1.02, 1.49)	0.019
Excluded participants with family history of colorectal cancer[d]	1.22 (1.01, 1.48)	0.031
Excluded cases observed within the first 2 years of follow-up	1.23 (1.02, 1.47)	0.017
Excluded cases observed within the first 4 years of follow-up	1.27 (1.04, 1.56)	0.012
Further adjusted for Healthy Eating Index-2015[e]	1.23 (1.01, 1.50)	0.029

HR, hazard ratio; CI, confidence interval.
[a]HRs were adjusted for age (continuous), sex (male, female), race (white, no-white), education levels (college below, college graduate, postgraduate), smoking status (never, current, former), pack-years of smoking (continuous), BMI (continuous), aspirin use (no, yes), history of hypertension (no, yes), history of diabetes (no, yes), family history of colorectal cancer (no, yes), total energy intake (continuous), history of diverticulitis or diverticulosis (no, yes), history of colonoscopy in past 3 years (no, yes), and physical activity level (continuous).
[b]HR was not adjusted for history of diverticulitis or diverticulosis.
[c]HR was not adjusted for history of diabetes.
[d]HR was not adjusted for history of colorectal cancer.
[e]This covariate was treated as the continuous variable in multivariable Cox regression.

cancer and adenoma (52, 53), the variation in the association between obesity and adherence to the SMD pattern across genders may be the reason why the association between SMD and colorectal adenoma risk is more significant in males.

This study has several strengths. First, unlike previous studies that conducted their study only on health professionals (10, 11, 22), the population in this study was more representative because an almost equal proportion of male and female participants were involved, with

no occupational restrictions, who received the same care in different practice settings across the United States. Second, participants with inadequate flexible sigmoidoscopy were excluded, which guaranteed the effectiveness of the colonoscopy. Third, considering the inherent influence of colon-related complications with a genetic predisposition on the incidence of colorectal cancer (such as Crohn's disease, Gardner's syndrome, ulcerative colitis, or familial polyposis) (54–57), participants with colon-related complications were excluded to minimize the interference of genetic factors on the study results. Notably, this research confirms for the first time that SMD is linked to an elevated risk of colorectal adenoma in the older individuals. Given the higher risk of colorectal tumors in the elderly population compared to the younger population (4), this research will provide a new dietary guideline for them to minimize the incidence of CRC in this high-risk population.

This research is restricted in some aspects. The microbiota in the stool samples of participants was not analyzed due to some limitations, therefore, the shift in the intestinal microbiota of participants could not be guaranteed to be consistent with previous studies. However, SMD-related analyses have been adequately validated in several various study cohorts (10, 11, 22), making this deficiency acceptable. In addition, the dietary intake of SMD using DQX was calculated only once at baseline, rather than calculating the cumulative mean at long-term follow-up, which may lead to nondifferential bias. However, based on a classical assumption in nutrition, the exposure measured at baseline is more reflective of the daily dietary habits of participants in the years before and following inclusion in the study (24). Hence, these calculations for the dietary intake of participants can be considered valid.

Conclusion

To summarize, our study findings revealed a positive correlation between SMD score and conventional colorectal adenomas risk in an elderly population in the United States, with a median follow-up of 11 years. Furthermore, this positive association is more significant in males. Smoking may have a synergistic effect on the positive association between SMD and colorectal adenoma by modulating intestinal microbiota, which differed from the sulfur-metabolizing bacteria, and the exact mechanism needs to be elucidated by subsequent in-depth studies on the mechanism of intestinal microbiota interactions.

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 Institutional Review Board of the National Cancer Institute. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HH, YW, YJ, and YX contributed to the study design and data analysis. YX and YJ contributed to the data interpretation and writing of the manuscript. YX, LX, ZX, XR, BL, YJ, ZyZ, HZ, YT, HL, QW, ZhZ, HH, and HG contributed to the data collection, and data curation of the present analysis. LP, LX, YW, HH, and HG assisted with statistical analysis and funding acquisition. YJ and HH made significant contributions to the revised manuscript. All of the authors reviewed or revised the manuscript. All authors contributed to the article and approved the submitted version. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1167372/full#supplementary-material

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Adherence to the Mediterranean diet and risk of gastric cancer: a systematic review and dose–response meta-analysis

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Background: Despite growing evidence for the association of adherence to the Mediterranean diet with gastric cancer risk, the results remain inconclusive. The purpose of this systematic review and meta-analysis was to summarize the evidence from previous observational studies and assess the potential association between adherence to the Mediterranean diet and risk of gastric cancer using a dose–response meta-analysis.

Methods: A comprehensive literature search for all observational studies published up to June 30, 2023 was conducted using the databases of PubMed, ISI Web of Science, EBSCO, China National Knowledge Infrastructure (CNKI) and Wanfang Data. The pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated for the highest versus the lowest categories of Mediterranean diet score in relation to gastric cancer risk, using random-effects models. The Cochran's *Q* test and *I*-squared (I^2) statistic were used to detect the sources of heterogeneity among the included studies.

Results: Overall, 11 studies (five cohort and six case–control studies) with a total number of 1,366,318 participants were included in the final analysis. Combining 14 effect sizes from 11 studies revealed that compared with the lowest category, the highest adherence to the Mediterranean diet was associated with a 29% reduction in the risk of gastric cancer (RR:0.71; 95%CI:0.59–0.84, $p < 0.001$). In addition, linear dose–response analysis showed that each 1-score increment in Mediterranean diet score was associated with a 5% lower risk of gastric cancer (RR:0.95; 95%CI: 0.94–0.96, $p < 0.001$). Stratified analysis showed a significant association between adherence to the Mediterranean diet and risk of gastric cancer in case–control studies (RR = 0.44;95%CI:0.32–0.61, $p < 0.001$), and a marginally significant association in prospective cohort studies (RR = 0.88; 95%CI: 0.79–0.98, $p = 0.024$), respectively. At the same time, a more significant association between Mediterranean diet and reduced risk of gastric cancer was observed in other countries (RR = 0.28; 95%CI:0.16–0.49, $p < 0.001$) than in Western countries (RR = 0.75; 95%CI:0.64–0.88, $p = 0.001$).

Conclusion: Our results demonstrate that high adherence to the Mediterranean diet is associated with 29% reduced risk of gastric cancer. Further large prospective studies and randomized controlled trials are warranted to confirm our findings.

KEYWORDS

Mediterranean diet, gastric cancer, systematic review, meta-analysis, dose–response, epidemiology

Introduction

Gastric cancer, also known as stomach cancer, is one of the most common malignancies worldwide, and its incidence and mortality rate has steadily declined over the last one-half century (1). According to the latest estimates released by GLOBOCAN, in 2020, gastric cancer remains the fifth most commonly diagnosed cancer and fourth leading cause of cancer-related mortality globally, with >1 million new case and an estimated 769,000 deaths (2). Notably, the incidence of gastric cancer is significantly higher in Eastern Asia compared to North America and Europe (2, 3). In China, gastric cancer has been the third leading cause of death in all cancers, and 0.33 million new cases and 0.37 million deaths occurring in 2020 (3). This trend reflects the urgency and necessity of implementing effective strategies for the prevention of gastric cancer. As far as we know, increasing evidence has shown that gastric cancer is induced by the combined synergistic effects of genetic factors, *Helicobacter pylori* (*H. pylori*) infection, cigarette smoking, alcohol intake, and dietary factors (4).

Over the past decades, diet has been recognized as a leading contributor to gastric cancer (5). Mounting epidemiological studies have mostly examined the correlations between intakes of individual foods (6), nutrients (7) or overall dietary patterns (8) and the risk of gastric cancer. In the meantime, the latest report by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) states that high consumption of alcoholic drinks and foods preserved by salting are associated with an increased risk of gastric cancer (9). The Mediterranean diet, characterizing by a high intake of fruits, vegetables, nuts, legumes, whole grains and extra-virgin olive oil; a moderate intake of poultry, fish and alcohol; and a low intake of red and processed meats (10), represented a healthy dietary pattern usually consumed in the populations bordering the Mediterranean sea (11). Up to date, accumulating epidemiological evidence has suggested the beneficial role for high adherence to the Mediterranean diet on certain chronic non-communicable diseases, such as cardiovascular diseases, non-alcohol fatty liver disease and some types of cancers (12–14). Still, little is known with regard to the relationship between *a priori* defined the Mediterranean diet adherence and risk of gastric cancer. Nonetheless, based on the characteristics of the Mediterranean diet, it could be an ideal dietary pattern to reduce the risk of gastric cancer.

The relationship between adherence to the Mediterranean diet and cancers has been a focus for researchers in recent years (15). Only a few studies have so far explored the association between adherence to the Mediterranean diet and risk of gastric cancer (16–26), but the conclusions of previous studies are not entirely consistent. Several case–control studies have shown a significant inverse relationship between adherence to the Mediterranean diet and gastric cancer risk (16, 17, 19, 20, 22, 24, 26), while other studies showed the null association (18, 21, 23, 25). For example, in a hospital-based case–control study by Amiry et al., greater adherence to the Mediterranean diet was associated with a lower odds of gastric cancer (OR:0.17; 95%CI: 0.03–0.80) (16). However, no significant association was observed between adherence to the alternate Mediterranean diet and gastric cancer risk in the Multiethnic cohort study (25). Besides, to our knowledge, a recent systematic review and meta-analysis (Morze et al., 2021) reported a reduction of 30% in the incidence of gastric cancer for the highest adherence to the Mediterranean diet (27). Nevertheless, this meta-analysis included only seven articles, and neither dose–response relationship or subgroup analyses were performed in the main analysis. Since then, several new observational studies on this topic have been published (16, 19, 20, 25). Thus, to address the current gaps in knowledge regarding the relationship between adherence to the Mediterranean diet and gastric cancer risk, we performed a comprehensive systematic review and dose–response meta-analysis to summarize the current evidence of observational studies published from inception up to June 2023.

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; CIs, confidence intervals; DASH, dietary approaches to stop hypertension; FFQ, food frequency questionnaire; HRs, Hazards ratios; IARC, International Agency for Research on Cancer; ORs, odds ratios; RR, relative risks; PRISMA, preferred reporting items for systematic reviews and meta-analyses; WHO, World Health Organization; WCRF, World Cancer Research Fund.

Materials and methods

This study was carried out in accordance with the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (28). Moreover, the protocol of this systematic review and meta-analysis has not been registered in the International Prospective Register of Systematic reviews.

Literature search strategy

We carried out a comprehensive search of articles published up to June 30, 2023 using PubMed, ISI Web of Science, EBSCO, CNKI and Wanfang Data with no restrictions in language or publication date. The following terms were used in our search: {("stomach cancer"[all fields] OR "stomach neoplasm" [all fields] OR "gastric cancer"[all fields] OR "gastric neoplasm"[all fields] OR "cancer of the stomach"[all fields]) AND ("MedDiet"[all fields] OR "Mediterranean diet" [all fields] OR "Mediterranean"[all fields] OR "Dietary pattern"[all fields] OR "dietary score"[all fields] OR "dietary adherence"[all fields])}. In addition, a manual search in the reference lists from the retrieved articles or reviews or meta-analyses was performed to find the potentially eligible studies. All of these steps were accomplished by two independent reviewers (ZQ and SL), and any disagreements with article selection were resolved through discussion with Y-LF. Our selection criteria was based on the PECOS (e.g., participant, exposure, comparison, outcome, and study design) framework, which is shown in Supplementary Table S1.

Studies included criteria

Two independent reviewers (QZ and LS) carried out an initial screening of all titles and abstracts from retrieved articles to identify eligible studies that should be included in the analysis. Any disagreements were settled by discussion or in consultation with the third reviewer (Y-LF). When all reviewers agreed, the full-text articles were reviewed against inclusion and exclusion criteria for the present systematic review and updated meta-analysis. To be included in the present meta- analysis, articles had to meet the following criteria: (1) observational studies (i.e., case–control and cohort studies) conducted in adult population (aged ≥18 years); (2)considered adherence to the

Mediterranean diet as the exposure; (3) assessed the association between adherence to the Mediterranean diet and risk of gastric cancer; (4) provided estimates of RRs, HRs, ORs with their corresponding 95%CIs; (5) If the data in retrieved article lacked sufficient detail, the corresponding author of the original study was contacted by email; (6) gastric cancer diagnoses were confirmed by clinical interviews, or self-report on a previous physician-made diagnosis of gastric cancer. Moreover, studies were excluded if they fulfilled one of the following criteria: (1) unrelated articles; (2) non-observational studies, e.g., reviews, editorials, case reports and conference letters; (3) animal, cell culture, and *in vitro* studies; (4) studies not reported as HRs, RRs or ORs with 95%CIs.

Data extraction

After completing selection of all eligible studies, two independent authors (LS and FZ) extracted the following information: first author's last name, publication year, study design, country, sample size, number of gastric cancer cases, mean age/age range, follow-up time (cohort studies), components of the Mediterranean diet score, methods of dietary assessment, reported risk estimates (HR/OR/RR) and the corresponding 95%CIs and confounding factors that were adjusted for in the multivariate analyses. Any discrepancies and disagreements about data extraction were resolved by consensus or discussion with the third author (Y-LF).

Quality assessment of included studies

The Newcastle-Ottawa Scale (NOS) was used to evaluate the overall quality of the included studies in the present study (29). We assigned 0 ~ 9 "stars" to each study based on three major domains: the population selection (maximum of 4 stars), comparability of the groups (maximum of 2 stars), and outcome/exposure assessment (maximum of 3 stars). For this analysis, we considered that an NOS score ≥ 7 indicated high methodological quality (10). Differences were resolved by consensus with a third author (ZQ).

Statistical analysis

The reported HRs in the primary studies were considered as equal as RRs (30). ORs were converted into RRs using the formula:RR = OR/[(1-P_0) + (P_0*OR)], in which P_0 indicates the incidence of the outcome of interest in the non-exposed group (31). Log-transformed RRs with their corresponding standard errors (SEs) were obtained using risk ratios (ORs, HRs, and RRs and corresponding 95% CIs) which were previously extracted for the relationship between adherence to the Mediterranean diet and risk of gastric cancer. Heterogeneity across studies was tested using the Cochran's *Q* test and the I^2 statistic. If *p*-values of Cochran's *Q*-test ≤0.10 or $I^2 \geq 50\%$ indicated an absence of heterogeneity among studies, and the random-effects model (DerSimonnian and Laird method) was used to pool the RRs and 95%CIs of the highest versus the lowest category of Mediterranean diet in relation to gastric cancer. Otherwise, the fixed effect model is used (32). If significant between-study heterogeneity was observed, sensitivity and subgroup analyses would be performed to further find out the source of heterogeneity. In our analyses, subgroup analyses were performed based on sex (male or female), study design (cohort or case–control studies), anatomical site (gastric cardia or non-cardia), study area [Western countries or other countries (Afghanistan and Jordan)], mean age (≥50 or < 50), and sample size (<5,000 or >5,000). Sensitivity analysis was performed by removing one study at a time, and to clarify whether the results were robust or sensitive to the influence of a single study. If ≥10 comparisons were available, publication bias was evaluated through the visual inspection of the funnel plot and quantified by the Begg's test and Egger's test, respectively (33). If there was evidence of publication bias, we further evaluated the number of missing studies in a meta-analysis by the application of the Duval and Tweedie trim- and- fill method and recalculated the pooled estimates with the addition of those missing studies (34). Finally, we also performed a dose–response meta-analysis to estimate the RRs for each 1-score increment in Mediterranean diet adherence. A two-stage GLST model based on generalized least squares method was used to test the potential linear or non-linear dose–response association between adherence to a Mediterranean diet and risk of gastric cancer. We modeled Mediterranean diet scores by using restricted cubic splines with 3 knots at fixed percentiles (10, 50, and 90%) of the distribution. A *p*-value for curve linearity or non-linearity was computed by testing the null hypothesis that the coefficient of the first spline is equal to the second spline. All the mentioned data analyses were performed using STATA, version 12.0 (StataCorp, College Station, Texas, USA). A *p-value* less than 0.05 (two-tailed) was considered statistically significant.

Results

Search results

Figure 1 indicates the process of study selection. Our initial search yielded 348 potential articles, of which 52 were duplicates. Of the remaining 296 articles, we excluded 225 articles on the basis of the titles and/or abstracts; 42 articles on the basis of irrelevant studies. Then, after reading the full-text versions of the remaining 29 articles, 18 articles were excluded for the following reasons: 7 were systematic review or meta-analyses, 4 did not evaluate gastric cancer risk; 2 were conference abstracts; 1 reported the same participants; 4 did not mention Mediterranean diet score. Finally, 11 studies met the eligibility criteria and were included in this meta-analysis.

Study characteristics

Table 1 shows the general characteristics of all included studies. A total of 11 studies, including 5 prospective cohort (18, 21, 23, 25, 26) and 6 case–control (16, 17, 19, 20, 22, 24) studies, met the inclusion criteria and was included in this study. These included studies were published between 2010 and 2023. The age of participants ranged from ages 18 to above. Two of the included studies were carried out in the United States (21, 25), two in Spain (19, 22), two in Italy (17, 24), one in Afghanistan (16), one in Sweden (23), one in Netherlands (18), one in Jordan (20), and one study in European countries (26). Thus, United States, Spain, Italy, Sweden, Netherlands and European countries were regarded as Western countries, while Afghanistan and

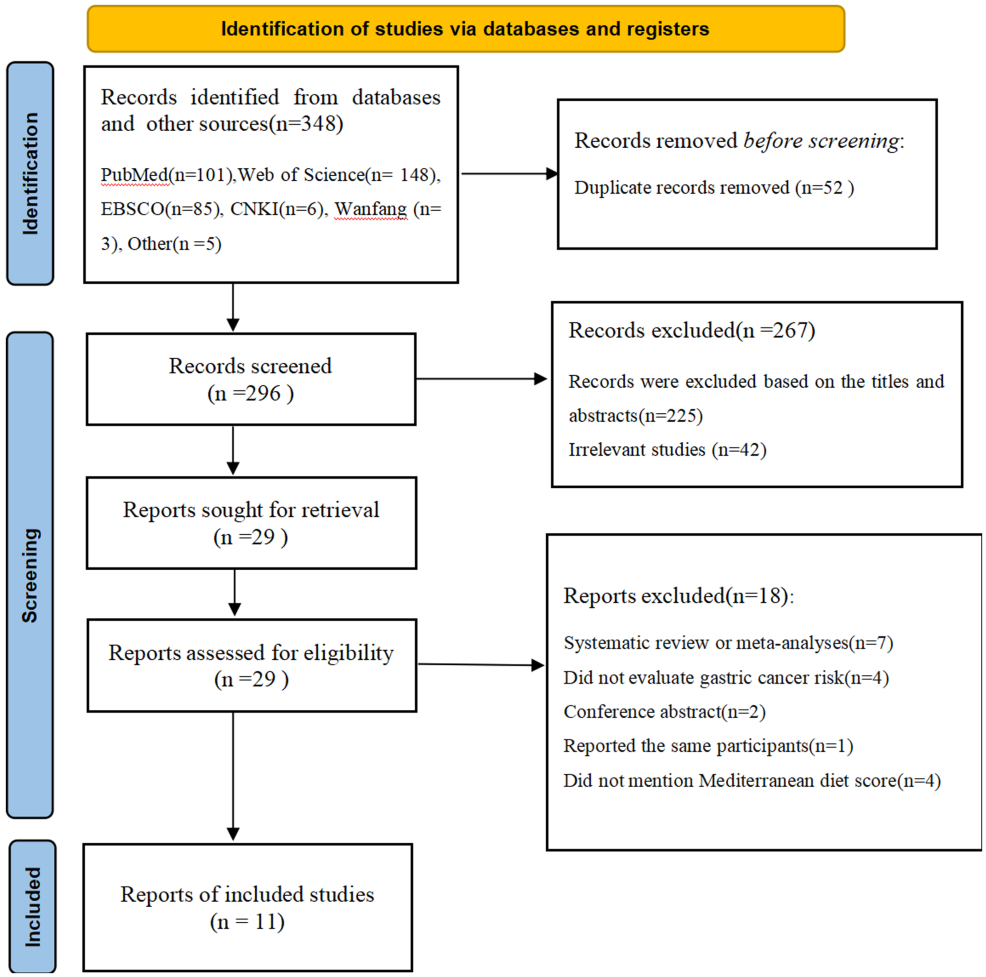

FIGURE 1
Flow chart of the process of study selection.

Jordan were regarded as other countries. In all included studies, dietary intake was measured by using an FFQ (16–26). For outcome assessment, four studies had used cancer registries (18, 21, 23, 25), two studies used medical records (20, 24), and five studies used pathology reports (16, 17, 19, 22, 26). All included studies had an NOS score ≥ 7, which were of high quality (16–26). Among these studies, three studies (18, 21, 25) separately reported the relationship between adherence to Mediterranean diet and gastric cardia adenocarcinoma and non-cardia adenocarcinoma. The number of study participants varied between 270 and 494,968.

Adherence to the Mediterranean diet and gastric cancer incidence

Eleven articles comprising 5,708 gastric cancer cases and 1,366,318 participants, were included to assess the link between adherence to the Mediterranean diet and the risk of gastric cancer. Combining 14 effect sizes from 11 studies, Figure 2 showed the evidence of a decreased risk of gastric cancer in the highest compared with the lowest categories of Mediterranean diet (RR = 0.71; 95%CI:0.59–0.84, $p < 0.001$). There was evidence of substantial heterogeneity between studies ($I^2 = 79.7\%$, $p < 0.001$), and therefore the effect was assessed using the random-effects model.

Dose–response analysis

Ten studies (16–22, 24–26) containing 6 case–control studies with Mediterranean diet scores on the same scale (0–9) were included in the dose–response analysis for gastric cancer risk. A linear dose–response analysis showed that each 1-score increment in Mediterranean diet score was associated with a 5% lower risk of gastric cancer (RR = 0.95;95%CI:0.94–0.96, $p <$ 0.001; $P_{\text{non-linearity}} = 0.330$) (Figure 3). The analysis of six case–control studies showed a positive linear relationship between Mediterranean diet and risk of gastric cancer (OR = 0.89; 95%CI:0.80–0.98; $p = 0.018$; $P_{\text{non-linearity}} = 0.382$) (Figure 4). In addition, the analysis of four cohort studies also showed a positive linear relationship between Mediterranean diet and risk of gastric cancer (HR = 0.98, 95%CI:0.96–0.99; $p = 0.002$; $P_{\text{non-linearity}} = 0.538$) (Figure 5).

TABLE 1 Characteristics of included studies on the relationship between adherence to the Mediterranean diet and risk of gastric cancer.

Author Publication Year	Country	Study design	Total number of participants	Mean age/age range	Dietary assessment method	Adjustment or matched for in analyses	Effect sizes OR/RR (95%CI)
Amiry et al. 2022 (16)	Afghanistan	Case–control	270 (90 cases)	20-75y	FFQ	Age, sex, physical activity, Marriage status (married/not married), Kebab food (yes/no), smoking usage (yes/no), tooth brushing (do not brush, brush), job (former and worker, others), education (non-university graduate, university graduate), alcohol usage (yes/no), BMI (categorical).	0.17 (0.03–0.80)
Praud et al. 2014 (17)	Italy	Case–control	3,627 (999 cases)	19-80y	FFQ	Age, sex, study, year of interview, education, body mass index, tobacco smoking, family history, and total energy intake.	0.57 (0.45–0.70)
Schulpen et al.2019 (18)	Netherlands	Cohort	12,085 (777 cases)	55-69y	FFQ	Age at baseline (years), sex (men, women), cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (kg/m^2), daily energy intake (kilocalories), alcohol consumption (g/day), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), non-occupational physical activity ($\leq$30, >30- $\leq$60, >60- $\leq$90, >90 min per day), family history of esophageal cancer (for esophageal cancer subtypes; no, yes), and family history of gastric cancer (for gastric cancer subtypes; no, yes)	Gastric cardia adenocarcinoma:0.86 (0.71–1.04); gastric non-cardia adenocarcinoma:0.83 (0.73–0.93)
Álvarez-Álvarez et al. 2021 (19)	Spain	Case–control	3,394 (354 cases)	20-85y	FFQ	Sex, age, education, family history of gastric cancer (first degree), tobacco status, total energy consumed, BMI (the year before diagnosis), consumption of NSAIDs, and total time of physical activity as fixed terms and area of residence	0.32 (0.22–0.46)
Tayyem et al. 2022 (20)	Jordan	Case–control	486 (172 cases)	≥18y	FFQ	Age, marital status, BMI, education, smoking, physical activity, family history, and energy (Kcal).	0.21 (0.11–0.42)
Li et al. 2013 (21)	United States	Cohort	494,968 (954 cases)	50-71y	FFQ	Age, sex, race, smoking, alcohol intake, education, BMI, vigorous physical activity, usual activity, and total energy intake	Gastric cardia adenocarcinoma: 1.10 (0.76–1.61);gastric non-cardia adenocarcinoma: 0.75 (0.52–1.09)
Castelló et al. 2018 (22)	Spain	Case–control	3,092 (271 cases)	20-85y	FFQ	Sex, age, education, BMI, family history of gastric cancer, physical activity (METs), smoking status, caloric intake, and alcohol intake as fixed effects and province of residence	0.53 (0.34–0.82)
Bodén et al.2019 (23)	Sweden	Cohort	100,881 (163 cases)	40-60y	FFQ	Energy intake, BMI, physical activity, smoking, educational status	0.85 (0.69–1.03)
Stojanovic et al.2017 (24)	Italy	Case–control	446 (223 cases)	≥18y	FFQ	Sex, tobacco smoking, and total energy intake.	0.70 (0.61–0.81)
Acuna et al.2023 (25)	United States	Cohort	176,752 (1,043 cases)	45-75y	FFQ	Age at cohort entry, sex, self-identified race and ethnicity (including birthplace), a family history of gastric cancer, education, smoking status, pack-years of cigarette smoking, aspirin use status, and total energy intake.	Gastric cardia adenocarcinoma: 1.56 (0.95–2.54); Gastric distal adenocarcinoma:0.99 (0.78–1.26)
Buckland et al.2010 (26)	European countries	Cohort	485,044 (449cases)	35-70y	FFQ	Center and age and adjusted for sex, BMI, educational level, smoking status, cigarette smoking intensity, and total energy intake	0.67 (0.47–0.94)

BMI, body mass index; FFQ, food frequency questionnaire; NSAIDs, non-steroidal antiinflammatory drugs; "Schulpen 1, Li 1 and Acuna1"indicate gastric cardia adenocarcinoma;"Schulpen2, Li 2 and Acuna12" indicate gastric non-cardia adenocarcinoma.

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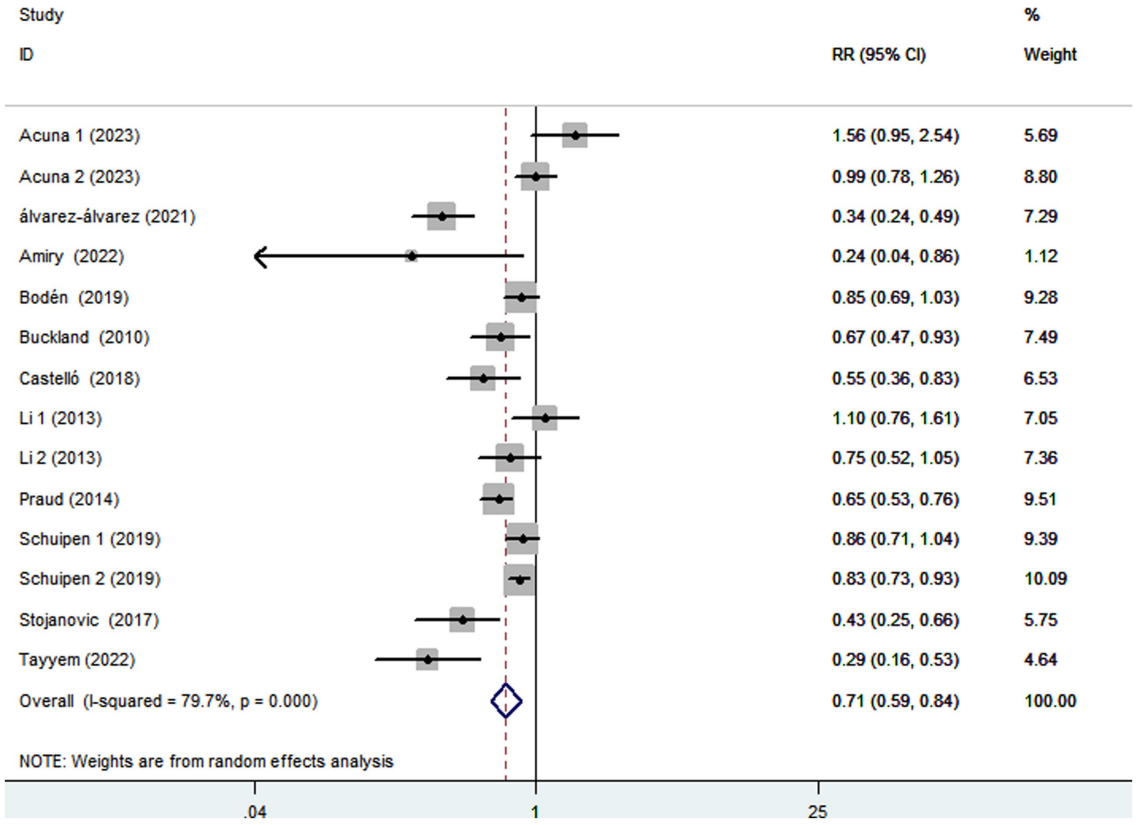

FIGURE 2
Forest plot of the association between adherence to the Mediterranean diet and risk of gastric cancer.

Subgroup analyses

Given the high heterogeneity of this study ($I^2 = 79.7\%$; $p < 0.001$), subgroup analyses were performed to explore the potential sources of heterogeneity (Table 2). In this study, subgroup analyses were carried out basing on study design (cohort or case–control studies), study area (Western countries or other countries), mean age (≥50 or <50), sample size (<5,000 or >5,000), anatomical site (gastric cardia or non-cardia) and sex (male or female). When we conducted analyses separately by study design, results showed an inverse relationship between Mediterranean diet and risk of gastric cancer in cohort studies (RR = 0.88; 95%CI: 0.79–0.98, $p = 0.024$), with less evidence of heterogeneity between studies ($p = 0.115$; $I^2 = 39.6\%$). In contrast, there was also significant association between Mediterranean diet and decreased risk of gastric cancer in case–control studies (RR = 0.44; 95%CI: 0.32–0.61, $p < 0.001$), with evidence of heterogeneity ($p = 0.005$; $I^2 = 69.8\%$). For study area, we found a significant inverse association between adherence to Mediterranean diet and gastric cancer risk in other countries (RR = 0.28; 95%CI: 0.16–0.49, $p < 0.001$). There was no evidence of heterogeneity between studies ($p = 0.822$; $I^2 = 0.0\%$). When the results were stratified by mean age, we found a significant inverse association between Mediterranean diet and gastric cancer risk in age ≥ 50 and age < 50 (for age ≥ 50: RR = 0.70; 95%CI: 0.57–0.87, $p = 0.001$ and for age < 50: RR = 0.71; 95%CI: 0.53–0.95, $p = 0.022$). The heterogeneity was most apparent in age ≥ 50 ($p < 0.001$; $I^2 = 82.5\%$). For sample size, we found a significant inverse relationship between Mediterranean diet and gastric cancer risk in the subgroups of sample size > 5,000 (RR = 0.88; 95%CI: 0.79–0.98, $p = 0.024$). However, the heterogeneity was less ($p = 0.115$, $I^2 = 39.6\%$). In addition, a protective association was found between Mediterranean diet and gastric cancer risk in the studies with sample size<5,000 (RR = 0.44; 95%CI: 0.32–0.61, $p < 0.001$), and there was significant heterogeneity ($p = 0.005$, $I^2 = 69.8\%$). We also performed stratified analysis based on sex, and results showed the inverse association between Mediterranean diet and gastric cancer risk in male and female (0.77 vs. 0.91). however, there was no evidence of heterogeneity in female ($p = 0.604$; $I^2 = 0.0\%$).

Publication bias and quality assessment

Funnel plots showed little evidence of asymmetry (Supplementary Figure S1) and therefore no evidence of publication bias existed (highest compared with lowest category of Mediterranean diet: Begg's test, $p = 0.324$; Egger's test, $p = 0.161$). Due to no evidence of publication bias, we could not perform the trim and fill analysis to adjust the pooled effect estimates. All included studies in our analyses have received a NOS score ≥ 7, and these studies were regarded to be of high quality (16–26) (Table 3).

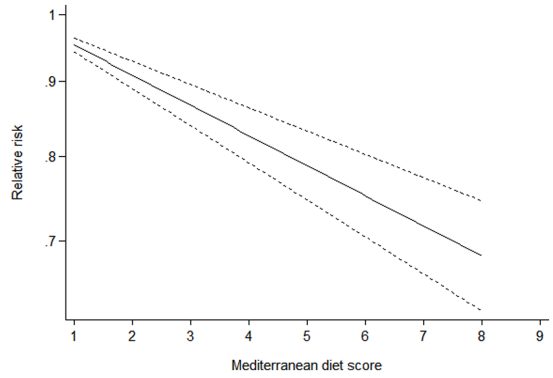

FIGURE 3
Forest plot of the association between each 1-score increment in Mediterranean diet and risk of gastric cancer.

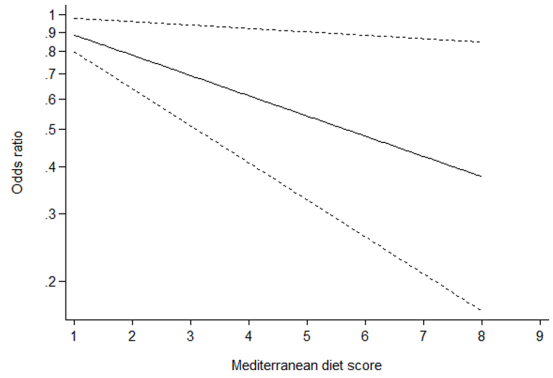

FIGURE 4
Dose-response association between adherence to the Mediterranean diet and risk of gastric cancer in the analysis of six case-control studies.

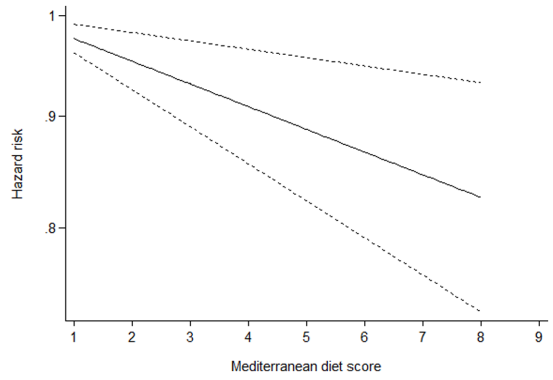

FIGURE 5
Dose-response association between adherence to the Mediterranean diet and risk of gastric cancer in the analysis of four cohort studies.

Sensitivity analyses

Based on the results of sensitivity analysis, the pooled results of Mediterranean diet on gastric cancer did not materially change when removing any single studies in the main analysis (RR ranged between 0.65 and 0.76) (Supplementary Figure S2).

Discussion

To our knowledge, this is the latest systematic review and meta-analysis to evaluate the association between adherence to the Mediterranean diet and gastric cancer risk with 1,366,318 participants and 5,708 cases of gastric cancer. The current systematic review and meta-analysis of 11 epidemiological studies shows that greater adherence to the Mediterranean diet was significantly associated with a 29% reduction in the risk of gastric cancer. In addition, the dose–response analysis also shows that each 2-score increment in Mediterranean diet was associated with a 6% reduction in the risk of gastric cancer. In a meantime, sensitivity analysis revealed that the summary effect of Mediterranean diet on gastric cancer was not substantially modified by excluding a certain study. Collectively, the results of this systematic review and meta-analysis provide further scientific evidence supporting the adoption of adherence to the Mediterranean diet for the primary prevention of gastric cancer.

Thus far, many epidemiological studies have examined different dietary patterns in relation to the risk of gastric cancer (16, 17, 35–37). However, most previous studies have mainly used *a posteriori* methods to evaluate the association between certain dietary patterns (e.g., healthy/prudent and Western patterns) and gastric cancer (35–37). In contrast, the impact of *a priori*-defined dietary pattern, e.g., Mediterranean diet on gastric cancer has rarely been investigated (16, 17). Still, the impact of Mediterranean diet on gastric cancer has also attracted much attention. Also of note, current research findings on the relationship between adherence to the Mediterranean diet and gastric cancer risk are in debate. For example, in a prospective cohort of the National Institutes of Health (NIH)-AARP Diet and Health Study, Li et al., found that aMED scores were not significantly associated with gastric cardia or non-cardia adenocarcinomas (21). On the contrary, in a hospital-based case–control study, Amiry et al., found that greater adherence to Mediterranean diet might be associated with a lower odds of gastric cancer (16). These inconsistent findings in previous studies might be explained by the differences in study design and study populations. In our analyses, adherence to the Mediterranean diet was associated with a reduced risk of gastric cancer. Our findings were aligned with previous meta-analyses (8, 38), which showed that the healthy/prudent dietary patterns were associated with a decreased risk of gastric cancer. Similarly, in a hospital-based case–control study by Toorang et al., high adherence to the DASH dietary pattern was associated with a 54% decrease risk of gastric cancer (OR:0.46; 95%CI: 0.26–0.83) (39). In fact, the healthy/prudent and DASH dietary patterns share some similarities with the Mediterranean diet, such as high consumption of vegetables, fruits and whole grains. Several previous studies have reported the favorable effect of fruit and vegetables intake on gastric cancer (40, 41). Furthermore, a recent systematic review and meta-analysis of Mediterranean diet and risk of cancer also reported that highest adherence to the Mediterranean diet was related to lower risk of gastric cancer (27). However, the above mentioned meta-analysis only included seven articles and dose–response relationship and subgroup analyses were not conducted in their analyses. Also, due to the limited number of studies, Morze et al. did not performed the publication bias. In this context, identifying the link between adherence to the Mediterranean diet and gastric cancer risk through a dose–response meta-analysis would appear to have value. Whilst current evidence on the

TABLE 2 Subgroup analyses for the relationship between adherence to Mediterranean diet and stomach cancer risk.

Study characteristic	No. of studies	RR (95%CI)	Heterogeneity	
			I^2(%)	*P*
All	11	0.71 (0.59–0.84)	79.7	<0.001
Study design				
Case–control	6	0.44 (0.32–0.61)	69.8	0.005
Cohort	5	0.88 (0.79–0.98)	39.6	0.115
Study area				
Western countries	9	0.75 (0.64–0.88)	78.6	<0.001
Other countries	2	0.28 (0.16–0.49)	0.0	0.822
Mean age				
≥50	8	0.70 (0.57–0.87)	82.5	<0.001
<50	3	0.71 (0.53–0.95)	65.7	0.054
Sample size				
>5,000	5	0.88 (0.79–0.98)	39.6	0.115
<5,000	6	0.44 (0.32–0.61)	69.8	0.005
Anatomical site				
Gastric non-cardia	7	0.74 (0.60–0.91)	79.7	<0.001
Gastric cardia	7	0.77 (0.61–0.98)	66.6	0.006
Sex				
Male	5	0.77 (0.68–0.88)	67.7	0.015
Female	5	0.91 (0.86–0.96)	0.0	0.604

RR, relative risk; CI, confidence interval; Afghanistan and Jordan were defined as other countries.

TABLE 3 Mediterranean diet and risk of gastric cancer: Assessment of Study Quality.

Studies	Selection				Comparability		Outcome			Score
	1	2	3	4	5A	5B	6	7	8	
Cohort										
Schulpen et al. 2019 (18)	*	*	*	*	*	*	*	*	*	9
Li et al. 2013 (21)	*	*	*	*	*		*	*	*	8
Bodén et al. 2019 (23)	*	*	*	*	*	*	*	*	*	9
Acuna et al. 2023 (25)	*	*	*	*	*	*	*	*	*	9
Buckland et al. 2010 (26)	*	*	*	*	*		*	*	*	8
Case–control										
Amiry et al. 2022 (16)	*			*	*	*	*	*	*	7
Praud et al. 2014 (17)	*			*	*	*	*	*	*	7
Álvarez-Álvarez et al. 2021 (19)	*	*	*	*	*		*	*		7
Tayyem et al. 2022 (20)	*	*		*	*	*	*	*		7
Castelló et al. 2018 (22)	*	*	*	*	*		*	*		7
Stojanovic et al.2017 (24)	*			*	*	*	*	*	*	7

*For case–control studies, 1 indicates cases independently validated; 2, cases are representative of population; 3, community controls; 4, controls have no history of gastric cancer; 5A, study controls for the most important factor; 5B, study controls for additional factors, e.g., cigarette smoking body mass index, total energy intake; 6, ascertainment of exposure by secure record or blinded interview or record; 7, same method of ascertainment used for cases and controls; and 8, the same for cases and controls. For cohort studies, 1 indicates exposed cohort truly representative; 2, non-exposed cohort drawn from the same community; 3, ascertainment of exposure by secure record (e.g., surgical records) or structured interview; 4, outcome of interest was not present at start of study; 5A, study controls for the most important factor; 5B, study controls for additional factor(s); 6, assessment of outcome is based on independent blind assessment or record linkage; 7, follow-up long enough (≥5 years) for outcomes to occur; and 8, adequacy of follow up of cohorts (all participants complete follow up or > 90% participants complete follow up).

relationship of Mediterranean diet with gastric cancer risk remains inconsistent, several probable mechanisms have been put forward to explain the observed beneficial association. First, it is commonly known that vegetables and fruits are two main components of the Mediterranean diet. As reported in previous studies, fruits and vegetables intake have a favorable effect on lowering the risk of gastric cancer (40, 41). As far as we know, vegetables, fruits and whole grains are a rich source of dietary fiber. A previous meta-analysis based on 21 observational studies showed that dietary fiber intake was inversely associated with the risk of gastric cancer (42). Meanwhile, prior studies have also demonstrated that high intake of dietary fiber was associated with a lower risk for insulin resistance, an important risk factor for gastric cancer (43). Second, Mediterranean diet often contains high amounts of fruits, vegetables, legumes, and these foods are rich in antioxidants, e.g., vitamin C, vitamin E and other carotenoids compounds. Previous studies have clearly shown that these antioxidants can neutralize reactive oxygen species and protect against free radical damage involved in carcinogenesis (44). For instance, earlier studies have shown that vitamin C can protect cells from oxidative DNA damage, thereby blocking carcinogenesis (45). In addition, Mei et al. also reported that high intake of vitamin C can not only ameliorate gastric mucosal inflammation by scavenging reactive oxygen species, but also inhabit the growth of *H. pylori*, an important risk factor for stomach cancer (46). Third, fruits and vegetables are rich sources of folate. A previous study showed that folate was necessary for synthesis of thymine and play an important role in the synthesis, repair, and methylation of DNA, and thus preventing carcinogenesis (47). Fourth, nuts and legumes that provide a good source of polyphenols, including flavonoids and proanthocyanidins, are also recommended in the Mediterranean diet. The growing body of scientific evidence indicates that flavonoids can prevent cancer through inactivation of carcinogens, inhibition of cell proliferation, enhancement of DNA repair processes, and reduction in oxidative stress (48). Fifth, it is well-known that the Mediterranean diet is characterized by lower intake of red and processed meats. A recent dose–response meta-analysis found that red and processed meats could increase the risk of gastric cancer (6). In fact, processed meats often contain high amount of salt, nitrates or nitrites, and nitrosamine compounds, which have been thought to be carcinogenic (6, 49). Finally, high adherence to the Mediterranean dietary pattern is significantly associated with reduced risks of weight gain and obesity, which are established risk factors for gastric cancer (50). All together, the aforementioned these mechanisms may account for the beneficial association between adherence to the Mediterranean diet and gastric cancer.

Although we found a significant inverse association between adherence to the Mediterranean diet and gastric cancer, statistical heterogeneity between studies was significant ($I^2 = 79.7\%$; $p < 0.001$). As far as we know, inter-study heterogeneity is common in previous meta-analyses (38, 42, 51), but exploring the potential sources of high heterogeneity is necessary. In this study, subgroup analyses were carried out basing on study design (cohort or case–control studies), study area (Western countries or other countries), mean age (≥50 or < 50), sample size (<5,000 or >5,000), anatomical site (gastric cardia or non-cardia) and sex (male or female). The results of subgroup analyses showed that high statistical heterogeneity might mainly be attributed to the differences in study design, study area, sample size and sex. When we performed analyses separately by study area and sex, the heterogeneity decreased from 79.7 to 0.0%. Similarly, when we analyzed study design and sample size separately, results suggested that the heterogeneity decreased from 79.7 to 39.6%. Although the significant heterogeneity found between included studies cannot be fully explored by any of the above variables, there are several possible explanations for this high heterogeneity. First, all included studies assessed dietary intakes using FFQs, in which recall bias is unavoidable. Meanwhile, the only five cohort studies were included in this meta-analysis, which somewhat limits the significance of the pooled results. Second, despite all of the included studies have adjusted for potential confounders, we cannot fully exclude the effect of residual or unmeasured confounding factors on the observed relationship. Consequently, we inevitably have a high level of heterogeneity when pooling studies. Third, given the differences in the Mediterranean diet among different populations, despite HRs or RRs or ORs were all from the highest category (taking the lowest category as the reference), different studies may define Mediterranean diet slightly differently, resulting in significant heterogeneity. Additionally, the results were combined from retrieved studies conducted in different populations, resulting in significant heterogeneity. Finally, significant heterogeneity still persisted in the subgroup analyses, suggesting the presence of other unmeasured confounding factors.

Strengths and limitations

The current meta-analysis has several notable strengths. First, this is the first comprehensive systematic review and dose–response meta-analysis so far evaluating the association between adherence to the Mediterranean diet and gastric cancer risk. Our findings add the available evidence and underline the importance of supporting the people in adhering to the Mediterranean diet for prevention of gastric cancer. Second, we used a comprehensive search strategy of five main databases which identified all the observational studies available. Third, the cases of gastric cancer have been diagnosed through view of cancer registry or medical records or pathological records by clinicians, avoiding misdiagnosis. Fourth, no signs of publication bias were evident in the funnel plot, and the Begg's and Egger's tests for publication bias were non-significant. Thus, our results were relatively stable. Fifth, the quality assessment showed that all of the included studies in this meta-analysis were of high quality, and the reported ORs/RRs/HRs were multivariate and adjusted for some known confounders. Finally, the adequate number of included studies allowed us to perform subgroup analyses for some important risk factors, e.g., study design, sex and anatomical site. Besides, the dose–response analysis was performed to strengthen the relationship between adherence to the Mediterranean diet and gastric cancer risk. Despite the above-mentioned strengths, some limitations of the current meta-analysis should also be acknowledged in interpretation of our findings. First, 6 out of 11 studies included in current study used the case–control design, which is more prone to recall and selection biases. In addition, owing to the observational nature of included studies, the possibility of residual bias from unmeasured or unknown confounders remains. Hence, further prospective cohort

studies or randomized controlled trials are needed to confirm the role of Mediterranean diet in the prevention of gastric cancer. Second, in all of the included studies, dietary intake was measured through FFQs, which carried an inherent recall bias. Meanwhile, the levels of the highest and the lowest categories of Mediterranean diet scores were inconsistent in the included studies, which might have attenuated the true association. Third, although some known confounding factors have been adjusted in all eligible studies, the existence of residual confounding from unmeasured factors cannot be completely excluded. Fourth, significant heterogeneity was observed in our analyses. Even though we performed subgroup and sensitivity analyses to explore the potential sources of heterogeneity, we could not ascertain and explain the sources of inter-study heterogeneity sufficiently. Finally, this meta-analysis had a geographical restriction, as the majority of included studies came from the United States and European countries. Hence, the generalization of our findings to other populations should be taken with caution. Further large prospective studies are needed in other populations with different environmental conditions and dietary preferences.

Conclusion

In conclusion, this study showed that high adherence to the Mediterranean diet was significantly associated with a reduced risk of gastric cancer. Our findings add to the current evidence that healthy dietary pattern, like the Mediterranean diet, could offer a practical strategy in the prevention of gastric cancer. To further reinforce the significance of our findings, prospective cohort studies and clinical trials are required to corroborate the observed association between high adherence to the Mediterranean diet and reduced risk of gastric cancer.

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.

Author contributions

QZ: conceptualization, formal analysis, funding acquisition, writing – original draft. LS: data curation, formal analysis, funding acquisition, methodology, writing – review and editing. FZ: data curation, writing – review and editing. L-PC: methodology, writing – review and editing. Y-LF: supervision, writing – review and editing.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1259453/full#supplementary-material

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Adherence to diabetes risk reduction diet and the risk of head and neck cancer: a prospective study of 101,755 American adults

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Background: Adherence to the diabetes risk reduction diet (DRRD) may potentially reduce the risk of developing head and neck cancer (HNC) as the diet includes fruits and limits red and processed meats, known risk factors for HNC. However, there is currently no epidemiological research to investigate this potential association.

Methods: The present study utilized data on demographics, lifestyles, medications, and diets of participants from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial to explore the potential association between adherence to DRRD and the risk of HNC. We used a DRRD score to evaluate adherence to the dietary pattern and employed Cox regression analysis to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for HNC risk. Several subgroup analyses were carried out to identify potential effect modifiers, and multiple sensitivity analyses were performed to evaluate the stability of the correlation. The nine components of the DRRD was assessed separately for its association with the risk of HNC.

Results: During a mean follow up of 8.84 years, 279 cases of HNC were observed. DDRD score was found to be inversely associated with the risk of HNC ($HR_{Q4\ vs.\ Q1}$: 0.582; 95% CI: 0.396, 0.856; $p = 0.005$ for trend) in a linear dose–response manner ($p = 0.211$ for non-linearity). Subgroup analysis indicated this inverse correlation was more pronounced among participants who had never smoked ($HR_{Q4\ vs.\ Q1}$: 0.193; 95% CI: 0.073, 0.511; $p < 0.001$ for trend) compared to current or former smokers ($p = 0.044$ for interaction). The primary association of DDRD and HNC risk remained robust after several sensitivity analyses. Regarding the individual components of DRRD, an inverse association was also observed between the risk of HNC and increased intake of cereal fiber and whole fruit (all $p < 0.05$ for trend).

Conclusion: Our findings provide evidence that following the DRRD pattern may reduce the risk of NHC, especially for non-smokers.

KEYWORDS

diabetes risk reduction diet, head and neck cancer, epidemiology, cohort study, diet

Introduction

Head and neck cancer (HNC) is a prevalent type of cancer, ranking as the seventh most common globally (1). In the United States, 53,000 new cases of HNC and 10,860 deaths caused by HNC were reported in 2019 (2). Numerous studies have consistently shown that exposure to smoking and alcohol, poor oral hygiene, infection with Epstein–Barr virus (EBV) or human papillomavirus (HPV), as well as exposure to certain chemicals or radiation, are established as primary risk factors for HNC (3, 4). Recent researches in the field of HNC has highlighted the potential influence of dietary factors on the development of HNC (5). A diet rich in fruits and vegetables may be associated with a decreased risk of developing HNC (6), while high intake of red and processed meats may increase the risk of HNC (5). However, it should be emphasized that assessing the influence of singular foods or nutrients on tumor susceptibility may not provide a comprehensive understanding of the impact of dietary intake as a whole.

The diabetes risk reduction diet (DRRD) has gained popularity as a dietary pattern designed to prevent and control diabetes (7). The DRRD emphasizes a high proportion of cereal fiber, coffee, nuts, whole fruits, and a ratio of polyunsaturated to saturated fat, while limiting trans-fat, glycemic index (GI), sugar-sweetened beverages (SSBs), and red and processed meats (8). Since the DRRD dietary pattern includes a high intake of fruits and limits red and processed meats, it is possible that adhering to DRRD may reduce the risk of developing HNC. Additionally, although originally developed for diabetes prevention, studies have shown that following the DRRD may also reduce the incidence of several types of cancer, including lung (9), endometrial (10), breast (8), and pancreatic (11) cancers. Furthermore, the increased susceptibility of people with diabetes to HNC (12) further supports that adherence to the DRRD may have a potential link to reduced risk of HNC. However, there is currently limited research on this potential association.

To address this gap, we performed a prospective study to clarify the association of DRRD dietary pattern and the risk of HNC in a large American population. By conducting this prospective designed analysis, we aim to gain a better understanding of the potential role of the DRRD in preventing HNC, and to provide more comprehensive dietary recommendations to the public for reducing the risk of HNC.

Materials and methods

Study design and population

This study utilized data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. The PLCO trial is a large randomized controlled trial that was designed to evaluate the effectiveness of cancer screening tests for reducing cancer mortality rates. This trial was conducted between 1993 and 2001 at 10 clinical centers in the United States and enrolled 154,887 participants aged 55–74. All participants were randomly assigned to either a control group or an intervention group involving screening tests. The follow-up period extended until 2009 for the incidence of over 20 types of cancer, including HNC, and until 2018 for cancer-related mortality. The PLCO trial extensively collected data on the demographic characteristics, health history, lifestyle factors, and diet information of the participants through self-reported questionnaires. In this trial, participants were asked to complete two questionnaires: the baseline questionnaire (BQ) and the diet history questionnaire (DHQ) at the beginning of the trial. The DHQ relied on a 137-item food frequency questionnaire (FFQ) to gather data on dietary information over the past year, and the DRRD dietary pattern can be well established using the dietary data collected through DHQ. Detailed information on the PLCO trial has been reported in related literature (13).

The objective of our current study was to investigate whether adherence to the DRRD is related to the risk of HNC. The primary endpoint was defined as the diagnosis of HNC among participants, and the follow-up time was determined as the period from DHQ completion to the occurrence of HNC, death, loss during follow-up, or the end of the follow-up period (i.e., December 31, 2009), whichever occurred first (Figure 1). To achieve the study objective, a set of exclusion criteria were employed to establish an appropriate study cohort from an initial pool of 154,887 participants. Firstly, 4,918 participants who did not return the BQ were excluded. Secondly, 38,463 participants who either did not return the DHQ or returned an incomplete DHQ that having at least 8 missing frequency responses of dietary items, a missing completion date, completion date after death, or extreme energy consumption (top 1% and bottom 1%) were excluded. Thirdly, 9,683 participants with a history of any cancer prior to DHQ entry were excluded. Fourthly, 68 participants who experienced an outcome event between DHQ entry and DHQ completion were excluded. Ultimately, the remaining cohort comprised 101,755 individuals in our study, as illustrated in Figure 2.

Assessment of DRRD dietary pattern

To evaluate the adherence of each participant to DRRD, a DRRD score was calculated based on the methodology described in previous studies (9). Briefly, the intakes of the nine DRRD components were obtained from the DHQ, and then each component was categorized into five groups based on its quintile values of dietary intake, and assigned scores ranging from 1 to 5. For cereal fiber, coffee, nuts, whole fruits, and the ratio of polyunsaturated to saturated fat, a higher quintile value indicated a higher score. Conversely, for trans-fat, GI, SSBs, and red and processed meats, a lower quintile value indicated a higher score. The DRRD score was then calculated by summing the scores of the nine components, resulting in a range of 9 to 45. An increased DRRD score indicates greater adherence to the DRRD dietary pattern. Detailed data for determining DRRD score was shown in Supplementary Table S1.

HNC ascertainment

The ascertainment of HNC cases primarily relied on the administration of an annual study update form, which was disseminated by each screening center to participants. This form was

Abbreviations: BQ, Baseline questionnaire; CIs, Confidence intervals; DHQ, Diet history questionnaire; DRRD, Diabetes risk reduction diet; EBV, Epstein-barr virus; FFQ, Food frequency questionnaire; GI, Glycemic index; HNC, Head and neck cancer; HPV, Human papillomavirus; HRs, Hazard ratios; NCI, National cancer institute; PLCO, Prostate lung colorectal and ovarian; SSBs, Sugar-sweetened beverages.

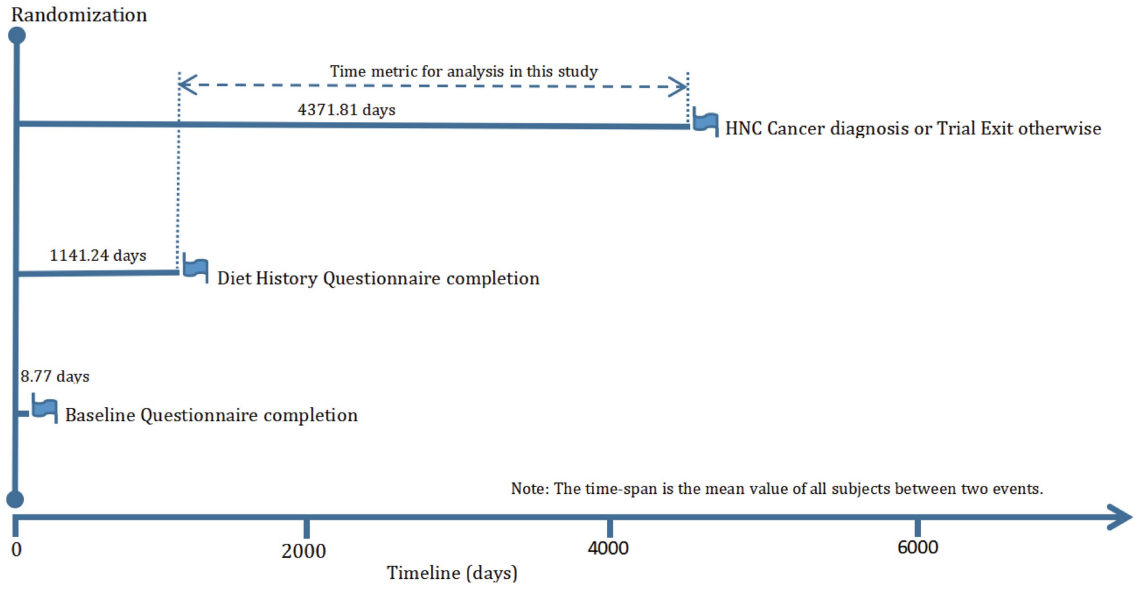

FIGURE 1
The timeline and follow-up scheme of our study.

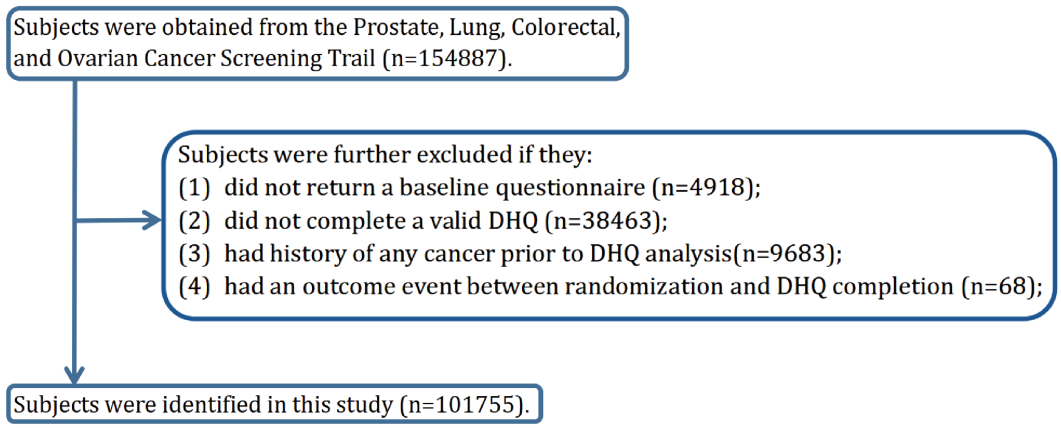

FIGURE 2
The flow chart of identifying eligible participants. PLCO, Prostate, Lung, Colorectal, and Ovarian; BQ, baseline questionnaire; DHQ, diet history questionnaire.

designed to elicit information on whether individuals had received a diagnosis of HNC, along with the date and location of the diagnosis, and the contact details of their healthcare providers. HNC cases were defined based on the following ICD-O-2 codes for malignant tumors: (1) oral cavity: C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8 and C06.9; (2) oropharynx: C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2–C10.4, C10.8 and C10.9; (3) hypopharynx: C12.9, C13.0–C13.2, C13.8 and C13.9; (4) oral cavity or pharynx NOS: C02.8, C02.9, C05.8, C05.9, C14.0, C14.2 and C14.8; and (5) larynx: C10.1, C32.0–C32.3 and C32.8–C32.9. Cases of NHC reported through this form were subjected to further verification by scrutinizing any available medical records. In addition, supplementary sources such as death certificates and family reports were utilized to augment the ascertainment process. To ensure consistency in case selection, only participants who had received a diagnosis of HNC were included in the study.

Assessment of covariates

The study gathered information on age at DHQ completion, drinking status and alcohol consumption, energy intake, food and nutrient consumption via the DHQ. Daily food intake was determined by multiplying food frequency by portion size, while daily nutrient intake was estimated using the USDA's 1994–96 Continuing Survey of Food Intakes by Individuals and the Nutrition Data Systems for Research (14). The detailed calculation methods of dietary fiber, GI, and trans-fat are available in previously published literatures (15–17). Additional data or covariates, such as gender,

race, body mass index (BMI), educational level, marital status, smoking status, pack-years of smoking, history of diabetes, and family history of HNC, were obtained using a self-administered baseline questionnaire.

Statistical analysis

To reduce potential biases and enhance the statistical power of our study, imputation was performed using modal values for categorical variables and median values for continuous variables. Supplementary Table S2 displays the distribution of variables with missing values before and after imputation. To examine the potential impact of data imputation on our results, we also repeated the primary statistical analyses in the population with complete covariate data in the subsequent sensitivity analysis.

To evaluate the association between DRRD and HNC risk, the study employed Cox proportional hazards regression as the primary analysis model, with follow-up period as the time metric. The DRRD score was categorized into quartiles, with the lower quartile serving as the reference group. Person-years of each quartile were estimated based on the duration of follow-up. To assess whether a linear trend could be observed across quartiles of DRRD scores for estimating HNC risk, median values of each quartile were assigned to individuals within the corresponding quartile and treated as a continuous variable in regression models. After examining the Schoenfeld residuals, we found that the proportional hazards assumption of the Cox regression model was satisfied (P for global test > 0.05). Multivariable regression models were utilized to further adjust potential covariates. Specifically, model 1 was adjusted for age, sex, and race. Model 2 included additional adjustments for marital status, educational level, BMI, family history of HNC, smoking status, pack-years of smoking, drinking status, alcohol consumption, history of diabetes, and energy from diet. A restricted cubic spline model with three knots (i.e., 10th, 50th, and 90th percentiles of DRRD score) was employed to analyze HNC risk across the entire range of the DRRD score. Additionally, we conducted further analyses to investigate the association between the nine dietary components of the DRRD and HNC risk using similar Cox regression model as described above. Specifically, we obtained the intake of each dietary component of the DRRD from the DHQ and divided them into quartiles, with the lowest quartile serving as the reference group.

To investigate whether the association between DRRD score and HNC risk was modified by various factors, subgroup analyses were conducted. Participants were divided into categories based on age (>65 vs. ≤65 years), sex (male vs. female), BMI (≤25 vs. >25 kg/m2), smoking status (never vs. current or former), pack-years of smoking (≤medium vs. >medium), drinking status (no vs. yes), alcohol consumption (≤medium vs. >medium), history of diabetes (no vs. yes), Family history of HNC (no vs. yes), and energy from diet (≤medium vs. >medium). Interaction *p* values were computed by comparing models with and without multiplicative interaction terms before subgroup analyses to avoid spurious subgroup effects. Additionally, sensitivity analyses were conducted to confirm the robustness of the primary results. These included repeating the primary analysis in participants with complete data, excluding participants with diabetes, excluding participants with follow-up less than 2 years, excluding participants with extreme energy intake (>4,000 kcal/day or <500 kcal/day), and excluding participants with extreme BMI (top 1% and bottom 1%).

The statistical significance level was set at a p value of < 0.05. R 4.2.1 software was utilized for all statistical analyses.

Results

Baseline characteristics

In this study, a total of 101,755 individuals were included and categorized into quartiles based on their DRRD scores: quartile 1 ($n = 27,890$) with scores between 9 and 23, quartile 2 ($n = 28,970$) with scores between 24 and 27, quartile 3 ($n = 19,784$) with scores between 28 and 30, and quartile 4 ($n = 25,111$) with scores between 31 and 45. The mean (standard deviation) DRRD score for all participants was 26.84 (5.31), and their baseline characteristics were presented in Table 1. Compared to the lowest quartile group, individuals in the highest quartile group tended to be female, older, have a lower BMI, non-smoker or have fewer pack-years of smoking, a drinker or have high alcohol consumption, and have no history of diabetes. Moreover, those in the highest quartile of DRRD scores had a lower intake of energy compared to those in the lowest quartile.

Association between DRRD score and HNC risk

This study followed up with a total of 900001.9 person-years and recorded 279 cases of malignant primary HNC. The overall incidence was 3.1 cases/10,000 person-years with a mean (standard deviation) follow-up duration of 8.84 (1.92) years. The results of Cox regression analysis of the entire study population are presented in Table 2. The unadjusted model analysis showed that individuals in the highest quartile group had a lower risk of HNC compared to those in the lowest quartile group ($HR_{Q4\ vs.\ Q1}$: 0.392; 95% CI: 0.271, 0.568; $p < 0.001$ for trend). After adjusting for all potential confounding factors, the inverse association between DRRD score and HNC risk remained significant ($HR_{Q4\ vs.\ Q1}$: 0.582; 95% CI: 0.396, 0.856; $p = 0.005$ for trend). In the restricted cubic spline regression model, DRRD score was found to have an inverse association with the risk of HNC in a linear dose-response manner ($p = 0.211$ for non-linearity), as shown in Figure 3.

Subgroup analyses

The subgroup analyses results are presented in Table 3, indicating that the inverse correlation between DRRD score and HNC risk was not modified by various factors such as age, sex, BMI, pack-years of smoking, drinking status, alcohol consumption, history of diabetes and energy from diet (all P for interaction > 0.05). However, the inverse correlation was more pronounced among participants who had never smoked ($HR_{Q4\ vs.\ Q1}$: 0.193; 95% CI: 0.073, 0.511; $p < 0.001$ for trend) compared to current or former smokers ($p = 0.044$ for interaction).

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TABLE 1 Baseline characteristics of study population according to overall diabetes risk reduction diet score.

Characteristics	Overall	Quartiles of diabetes risk reduction diet scores				*p*-value
		Quartile 1 (9–23)	Quartile 2 (24–27)	Quartile 3 (28–30)	Quartile 4 (31–45)	
Number of participants	101,755	27,890	28,970	19,784	25,111	
Diabetes risk reduction diet score	26.84 ± 5.31	20.43 ± 2.37	25.53 ± 1.11	28.93 ± 0.81	33.80 ± 2.56	0.000
Age (years)	65.53 ± 5.73	64.66 ± 5.61	65.54 ± 5.71	65.90 ± 5.77	66.18 ± 5.75	<0.001
Sex						0.000
Male	49,496 (48.6%)	16,282 (58.4%)	14,856 (51.3%)	8,839 (44.7%)	9,519 (37.9%)	
Female	52,259 (51.4%)	11,608 (41.6%)	14,114 (48.7%)	10,945 (55.3%)	15,592 (62.1%)	
Race						0.899
Non-hispanic	100,136 (98.41%)	27,449 (98.42%)	28,497 (98.37%)	19,478 (98.45%)	24,712 (98.41%)	
Hispanic	1,619 (1.59%)	441 (1.58%)	473 (1.63%)	306 (1.55%)	399 (1.59%)	
Marital status						<0.001
Live together	79,826 (78.45%)	22,143 (79.39%)	23,066 (79.62%)	15,509 (78.39%)	19,108 (76.09%)	
Live alone	21,929 (21.55%)	5,747 (20.61%)	5,904 (20.38%)	4,275 (21.61%)	6,003 (23.91%)	
Education level						<0.001
College below	42,937 (42.20%)	13,845 (49.64%)	12,756 (44.03%)	7,850 (39.68%)	8,486 (33.79%)	
College and beyond	58,818 (57.80%)	14,045 (50.36%)	16,214 (55.97%)	11,934 (60.32%)	16,625 (66.21%)	
Body mass index (kg/m^2)	27.2 ± 4.8	28.2 ± 5.0	27.5 ± 4.7	26.9 ± 4.6	26.0 ± 4.4	0.000
Smoking status						<0.001
Never	48,580 (47.74%)	12,409 (44.49%)	13,572 (46.85%)	9,700 (49.03%)	12,899 (51.37%)	
Current	9,401 (9.24%)	3,772 (13.52%)	2,841 (9.81%)	1,488 (7.52%)	1,300 (5.18%)	
Former	43,774 (43.02%)	11,709 (41.98%)	12,557 (43.34%)	8,596 (43.45%)	10,912 (43.46%)	
Pack-years of smoking	17.65 ± 26.59	21.68 ± 30.02	18.37 ± 26.98	16.13 ± 25.02	13.55 ± 22.23	<0.001
Drinking status						< 0.001
No	27,757 (27.28%)	8,654 (31.03%)	7,780 (26.86%)	5,006 (25.30%)	6,317 (25.16%)	
Yes	73,998 (72.72%)	19,236 (68.97%)	21,190 (73.14%)	14,778 (74.70%)	18,794 (74.84%)	
Alcohol consumption (g/day)	9.53 ± 25.25	8.38 ± 23.51	9.69 ± 24.36	10.66 ± 28.09	9.75 ± 25.71	<0.001
History of diabetes						<0.001
No	94,949 (93.31%)	25,675 (92.06%)	26,957 (93.05%)	18,531 (93.67%)	23,786 (94.72%)	
Yes	6,806 (6.69%)	2,215 (7.94%)	2013 (6.95%)	1,253 (6.33%)	1,325 (5.28%)	
Family history of head and neck cancer						0.955
No	100,308 (98.58%)	27,490 (98.57%)	28,563 (98.60%)	19,496 (98.54%)	24,759 (98.60%)	
Yes	1,447 (1.42%)	400 (1.43%)	407 (1.40%)	288 (1.46%)	352 (1.40%)	
Energy from diet (kcal/day)	1738.63 ± 736.43	1796.97 ± 740.65	1739.26 ± 782.37	1715.34 ± 763.68	1691.48 ± 645.23	< 0.001
Diabetes risk reduction diet components						
Cereal fiber (g/day)	11.85 ± 5.70	9.32 ± 4.17	11.08 ± 5.15	12.49 ± 5.61	15.06 ± 6.20	0.000
Whole fruit (servings/day)	2.73 ± 2.04	1.68 ± 1.26	2.43 ± 1.73	3.03 ± 1.96	4.02 ± 2.38	0.000
Nuts (g/day)	6.73 ± 14.53	2.74 ± 5.68	4.95 ± 9.88	7.41 ± 14.83	12.68 ± 21.83	0.000
Coffee (g/day)	846.37 ± 794.46	730.20 ± 788.94	869.56 ± 802.57	892.66 ± 790.48	912.15 ± 780.59	<0.001
Ratio of polyunsaturated to saturated fat	0.76 ± 0.26	0.62 ± 0.18	0.72 ± 0.22	0.80 ± 0.24	0.95 ± 0.28	0.000
Glycemic index from diet	53.55 ± 3.31	55.64 ± 2.99	53.89 ± 3.01	52.78 ± 2.92	51.45 ± 2.74	0.000
Trans fat (g/day)	3.99 ± 2.39	4.94 ± 2.54	4.21 ± 2.50	3.67 ± 2.23	2.92 ± 1.65	0.000
Sugar-sweetened beverage (g/day)	264.50 ± 433.29	449.55 ± 565.48	264.39 ± 407.34	191.50 ± 329.20	116.61 ± 254.42	0.000
Red and processed meat (g/day)	12.42 ± 15.31	19.51 ± 19.26	13.41 ± 15.00	9.79 ± 11.83	5.46 ± 7.57	0.000

Values are means (standard deviation) for continuous variables and percentages for categorical variables.

TABLE 2 Hazard ratios of the association of DRRD score with the risk of HNC.

Quartiles of DRRD score	Number of cases	Person-years	Incidence rate per 100 person-years (95% confidence interval)	Hazard ratio (95% confidence interval)		
				Unadjusted	Model 1[a]	Model 2[b]
Quartile 1 (9–23)	105	243469.8	0.043 (0.036, 0.052)	1.000 (reference)	1.000 (reference)	1.000 (reference)
Quartile 2 (24–27)	91	256387.8	0.035 (0.029, 0.044)	0.822 (0.621, 1.088)	0.874 (0.659, 1.158)	0.951 (0.716, 1.264)
Quartile 3 (28–30)	45	175735.3	0.026 (0.019, 0.034)	0.593 (0.418, 0.840)	0.678 (0.477, 0.964)	0.761 (0.533, 1.087)
Quartile 4 (31–45)	38	224409.0	0.017 (0.012, 0.023)	0.392 (0.271, 0.568)	0.486 (0.334, 0.707)	0.582 (0.396, 0.856)
P for trend				**<0.001**	**<0.001**	**0.005**

[a]Adjusted for age, sex and race.
[b]Adjusted for model 1 plus marital status, educational level, BMI, smoking status, pack-years of smoking, drinking status, alcohol consumption, history of diabetes, family history of HNC, and energy from diet.
The bold values are indicate statistical significance, with *p*-values less than 0.05.

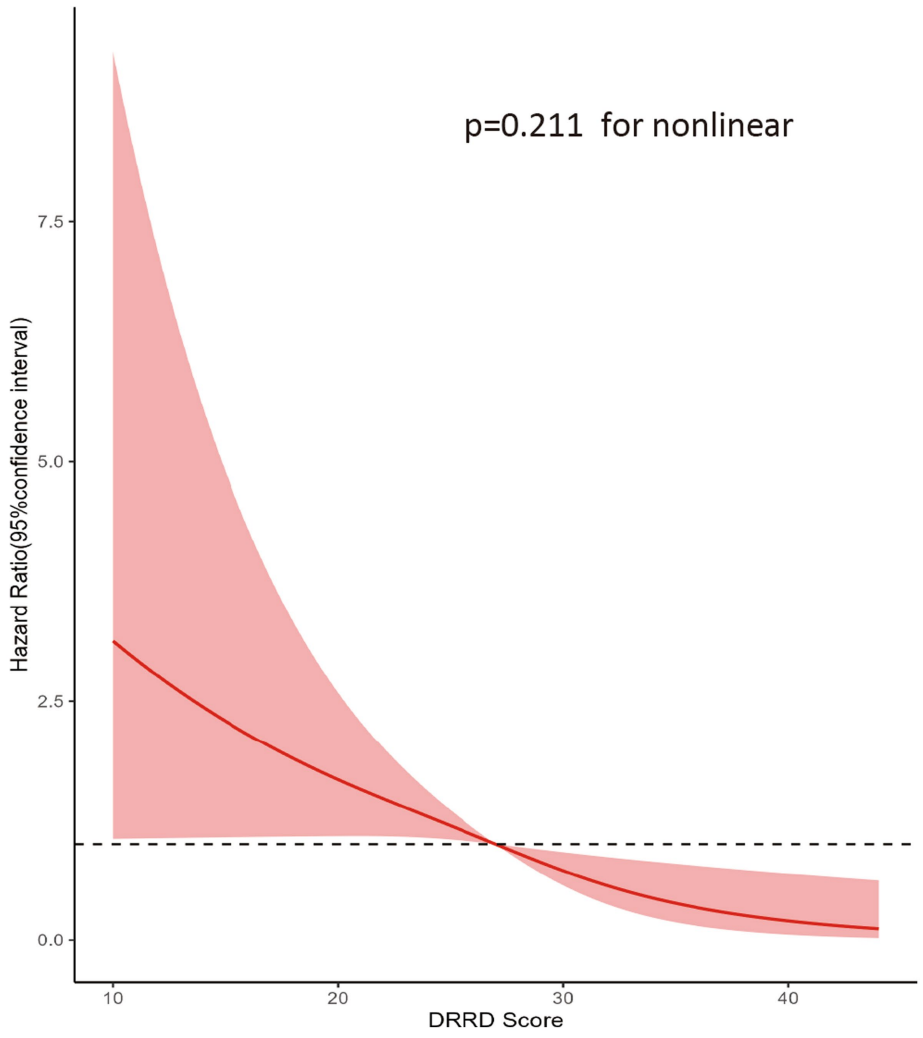

FIGURE 3
Dose-response association between DRRD score and the risk of HNC. Hazard ratio was adjusted for age, sex, marital status, race, educational level, BMI, family history of HNC, smoking status, pack-years of smoking, drinking status, alcohol consumption, history of diabetes, and energy from diet.

Sensitivity analyses

The results of several sensitivity analyses are presented in Table 4, and indicate that the inverse association between DRRD score and HNC risk did not change significantly, thereby further confirming the robustness of our primary findings. Specifically, when Cox regression analyses were repeated in participants with complete covariate data, we obtained similar results ($HR_{Q4\ vs.\ Q1}$: 0.542; 95% CI: 0.360, 0.816; $p = 0.003$ for trend).

TABLE 3 Subgroup analyses on the association of DRRD score with the risk of HNC.

Subgroup variable	No. of cases	Person-years	Hazard ratio (95% confidence interval) by DRRD score				P_{trend}	$P_{interaction}$
			Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Age								0.331
≤65 years old	128	469864.9	1.00 (reference)	0.706 (0.462, 1.079)	0.613 (0.359, 1.046)	0.518 (0.294, 0.912)	0.008	
>65 years old	151	430137.0	1.00 (reference)	1.129 (0.762, 1.673)	0.804 (0.496, 1.303)	0.534 (0.316, 0.901)	0.016	
Sex								0.795
Male	222	432707.9	1.00 (reference)	0.966 (0.707, 1.321)	0.753 (0.505, 1.121)	0.532 (0.34, 0.832)	0.004	
Female	57	467294.0	1.00 (reference)	0.656 (0.335, 1.284)	0.518 (0.238, 1.129)	0.454 (0.215, 0.957)	0.028	
Body mass index (kg/m^2)								0.43
≤25	97	307723.0	1.00 (reference)	0.677 (0.404, 1.134)	0.611 (0.335, 1.112)	0.557 (0.311, 0.997)	0.038	
>25	182	592278.9	1.00 (reference)	1.060 (0.753, 1.491)	0.793 (0.511, 1.231)	0.521 (0.311, 0.874)	0.018	
Smoking status								**0.044**
Never	63	436330.0	1.00 (reference)	0.686 (0.387, 1.216)	0.426 (0.199, 0.914)	0.193 (0.073, 0.511)	**<0.001**	
Current or former	216	463671.8	1.00 (reference)	1.007 (0.726, 1.397)	0.831 (0.556, 1.243)	0.687 (0.451, 1.046)	0.076	
Pack-years of smoking								0.069
≤medium	67	462817.4	1.00 (reference)	0.672 (0.386, 1.172)	0.444 (0.214, 0.918)	0.181 (0.069, 0.475)	<0.001	
>medium	212	437184.4	1.00 (reference)	0.962 (0.692, 1.337)	0.757 (0.504, 1.136)	0.613 (0.403, 0.932)	0.017	
Drinking status								0.393
No	62	243394.2	1.00 (reference)	1.056 (0.6, 1.858)	0.403 (0.154, 1.051)	0.487 (0.209, 1.135)	0.042	
Yes	217	656607.6	1.00 (reference)	0.878 (0.633, 1.218)	0.773 (0.525, 1.14)	0.521 (0.339, 0.801)	0.003	
Alcohol consumption (g/day)								0.549
≤medium	99	453246.6	1.00 (reference)	0.876 (0.554, 1.385)	0.507 (0.26, 0.989)	0.422 (0.214, 0.83)	0.005	
>medium	180	446755.2	1.00 (reference)	0.954 (0.664, 1.371)	0.848 (0.553, 1.3)	0.599 (0.375, 0.958)	0.039	
History of diabetes								0.582
No	262	843913.7	1.00 (reference)	0.911 (0.68, 1.222)	0.738 (0.514, 1.06)	0.508 (0.341, 0.756)	0.001	
Yes	17	56088.0	1.00 (reference)	0.913 (0.301, 2.764)	0.24 (0.029, 1.98)	0.692 (0.172, 2.79)	0.362	
Energy from diet (kcal/day)								0.375
≤medium	99	450318.8	1.00 (reference)	1.093 (0.684, 1.747)	0.546 (0.285, 1.048)	0.509 (0.267, 0.968)	0.016	
>medium	180	449683.0	1.00 (reference)	0.809 (0.564, 1.159)	0.793 (0.519, 1.211)	0.522 (0.324, 0.841)	0.009	

Hazard ratios were adjusted for age, sex, race, marital status, educational level, BMI, smoking status, pack-years of smoking, drinking status, alcohol consumption, history of diabetes, family history of HNC, and energy from diet.
The bold values are indicate statistical significance, with *p*-values less than 0.05.

Dietary components of DRRD and the risk of HNC

We further investigated the association between each dietary components of DRRD and the risk of HNC. Our Results indicated that individuals in the highest quartile of cereal fiber and whole fruit consumption, considered as "favorable" DRRD components, had a lower risk of HNC compared to those in the lowest quartile [(cereal fiber: $HR_{Q4\ vs.\ Q1}$: 0.471; 95% CI: 0.301, 0.739; $p = 0.002$ for trend) (Supplementary Table S3) and (whole fruit: $HR_{Q4\ vs.\ Q1}$: 0.555; 95% CI: 0.372, 0.829; $p = 0.002$ for trend) (Supplementary Table S4)]. However, there was no significant association between the risk of HNC and other DRRD components, such as nuts, coffee, polyunsaturated/saturated fatty acids, trans-fat, GI, SSBs, and red meat and processed meat (Supplementary Tables S5–S11).

Discussion

The present study provides evidence that a higher DRRD score is associated with a decreased incidence of HNC in a large US population of approximately 100,000 individuals, which was further confirmed by a series of sensitivity analyses. Moreover, subgroup analyses revealed that this inverse association was more pronounced in individuals who never smoked, indicating that adhering to the DRRD dietary pattern may benefit the population by reducing the risk of HNC, particularly among non-smokers. Additionally, among the nine components of the DRRD diet, it was found that high intake of cereal fiber and whole fruit was associated with a reduced risk of HNC, suggesting that promoting the intake of cereal fiber and whole fruit should be encouraged as part of the DRRD dietary pattern.

TABLE 4 Sensitivity analyses on the association of DRRD score with the risk of HNC.

Categories	HR $_{\text{Quartile 4 vs. Quartile 1}}$ (95% CI)[a]	*P* for trend
Repeating analysis in participants with complete data[b]	0.542 (0.360, 0.816)	**0.003**
Excluding participants with diabetes[c]	0.580 (0.388, 0.865)	**0.009**
Excluding participants with a follow-up less than 2 years	0.587 (0.383, 0.901)	**0.015**
Excluding participants with extreme energy intake[d]	0.551 (0.372, 0.816)	**0.002**
Excluding participants with extreme BMI[e]	0.581 (0.394, 0.858)	**0.005**

[a]HR was adjusted for age, sex, race, marital status, educational level, BMI, smoking status, pack-years of smoking, drinking status, alcohol consumption, history of diabetes, family history of HNC, and energy from diet.
[b]Sample size of participants with complete data: $n = 98,037$.
[c]HR was not adjusted for history of diabetes.
[d]The extreme energy intake was defined as >4,000 kcal/day or <500 kcal/day.
[e]The extreme BMI was defined as top 1% or bottom 1% in the included population.
The bold values are indicate statistical significance, with *p*-values less than 0.05.

Over the past four decades, there has been a steady increase in the number of adults worldwide suffering from diabetes, growing from 108 million in 1980 to 463 million in 2019 (18). Diabetes is a systemic disease known to cause serious health complications, including kidney failure, peripheral arterial disease, infections, and cardiovascular disease (19), and it increases the risk of hypertension, obesity, and dyslipidemia (20). Additionally, increasing evidence suggests that individuals with diabetes are more susceptible to developing cancer (21). For instance, A meta-analysis of 36 researches revealed that people with diabetes had an adjusted odds ratio of 1.82 for pancreatic cancer compared to those without diabetes (22). Another meta-analysis of 20 studies concluded that diabetes is related to higher risks of both breast and colorectal cancer incidence as well as cancer-specific mortality (23). Four systematic reviews also found consistent results, indicating that diabetes elevates the risk of developing ovarian cancer (24–27). Specifically, a study conducted in an Asia population reported that diabetes is closely related to an enhanced risk of HNC (12). To tackle diabetes, the DRRD dietary pattern was developed in 2015 and has since gained popularity (28). Although originally developed for the prevention and control of diabetes, previous prospective studies have highlighted that following DRRD may reduce the incidence of pancreatic (29), liver (30), breast (31), and lung (9) cancers. To our knowledge, this study is the first to establish the association between adherence to the DRRD and a reduced risk of HNC. Therefore, the findings of this study may provide valuable dietary guidance for preventing HNC in the general population.

Several potential mechanisms may explain the association between DRRD and the reduced risk of HNC. Firstly, DRRD may lower the risk of HNC by reducing chronic inflammation, which has been linked to the development of tumors (32). DRRD dietary pattern recommends high intakes of fiber (33), nuts (34), coffee (35), polyunsaturated fat (36), and fruits (37), which are associated with lower inflammation levels. In contrast, DRRD recommends limiting the intake of high glycemic index foods (38), trans fatty acids (39), SBBs (40), red and processed meats (41), which are positively correlated with higher levels of inflammation. Importantly, it has been well established that higher adherence to DRRD was associated with lower levels of inflammation (42). Secondly, diabetes may increase the risk of obesity, which leads to the expression of tumor-susceptibility genes, tissue hypoxia, and a higher differentiation rate in adipose stromal cells, ultimately transforming normal cells into malignant tumors (43). Therefore, adhering to DRRD, which may reduce the risk of diabetes and obesity (28), could potentially lower the risk of oncogenesis. Thirdly, hyperinsulinemia and hyperglycemia are closely related to accelerated biological aging and the stimulation of cellular signaling pathways associated with growth factor-dependent cell proliferation and cancer development (9). Additionally, cancer cells consume large amounts of glucose when growing and proliferating (44). It has been reported that insulin resistance directly promotes carcinogenesis in diabetic individuals (45), and insulin-like growth factor-1 initiates and progresses tumor growth (46). Therefore, we speculate that the reduced risk of HNC may be attributed to the reduction of chronic inflammation, obesity, hyperinsulinemia, hyperglycemia, and insulin resistance related to DRRD dietary pattern.

Interestingly, our subgroup analyses revealed that the inverse association between the DRRD score and HNC was more pronounced in non-smokers. This observation may be linked to inflammation, which has been demonstrated to play a critical role in the development and progression of HNC (47). Studies have shown that smoking or an increase in smoking can lead to elevated levels of somatic inflammation (48, 49), whereas adherence to the DRRD can decrease these levels. Additionally, Ramo et al. (50) discovered that smokers are more likely to engage in multiple health-risk behaviors, including poor dietary habits and lack of physical activity. Therefore, we speculate that non-smokers may be more inclined to follow a healthy dietary pattern, such as the DRRD, to maintain good health.

Our study has some limitations. Firstly, the dietary information used to calculate the DRRD score was collected only once, which may not accurately reflect changes in dietary habits over time, leading to non-differential bias. Nevertheless, as adults' dietary habits usually do not change significantly in nutritional epidemiology (51), this limitation may not be significant. Secondly, information on EBV and HPV infection was not obtained for each participant and could not be adjusted in the analysis due to data lacking, potentially affecting the results. However, since EBV and HPV infection status is unlikely to be specifically associated with dietary intake, it might not meet the properties of a confounder. Lastly, the study's population was limited to individuals aged 55–74 years in the US, and therefore, caution should be exercised in applying the findings to other populations. Further research is needed to confirm the universality of our observed results in other populations.

In conclusion, our findings suggest that DRRD dietary pattern is associated with a reduced risk of HNC in a large US population,

especially among non-smokers. These findings provide evidence that adherence to DRRD may be beneficial in preventing HNC.

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 authors.

Ethics statement

The present study involved human participants who were reviewed and approved by the Institutional Review Board of the NCI and the ten PLCO trial screening centers. Written informed consent was obtained from all individuals in the PLCO study. This study has been approved by the NCI (approval number: PLCO-1140).

Author contributions

LX designed the study. LP and LX request access to the original data. XW, CZ, and YX analyzed the data. XW, LP, HL, ZX, JW, HG, and YW assisted with statistical analysis. XW, CZ, and LX assisted in the interpretation of the results. XW, YX, CZ, and LX drafted the initial manuscript and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1218632/full#supplementary-material

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Dietary total antioxidant capacity and head and neck cancer: a large case-control study in Iran

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Background: Data on the association between head and neck cancer (HNC) and dietary factors are inconclusive. No study has so far investigated the association between dietary total antioxidant capacity (dTAC) and HNC concerning interactions with other risk factors.

Method: Pathologically confirmed new diagnosed HNC patients were included in this study. The control group was healthy hospital visitors who were frequently matched with patients on age (5years interval), gender, and province of residence. Trained interviewers administered a validated Food Frequency Questionnaire (FFQ) to assess the participants' food intake 1year before the cancer diagnosis. Data on TAC scores of foods was collected by Ferric Reducing Antioxidant Power (FRAP) and Total Radical-trapping Antioxidant Parameters (TRAP) from published data. We applied logistic regression adjusted for age, sex, energy intake, socioeconomic status, province, opium use, alcohol use, physical activity, and dental health. We also studied the interaction of dTAC with tobacco smoking status, and opium use on the risk of HNC.

Results: We recruited 876 HNC patients and 3,409 healthy controls. We observed a significant decrease in the odds of HNC with increasing dTAC scores. The OR of HNC for the third vs. the first tertile was 0.49 (95%CI 0.39–0.61) for FRAP and 0.49 (95%CI 0.39–0.62) for TRAP. Both dTAC scores were inversely associated with lip and oral (T3 ver. T1 OR = 0.51; 95%CI 0.36–0.71 for FRAP and OR = 0.59; 95% CI 0.44–0.82 for TRAP) and larynx (T3 ver. T1 OR = 0.43; 95%CI 0.31–0.61 for FRAP and OR = 0.38; 95% CI 0.26–0.55 for TRAP) cancers. There was no interaction between tobacco smoking, opium use; and TRAP or FRAP on the risk of HNC.

Conclusion: An antioxidant-rich diet in terms of FRAP or TRAP could decrease the risk of HNC and its subtypes.

KEYWORDS

head and neck cancer, dietary antioxidant capacity, case–control study, FRAP, TRAP

Highlights

- Data on the association between head and neck cancer (HNC) and dietary factors are inconclusive.
- An antioxidant-rich diet in terms of FRAP or TRAP could decrease the risk of HNC and its subtypes.
- Promoting consumption of high antioxidant foods such as fruit, vegetable, and whole grains may reduce the risk of HNC.

Background

Head and Neck Cancers (HNC) are the seventh most common cancer in the world, and these cancers account for 4% of cancer deaths worldwide (1, 2). In addition to the psychological problems of the patients and their families, disability, and death caused by HNC impose a tremendous economic burden on our society (3–5). Sixty-five percent of HNC cancers occur in low and middle-income countries (6). Unfortunately, the prognosis of HNC is poor (7) and survivors struggle with various problems, including breathing and eating disorders (8). Therefore, identifying risk factors and implementing prevention are the primary strategies for controlling these cancers.

Several risk factors are associated with HNC, including cigarette smoking, alcohol drinking, asbestos exposure, HPV infection, and opium use (6, 9) A recent comprehensive review of nutritional factors and cancer risk by the World Cancer Research Fund (WCRF) and the American Cancer Institute concluded that data on associations between several dietary components and HNC are inconclusive (6). This review concluded for limited evidence of a protective effect of non-starchy vegetables and a healthy nutritional lifestyle against HNC. No definitive conclusions can be drawn regarding other dietary factors, including fruits, legumes, animal foods, and other nutrients (6).

Chronic inflammation, shown by increased levels of inflammatory cytokines, plays an essential role in developing various types of cancer, including HNC (10, 11). Dietary factors can inhibit or accelerate inflammation in our bodies (12). Dietary components such as phenols, antioxidant vitamins, and inflammatory nutrients were associated with cancer (13). Also, consuming several foods, including fruits and vegetables or animal foods, can influence inflammatory pathways that alter cancer development (12, 14, 15). Some food factors increase inflammatory cytokines and endothelial growth factors, which increase angiogenesis and proliferation (15–17). Several studies have investigated the effects of these inflammatory factors on HNC development (10, 16). On the other hand, several studies have shown that consuming fruits, chocolate, berries, whole grains, and other antioxidant-rich foods can reduce cancer incidence (6, 18, 19). It is claimed that dietary antioxidants can reduce reactive oxygen or nitrogen species, thereby reducing DNA oxidation (11, 13).

Previous studies examined the association between one or more foods or nutrients and the risk of different cancers separately (20). However, dietary components are not eaten separately, and the interactions between different foods may increase or decrease the risk of different diseases (21). Therefore, the effect of the whole diet on disease risk will differ from each component alone (21). To consider this, total dietary antioxidant capacity (dTAC) scores were introduced to calculate the antioxidant effects of whole diets (22–24). Several studies have examined the association between these dietary scores and colon, breast, and endometrial cancer risk (14, 25, 26). Data on the association between HNC and nutritional components are limited, and the existing reports are inconclusive. In this study, we evaluated for the first time the association between dTAC and HNC in a large case–control study.

Methods

This study was conducted using data from the IROPICAN study. That study is a large multicenter case–control study that evaluated the relationship between opium use and the risk of lung, bladder, head and neck, and colorectal cancers. The data has been collected in 10 provinces in the east, south, north, and center of Iran (27). The participants were interviewed using standard questionnaires about their lifestyle and validated Food Frequency Questionnaire (FFQ) (28).

Pathologically confirmed incident HNC patients with no cancer history were included in this study. Tumor subsite was uniformly classified using ICD-O3 codes. HNC cases in this study included ICD-O3 HNC codes of oral, larynx, and pharynx (e.g., C00–C09, C11, C12, C14, C31, and C32). The control group was healthy hospital visitors, frequency matched on age (5 years apart), gender, and province of residence. Controls were independently matched to the patient group of each cancer type, but we used control data from all cancer types for our analysis. They were relatives or friends of non-cancer patients and were visiting the general hospitals where the cases were selected (29). The main inclusion criteria for patients was pathologically confirmed HNC. The exclusion criterion was being affected by other cancers rather than HNC. In controls, exclusion criterion was diagnosis of any cancers.

Trained interviewers conducted the face-to-face interview using a structured questionnaire to obtain demographic and other non-dietary data. A detailed description of the questionnaire and computing-related scores are described previously (16). Socioeconomic status (SES) was determined using principal component analysis by combining some data related to education, income, and ownership of some home appliances. Then we put subjects in three groups based on scores in control group. Physical activity workload (PPWL) was estimated based on job history of participants using the Finland Job Exposure Matrix (FINJEM) (30). Then, the participants were categorized to three groups of physical

activity based on PPWL scores: sedentary (zero PPWL-years), moderate (PPWL-years greater than zero and less than or equal to 4.80), and heavy (PPWL-years greater than 4.81). Dental health was defined by a score in our study considering decayed, missing and filled teeth, participants were categorized to three categorizes based on scores in control group.

dTAC scoring

Trained interviewers administered validated FFQs to assess the participants' food intake a year before the study (31). Long term dietary habits of individual are associated with their health outcomes. As HNC extremely affects patients' food habits, we asked patients to report their food intake before their cancer diagnosis. All study data, including dietary data, were entered into an online system that supervisors could continuously review. The food composition table was prepared using USDA food composition tables (32). Data on TAC scores of foods by Ferric Reducing Antioxidant Power (FRAP) and Total Radical-trapping Antioxidant Parameters (TRAP), which measure the reducing power and the chain-breaking antioxidant capacity, respectively, was gathered from published data (33, 34).

Statistical analysis

The TRAP and FRAP scores were adjusted for energy by the residual method suggested by Willett (35). Before analyzing the data 76 subjects were omitted because of incomplete questionnaires or pathological issues (unconfirmed pathological diagnosis or metastases). Subjects who reported energy intake less than 500 and over 4,500 Kcal/d were considered outliers and omitted. It caused a 2% reduction in both cases and controls (18 subjects out of 849 patients and 74 subjects out of 3,484 controls). Participants were classified into tertiles of dTAC scores based on the distribution in the control group. We applied unconditional logistic regression in crude and adjusted models to determine the association between dTAC scores and HNC. The full model was adjusted for age (5categories), sex(male/female), province of residence (10 provinces), energy intake (kcal/day, continuous), socioeconomic status (low, medium, high), opium use (yes, no), tobacco smoking (yes, no), water pipe smoking (yes, no) regular alcohol drinking (yes, no), physical activity (sedentary, moderate, heavy, unknown) and dental health (poor, moderate, good). We tested the linear trend by treating the median of TRAP or FRAP scores in each tertile as a continuous variable. An interaction term was added to models to analyze the interaction between anti-oxidant activity and smoking status, opium uses and physical activity, and the risk of HNC. The *p*-value for interactions was estimated by the likelihood ratio test between the models with and without the interaction term. Subjects were categorized to five groups based on their history of tobacco use: current users, occasional users, quitting tobacco use for less than 10 years, quitting tobacco use for more than 10 years and never users. The heterogenicity of the association between TRAP or FRAP scores and risk of HNC in different groups of tobacco use was analyzed. All statistical analysis was done in STATA software (Stata 14.1, College Station, Texas 77,845 USA). Two-sided p values < 0.05 were considered statistically significant.

Results

Totally 879 patients and 3,409 healthy controls were recruited for our study. Almost two third of participants were male in both groups (Table 1). Tobacco smoking and opium use were less common in controls. Regular alcohol use was uncommon in both groups. Energy and food group intakes were not significantly different between patients and controls (Table 2).

The contribution of food groups to dTAC scores is shown in Table 3. Cereals were the main provider of antioxidants in our study (37.2% for FRAP and 53.9% for TRAP). Other sources of FRAP and TRAP in our control group were fruits (32.6 and 8.3%), vegetables (19.6 and 31.7%), legumes (4.7 and 1%), nuts (3.3 and 3.8%), confectionaries (1.1 and 1.1%), and fruit juice (3.6 and 1.0%).

We observed a significant decrease in the OR of HNC with increasing dTAC scores (Table 4). Compared with the lowest tertile, the OR of HNC for the third tertile decreased by 51% for both FRAP (OR 0.49; 95%CI 0.39–0.61) and TRAP (OR 0.49; 95%CI 0.39–0.62). When we investigated subtypes of HCN cancers, a significant decrease in the risk of lip and oral cavity cancer was seen by higher FRAP (OR 0.51; 95%CI 0.36–0.71 for the third tertile compared to the first, Ptrend < 0.001) and TRAP (OR 0.59; 95%CI 0.44–0.82 for the third tertile compared to the first, Ptrend $= 0.003$). Considering larynx cancer, a 57% reduction in risk was observed in the third tertile of FRAP compared to the first tertile (OR 0.43; CI 95% 0.31–0.61, P trend<0.001). The corresponding figure was 62% for the TRAP score (OR 0.38; 95% CI 0.26–0.55, P trend < 0.001). The difference in association between lip and oral cavity and laryngeal cancer with FRAP ($p = 0.72$) and TARP ($p = 0.14$) was not statistically significant Moreover, the association of head and neck cancers with FRAP and TARP ($p = 0.38$) did not differ significantly. There was no interaction between TRAP or FRAP scores with cigarette smoking, opium use, tobacco and water pipe use, physical activity, gender and age in our study (Supplementary Table1). The differences in association between TRAP or FRAP scores and risk of HNC in different group of tobacco use was not significant.

Discussion

This study found that dTAC scores in terms of FRAP and TRAP are inversely associated with HNC risk. No interaction was found between gender, tobacco smoking, opium use, water pipe use, physical activity, and dTAC scores in determining the risk of HNC.

These scores assess the overall antioxidant capacity of the diet, which adds value to the simple analysis of individual antioxidants or food items. Several studies showed an inverse association between the dTAC and the risk of colon, rectum, breast, and gastric cancers (14, 25, 26). Although the association between HNC cancer and dTAC was not studied previously, several studies showed inverse associations between individual antioxidants such as vitamin C, selenium, carotenoids, retinol, and vitamin E intake and the risk of HNC (8, 19).

Generally, fruit and vegetables are considered the primary source of antioxidants. They were the second and third contributors of dTAC in our study. Several studies showed that the intake of antioxidant reach foods such as vegetables or fruit is associated with the risk of HNC (18, 36). The main contributor to dTAC in our

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TABLE 1 Characteristics of head and neck cancer patients and controls in the IROPICAN study.

Characteristics		Head and neck cancer patients *N* (%)	Controls *N* (%)
Total		876	3,409
Gender	Male	662 (76)	2,356 (69)
	Female	214 (24)	1,053 (31)
Age group	30–39	59 (6.7)	250 (7.3)
	40–49	135 (15.4)	548 (16.1)
	50–59	265 (30.3)	1,055 (30.9)
	60–69	287 (32.8)	1,071 (31.4)
	≥70	130 (14.8)	485 (14.2)
SES[1]	Low	342 (39)	953 (28)
	Median	290 (33)	1,141 (33)
	High	244 (28)	1,315 (39)
Opium use	No	474 (54)	2,954 (87)
	Yes	402 (46)	455 (13)
Smoking	No	382 (44)	2,448 (72)
	Yes	494 (56)	961 (28)
Water pipe use	No	796 (91)	3,185 (93)
	Yes	80 (9)	224 (7)
Regular alcohol use	No	805 (92)	3,268 (96)
	Yes	71 (8)	141 (4)
PPWL[2]	Sedentary	267 (30)	1,104 (32)
	Moderate	200 (23)	746 (22)
	Heavy	202 (23)	749 (22)
	Unknown	207 (24)	810 (24)
Dental health[3]	Poor	207 (24)	1,551 (46)
	Moderate	75 (9)	449 (13)
	Good	594 (68)	1,409 (41)
Province	Tehran	157 (17.9)	813 (23.9)
	Fars	376 (42.9)	933 (27.4)
	Kerman	156 (17.8)	523 (15.3)
	Golestan	36 (4.1)	369 (10.7)
	Mazandaran	17 (1.9)	134 (3.9)
	Kermanshah	37 (4.2)	250 (7.3)
	Khorasan-Razavi	29 (3.3)	155 (4.5)
	Bushehr	0 (0)	67 (1.9)
	Hormozgan	33 (3.7)	78 (2.3)
	Systan-Balouchestan	36 (4.0)	100 (2.9)

[1]SES: socio-economic status was determined using principal component analysis by combining some data related to education, income, and ownership of some home appliances.
[2]Physical activity workload (PPWL) was estimated based on the Finland Job Exposure.
[3]Dental health was defined by DMFT score sum of the number of decayed, missing and filled teeth.

TABLE 2 Dietary intake of head and neck cancer patients and controls in IROPICAN study.

Food group gram/day (Mean ± SD)	Head and neck cancer patients (*n* = 876)	Controls (*n* = 3,409)
Energy	1845.9 ± 796.6	1850.6 ± 682.9
Cereal	500.9 ± 258.0	493.1 ± 268.7
Vegetables	439.8 ± 407.7	442.8 ± 243.6
Fruits	357.5 ± 269.9	362.7 ± 258.7
Nuts	5.9 ± 7.6	5.9 ± 9.3
Legumes	31.6 ± 39.8	32.1 ± 27.5
Vegetable oils	17.2 ± 13.4	17.8 ± 14.2
Confectionary	38.7 ± 38.2	38.3 ± 37.9
Total meat	66.9 ± 47.8	68.7 ± 50.8
Red mea	22.2 ± 24.2	23.6 ± 28.3

population was cereals. It seems that this high contribution is mainly due to the high consumption of cereals in our society as the staple food of Iranian (37). However, limited studies showed an inverse association between grain intake and the risk of HNC (38). Assessing the association between dTAC scores with the risk of HNC allows us to highlight the importance of consuming antioxidants from different sources and not just focusing on fruit and vegetables.

As mentioned above, several studies have shown a significant association between individual antioxidant intake and the risk of HNC (19). No study investigated the association between dTAC and the risk of HNC, but several studies found an inverse association between healthy dietary patterns and the risk of HNC (39, 40). Other studies found a robust association between adherence to healthy dietary patterns and dTAC score and health outcomes, including several cancers (24, 41). The association between dietary pattern and scores with HNC emphasized the importance of the intake of a wide range of antioxidants through adherence to healthy dietary patterns rather than focusing on some individual dietary antioxidants or supplements.

Several studies showed that intake of a diet low in antioxidants accompanied by smoking could exacerbate the carcinogenesis effects of tobacco. Smoking and alcoholic drinks have both been linked with increased oxidative stress (42, 43). Analyses of the International Head and Neck Cancer Epidemiology (INHANCE) consortium showed that the risk of HNC in subjects with a low intake of carotenoids and high exposure to smoking is 30 times higher than in subjects with a high intake of carotenoids and no alcohol and smoking exposure (44). Moreover, studies found high intake of flavonoids could decrease the risk of cancer, particularly in smokers (45). In our study higher dTAC score was associated with a lower risk of HNC both in smokers and non-smokers.

Other sources of antioxidants and oxidants like endogenous production in body could affects the association between antioxidant intake and risk of HNC cancer. Several studies showed the association between the endogenous antioxidant level such as serum levels of them with risk of HNC (46–48). Serum antioxidant enzymes levels including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and malondialdehyde (MDA) concentrations in blood are lower in cancer patients and are associated with cancer prognosis (48) and several studies proposed prescription of antioxidants rich products to decreasing the treatment adverse effects or slowing the cancer progress (49–51).

TABLE 3 Correlation and contribution of food groups to overall dTAC intake among 3,409 controls in the IROPICAN study.

		Cereals	Fruits	Vegetables	Legumes	Nuts	Confectionaries	Juices
TRAP[1]	Correlation[3] R (95%CI)	0.51 (0.5–0.53)	0.07 (0.06–0.07)	0.38 (0.36–0.39)	0.005 (0.004–0.006)	0.03 (0.02–0.03)	0.006 (0.004–0.007)	0.005 (0.003–0.007)
	Contribution Percent(SD)	53.9 (17.2)	8.3 (6.5)	31.7 (14.5)	1.0 (1.1)	3.8 (4.1)	1.1 (1.7)	1.0 (2.6)
FRAP[2]	Correlation[4] R (95%CI)	0.21 (0.19–0.22)	0.5 (0.49–0.52)	0.18 (0.17–0.18)	0.03 (0.02–0.03)	0.05 (0.04–0.05)	0.01 (0.01–0.01)	0.05 (0.04–0.05)
	Contribution Percent(SD)	37.2 (16.5)	32.6 (15.8)	19.6 (9.7)	4.7 (4.0)	3.3 (4.8)	1.1 (1.8)	3.6 (6.3)

[1]FRAP: Ferric Reducing Antioxidant Power of the diet.
[2]TRAP: Total Radical-trapping Antioxidant Parameters of the diet.
[3,4]The Pearson's correlation coefficient for all these food groups was significant at $p < 0.05$ level.

TABLE 4 The association of dietary Total Antioxidant Capacity (dTAC) scores with head and neck squamous cell carcinoma and its subtypes in the IROPICAN study.

			First tertile	Second tertile	Third tertile	*p* trend[1]	OR and 95%CI (continuous)
FRAP[3]	All HNSCC	Case/Control	361/1138	261/1136	254/1135	-	-
		Crude	Reference	0.72 (0.61–0.87)	0.70 (0.59–0.84)	<0.001	0.74 (0.66–0.83)
		Adjusted[2]	Reference	0.63 (0.51–0.77)	0.49 (0.39–0.61)	<0.001	0.74 (0.66–0.83)
	Lip and oral cavity (313/3409)	Case/Control	147/1138	90/1136	76/1135	-	-
		Crude	Reference	0.61 (0.47–0.81)	0.52 (0.39–0.69)	<0.001	0.74 (0.63–0.86)
		Adjusted	Reference	0.62 (0.46–0.84)	0.51 (0.36–0.71)	<0.001	0.72 (0.60–0.86)
	Larynx (427/3409)	Case/Control	161/1138	129/1136	137/1135	-	-
		Crude	Reference	0.8 (0.63–1.03)	0.85 (0.67–1.09)	0.188	0.92 (0.81–1.03)
		Adjusted	Reference	0.62 (0.44–0.86)	0.43 (0.31–0.61)	<0.001	0.69 (0.58–0.82)
TRAP[4]	All HNSCC	Case/Control	390/1137	234/1137	252/1135	-	-
		Crude	Reference	0.60 (0.50–0.72)	0.64 (0.54–0.77)	<0.001	0.78 (0.71–0.87)
		Adjusted	Reference	0.49 (0.39–0.61)	0.49 (0.39–0.62)	<0.001	0.69 (0.60–0.79)
	Lip and oral cavity (313/3409)	Case/Control	109/1137	94/1137	110/1135	-	-
		Crude	Reference	0.86 (0.65–1.15)	1.0 (0.77–1.3)	0.938	0.96 (0.83–1.1)
		Adjusted	Reference	0.59 (0.43–0.81)	0.59 (0.44–0.82)	0.003	0.76 (0.63–0.92)
	Larynx (427/3409)	Case/Control	210/1137	106/1137	111/1135	-	-
		Crude	Reference	0.5 (0.39–0.65)	0.53 (0.41–0.68)	<0.001	0.72 (0.63–0.84)
		Adjusted	Reference	0.39 (0.28–0.55)	0.38 (0.26–0.55)	<0.001	0.59 (0.48–0.75)

The association between lip and oral cavity and laryngeal cancer with FRAP ($p = 0.72$) and TARP ($p = 0.14$) was not different. The difference between the association of head and neck cancers with FRAP and TARP ($p = 0.38$) was not significant.
[1]Analyzed by using the median value of TRAP or FRAP as a continuous variable in unconditional logistic models.
[2]Adjusted for age (5 categories), sex(male/female) and energy intake (kcal/day, continues), socioeconomic status (low, medium, high), province(10 different provinces), opium use (yes, no), smoking (yes, no), water pipe use (yes, no) regular alcohol use (yes, no), physical activity (sedentary, moderate, heavy, unknown) and, dental health(poor, moderate, good).
[3]FRAP: Ferric Reducing Antioxidant Power of the diet.
[4]TRAP: Total Radical-trapping Antioxidant Parameters of the diet.

This study has several strengths. First, we used a large sample based on a multicenter study, allowing us to study the association of dTAC for HNC overall and by its subsites, including oral cavity and laryngeal cancers. The patients were pathologically confirmed by specialist. We also adjusted for several confounding variables, including tobacco smoking, and opium use. Using a validated FFQ was the second strength of our study (31). Moreover, the interviews were conducted in the same setting in all provinces by trained interviewers. However, there are some limitations to this study. Some scientists believe that TRAP and FRAP do not cover all the antioxidant power of the diet, particularly when computed using FFQ (52). However, several studies showed a strong association between these scores and the total antioxidant capacity of a diet and the serum antioxidant level of healthy adults (23, 52). Moreover, several studies in Iran and other countries showed a strong association between these scores and healthy dietary patterns such as healthy eating index (HEI),

Mediterranean diet, and Dietary approach to stop hypertension (DASH) diet (22, 52, 53). The positive association between dTAC scores and fruit and vegetable consumption, along with the negative association with unhealthy foods such as red meat, fast food, and high-fat diets (52) also underlines the validity and importance of this score.

Conclusion

Consuming a diet rich in antioxidants determined by dTAC could decrease the risk of HNC cancer. Healthy dietary patterns which increase antioxidant intake should be encouraged, particularly in high-risk groups. These findings provided valuable insight for designing preventive policies such as promoting high antioxidant food intakes such as fruit and vegetable by subsidizing or providing free fruits in schools.

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 humans were approved by ethical committee of Tehran university of medical sciences. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

FT and KZ designed the current study. KZ, EM, RS, FN, AN-T, MS, MH, PB, and HR designed and managed the data collection and cleaning of primary data (IROPICAN study). FT, BS, and HR performed the nutritional and statistical analysis. FT wrote the draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1226446/full#supplementary-material

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Red and processed meat and pancreatic cancer risk: a meta-analysis

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Background: The relationship between red and processed meat consumption and pancreatic cancer risk is controversial and no study has looked specifically at the correlation for 6 years. We conducted a meta-analysis to summarize the evidence about the association between them.

Methods: We systematically searched PubMed, Embase and Cochrane Library for studies of red or processed meat consumption and pancreatic cancer published from December 2016 to July 2022. We performed random-effects models to pool the relative risks from individual studies. Subgroup analyses were used to figure out heterogeneity. We also performed publication bias analysis.

Results: Seven cohort studies and one case–control study that contained a total of 7,158 pancreatic cancer cases from 805,177 participants were eligible for inclusion. The combined RRs (95% CI) comparing highest and lowest categories were 1.07 (95% CI: 0.91–1.26; $p = 0.064$) for red meat and 1.04 (95% CI: 0.81–1.33; $p = 0.006$) for processed meat with statistically significant heterogeneity.

Conclusion: This meta-analysis suggested that red and processed meat consumption has no relationship with pancreatic cancer risk.

KEYWORDS

red meat, processed meat, pancreatic cancer, daily diet, meta-analysis

Introduction

Pancreatic cancer, ranking as the seventh leading cause of mortality from malignancies globally owing to its unfavorable prognosis, exhibits a higher incidence rate in nations with a High Human Development Index (HDI) countries (1). This trend can be attributed to the escalating prevalence of obesity, diabetes, and alcohol consumption within these high HDI countries alongside advancements in diagnostic techniques and enhanced cancer registration protocols (2). According to an analysis encompassing 28 European nations, pancreatic carcinoma is projected to surpass breast malignancy and become the third most prevalent fatal neoplasm by 2025 (3). Therefore, it is imperative to identify risk factors for pancreatic cancer, making it of paramount importance.

Strong evidence suggests that consumption of red and processed meat may elevate the risk of pancreatic cancer due to its high content of heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PHAs), and N-nitroso compounds (NOCs). In April 2017, Zhao et al. conducted a systematic review and meta-analysis investigating the association between intake of red and processed meat and the risk of pancreatic cancer. The analysis included a total of 28 cohort and case–control studies published before February 2016. Among the case–control studies, higher consumption of red meat and processed meat exhibited a positive correlation

with pancreatic cancer risk (Red meat, RR: 1.38, 95% CI: 1.05–1.81; Processed meat, RR: 1.62, 95% CI: 1.17–2.26); however, no overall association was observed in cohort studies (Red meat, RR: 1.12, 95% CI: 0.98–1.28; Processed meat, RR: 1.09, 95% CI: 0.96–1.23). Dose–response analysis indicated that every additional daily intake increment by 100 g in red meat was associated with an 11% increased risk for developing pancreatic cancer while each 50 g/d increase in processed meat intake led to an 8% rise in this risk. The findings from this study align with dietary guidelines while providing more comprehensive evidence based on robust epidemiological data. However, no clear relationship has been established between recent six-year trends in red or processed meat consumption and pancreatic cancer risk.

Therefore, we performed an updated meta-analysis incorporating epidemiological studies published from February 2016 to July 2022 (including cohort and case–control studies) to investigate associations between red or processed meat consumption and incidence or mortality of pancreatic cancer. Additionally, the potential influence of factors such as sex (men vs. women), geographic area (USA vs. Italy), duration of follow-up (less than 20 years vs. more than 20 years) and adjustments for alcohol intake, smoking, BMI, diabetes, family history pancreatic cancer, energy intake and physical activity were investigated.

Methods

Search strategy

Articles published from December 2016 to October 2022 were systematically searched in PubMed, Embase and Cochrane Library. The search strategy was a combination of medical subject headings and free text words. Following medical subject terms were used: "Pancreatic Neoplasms," "Red Meat" and "Meat Products." Free text words including "red meat*," "beef," "pork," "lamb," "mutton," "veal," "pancreatic neoplasm*," "Cancer of Pancreas," "pancreas cancer*," "pancreatic cancer*," "Cancer of the Pancreas," "diet*," "food*" and "processed meat." Moreover, we reviewed the reference lists from the included articles and those from previous meta-analysis to identify additional relevant studies.

Study selection

Studies were included in our meta-analysis when they meet the following criteria:

1. Be a cohort or case–control study.

2. Provide the 95% confidence intervals and adjusted estimates of the relative risk (RR) (or any statistical indicator to compute them like hazard ratio, odds ratio or risk ratio) for red and/or processed meat of pancreatic cancer incidence or mortality.

3. The study was published from December 2016 to July 2022.

4. The study was published in English. We considered "ham," "sausage," "bacon," "salami" and "hot dogs" as equivalent to "processed meat." When there were multiple published reports from the same study population, we chose the one with the largest population. For studies that researched for more than 1 cohort, the data of each cohort were selected (Supplementary Table S1) (4).

Data extraction and quality assessment

Two investigators independently extracted the following data from each study: the first author's name, the year of publication, the country where the study was performed, age of subjects, number of participants, follow-up time, type of the meat and their consumption strategy, adjusted RR/OR/HR with the corresponding 95% CI (highest to lowest) and other influencing factors. When some studies gave the RR values of processed red meat and unprocessed red meat, we extracted unprocessed red meat as the data of red meat in that study. When a study provided RR values for all age groups vs. people aged 50 years, we extracted data for all age groups (Supplementary Table S1) (5).

The Newcastle-Ottawa Scale (NOS) was applied to assess the study quality (6), which ranged from 1 to 9 stars. We considered studies with NOS scores higher than 7 to be of high methodologic quality.

Statistical analysis

Due to variations in the reporting methods of effect size and 95% CI across studies, we estimated these values by comparing the highest with the lowest consumption categories (e.g., quartile or quintile). For simplicity, we use the term RR (relative risk) for all estimates in this manuscript since hazard ratios in some cohort studies and odds ratios in case–control studies are closely approximate relative risks (7, 8) when pancreatic cancer incidence or mortality is low. The corresponding RR for each study was assigned to the highest level of red and processed meat intake within each category. In cases where the highest category was open-ended, we considered it equivalent to the adjacent interval. We employed a random effects model to calculate RRs and 95% CI. To stabilize variance and standardize distribution, RRs and their corresponding standard errors were converted into natural logarithm and then the logarithm is removed again to be reduced. To obtain a single RR from each study, RRs were combined when separate relative risk estimates were provided for populations that were over 60 or up to 60 years old (Supplementary Table S1; 9). The outcomes are presented as a forest plot with 95% CIs.

Q and I^2 statistics were used to evaluate statistical heterogeneity among studies (10), when $p < 0.10$ and $I^2 > 50\%$, the heterogeneity considered to be statistically significant. To investigate other influencing factors for the association between red or processed meat consumption and pancreatic cancer, we conducted subgroup analyses by sex (men vs. women), geographic area (USA vs. Italy), duration of follow-up (<20 years vs. >20 years) and adjustments for alcohol intake, smoking, BMI, diabetes, family history pancreatic cancer, energy intake and physical activity.

To evaluate the stability of the results, we performed sensitivity analyses of statistically significant results, which were more stable if the pooled effect size changed little and none of the 95% confidence intervals crossed 1 after removing a single study.

We also used Egger's regression asymmetry test (11) and Begg-Mazumdar test (12) to assess publication bias, $p < 0.05$ considered statistically significant.

All statistical analyses were performed with STATA version 17.0 software (Stata Corporation, College Station, TX).

Results

The literature search generated 471 records, of which 109 were considered potentially valuable (Figure 1). Finally, a total of 7 articles were included in the meta-analysis (6 cohorts and 2 case–controls) and reported 12 separate data (7 red meat and 5 processed meat) on the association between red or processed meat with pancreatic cancer (4, 5, 9, 13–17).

Study characteristics

The characteristics of included studies are outlined in Supplementary Table S1. We included 8 studies that contained a total of 7,158 pancreatic cancer cases from 805,177 participants. In eight included studies, all of them were carried in HDI countries, including six in USA and two in Italy. Seven of them consisted of men and women, of only women in one study. There are four reported the relationship between two types of meat with pancreatic cancer risk in addition to three only reported the red meat and one only reported the processed meat.

Red meat

Highest vs. lowest intake category

Seven cohort studies examined the relationship between red meat consumption with pancreatic cancer risk. In the meta-analysis comparing highest vs. lowest intake category, the summary RR for pancreatic cancer risk was 1.07 (95%CI: 0.91–1.26) with statistically significant heterogeneity observed ($I^2 = 49.5\%$, $p = 0.064$) (Figure 2).

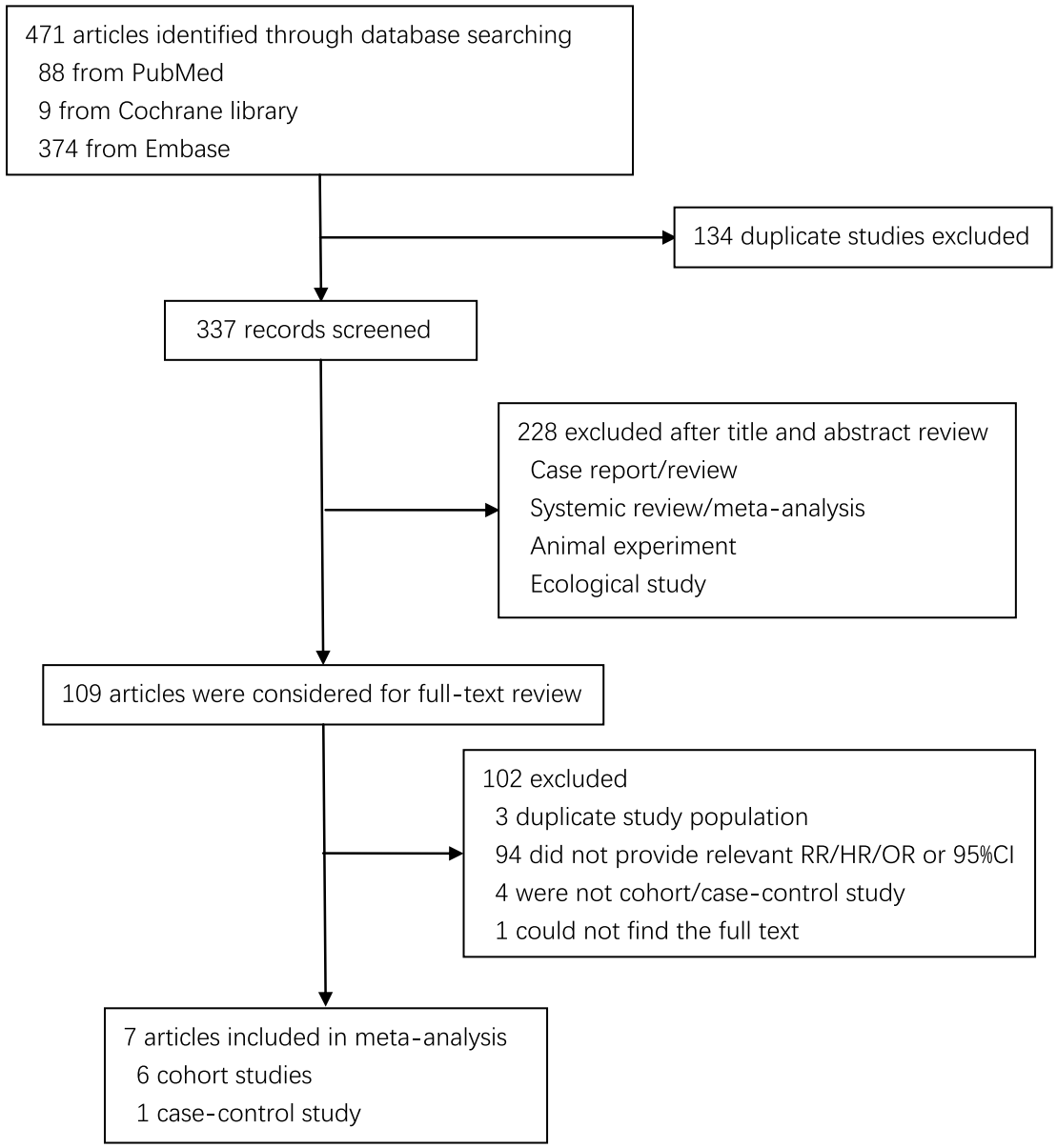

FIGURE 1
Flow chart of study selection.

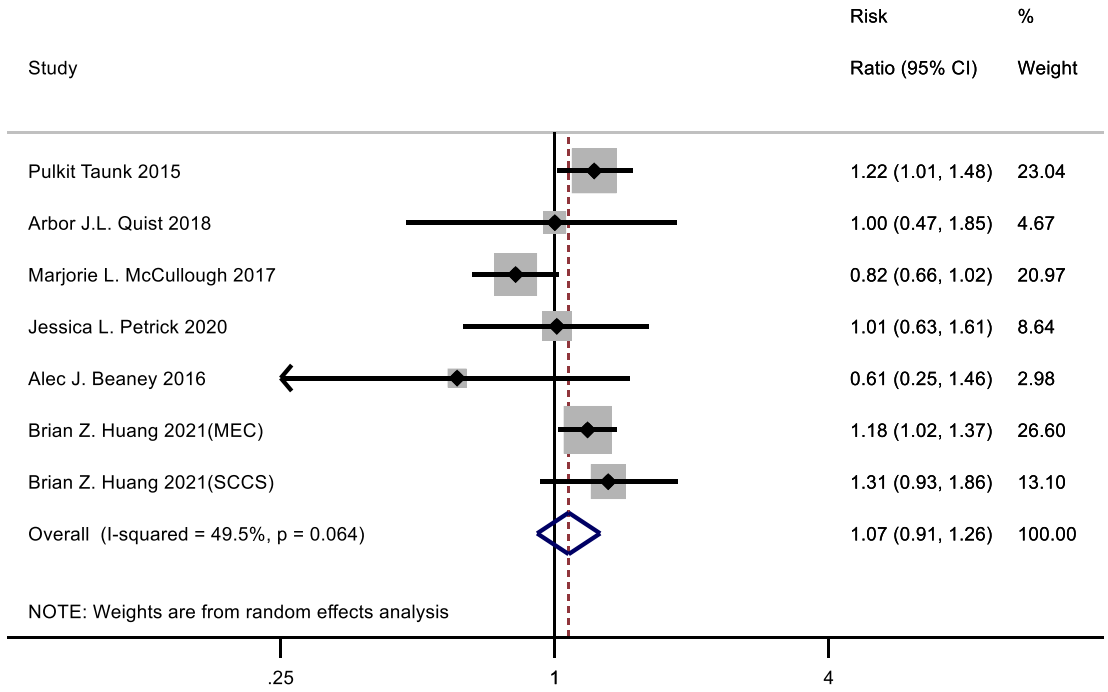

FIGURE 2
Forest plot of red meat consumption (highest versus lowest category) and pancreatic cancer risk.

Subgroup analysis

Subgroup analyses are shown in Table 1. In the subgroup analysis by sex, the RRs were 1.10 (95% CI: 0.71–1.70) in men and 0.92 (95% CI: 0.74–1.15) in women. In the subgroup analysis by geographic area, the RRs were 1.11 (95% CI: 0.93–1.33) for the studies in the USA and 0.61 (95% CI: 0.25–1.46) for the studies in Italy. In the subgroup analysis by duration of follow-up, the RRs were 1.18 (95% CI: 1.03–1.34) for those with more than 20 years of follow-up. Moreover, RRs were 1.19 (95% CI: 1.07–1.33) and 1.20 (95% CI: 1.05–1.37) for the studies adjusted for alcohol intake and family history pancreatic cancer, respectively. In other subgroup analyses, heterogeneity could be observed, but in adjustments for physical activity, the finding remained robust.

Sensitivity analysis and publication bias

In sensitivity analyses, the association between red meat intake and pancreatic cancer risk was not significantly altered after removing each single study (Figure 3). The Egger's test ($p = 0.438$) and Begg's test ($p = 0.230$) did not detect publication bias (Figure 4).

Processed meat

Highest vs. lowest intake category

Four cohort studies and one case–control study examined the relationship between processed meat consumption with pancreatic cancer risk. In the meta-analysis comparing highest vs. lowest intake category, the summary RR for pancreatic cancer risk was 1.04 (95%CI: 0.81–1.33) with statistically significant heterogeneity observed ($I^2 = 72.0\%$, $p = 0.006$) (Figure 5).

Subgroup analysis

Subgroup analyses are shown in Table 1. In the subgroup analysis by sex, the RRs were 0.92 (95% CI: 0.69–1.23) in men and 0.92 (95% CI: 0.74–1.14) in women. In the subgroup analysis by geographic area, the RRs were 0.91 (95% CI: 0.77–1.07) for the studies in the USA and 1.45 (95% CI: 1.16–1.82) for the studies in Italy. In other subgroup analyses, heterogeneity could be observed, but in adjustments for alcohol intake, the finding remained robust.

Sensitivity analysis and publication bias

In sensitivity analyses, the association between processed meat intake and pancreatic cancer risk was not significantly altered after removing each single study (Figure 6). After deleting the only one case–control study (Supplementary Table S1) (16), the results remained stable (Figure 7). The Egger's test ($p = 0.932$) and Begg's test ($p = 0.806$) did not detect publication bias (Figure 8).

Discussion

In our meta-analysis, we did not find any significant association between the consumption of red meat or processed meat and the risk of pancreatic cancer. However, subgroup analyses based on a limited number of studies indicated a positive association between processed meat consumption and pancreatic cancer incidence in Italy, while no such relationship was observed in the USA. Additionally, alcohol intake or family history of pancreatic cancer has been identified as independent factors associated with an increased incidence of pancreatic cancer; therefore, we adjusted our analysis to explore their influence. Surprisingly, our results revealed a positive correlation between red meat consumption and alcohol intake or family history of pancreatic cancer,

TABLE 1 Summary relative ratio (RR) and 95% confidence intervals (95% CI) of highest vs. lowest category of red and processed meat consumption and pancreatic cancer risk by subgroups.

Subgroups		Red meat						Processed meat					
		n	RR (95%CI)	I2% (within)	P1	I2% (between)	P2	n	RR (95%CI)	I2% (within)	P1	I2% (between)	P2
All studies		7	1.07 (0.91–1.26)	49.5	0.064	–	–	5	1.04 (0.81–1.33)	72	0.006	–	–
Sex						62.7	0.045					0	0.443
	Men	2	1.10 (0.71–1.70)	80.9	0.022			2	0.92 (0.69–1.23)	56.8	0.128		
	Women	2	0.92 (0.74–1.15)	0	0.41			2	0.92 (0.74–1.14)	0	0.557		
Geographic area						56.3	0.182					72	0.006
	USA	6	1.11 (0.93–1.33)	58.1	0.036			3	0.91 (0.77–1.07)	23.8	0.269		
	Italy	1	0.61 (0.25–1.46)	–	–			2	1.45 (1.16–1.82)	0	0.873		
Duration of follow-up						44.6	0.094					72.5	0.006
	<20 years	3	0.95 (0.68–1.32)	74.6	0.02			3	0.95 (0.77–1.18)	44.3	0.166		
	>20 years	4	1.18 (1.03–1.34)	0	0.803			2	1.11 (0.61–2.02)	81	0.022		
Adjustment for alcohol intake						45.4	0.089					9.1	0.354
	Yes	4	1.19 (1.07–1.33)	0	0.841			3	1.00 (0.85–1.17)	0	0.568		
	No	3	0.85 (0.69–1.03)	0	0.535			2	0.97 (0.59–1.58)	51.2	0.152		
Adjustment for smoking						–	–					–	–
	Yes	7	1.08 (0.93–1.25)	44.6	0.094			5	0.95 (0.82–1.10)	16	0.313		
	No	0	–	–	–			0	–	–	–		
Adjustment for BMI						45.4	0.089					72.4	0.006
	Yes	6	1.11 (0.97–1.27)	36.7	0.162			4	1.01 (0.77–1.33)	78.2	0.003		
	No	1	0.59 (0.29–1.19)	–	–			1	1.42 (0.69–2.91)	–	–		
Adjustment for diabetes						–	–					72.5	0.006
	Yes	7	1.08 (0.93–1.25)	44.6	0.094			4	0.93 (0.78–1.11)	26.9	0.251		
	No	0	–	–	–			1	1.46 (1.15–1.85)				
Adjustment for family history pancreatic cancer						45.4	0.089					–	–

(Continued)

TABLE 1 (Continued)

Subgroups		Red meat						Processed meat					
		n	RR (95%CI)	I2% (within)	P1	I2% (between)	P2	n	RR (95%CI)	I2% (within)	P1	I2% (between)	P2
	Yes	2	1.20 (1.05–1.37)	0	0.587			5	1.04 (0.81–1.34)	72.4	0.006		
	No	5	0.98 (0.78–1.23)	50.1	0.091			0	–	–	–		
Adjustment for energy intake						44.6	0.094					72.5	0.006
	Yes	3	1.02 (0.73–1.43)	48.9	0.141			4	1.14 (0.86–1.50)	63.7	0.041		
	No	4	1.08 (0.88–1.32)	55.5	0.081			1	0.82 (0.66–1.02)	–	–		
Adjustment for physical activity						42.1	0.11					73.3	0.005
	Yes	4	0.87 (0.73–1.05)	0	0.709			2	1.05 (0.54–2.03)	58	0.123		
	No	3	1.21 (1.08–1.35)	0	0.854			3	1.06 (0.78–1.45)	83.9	0.002		

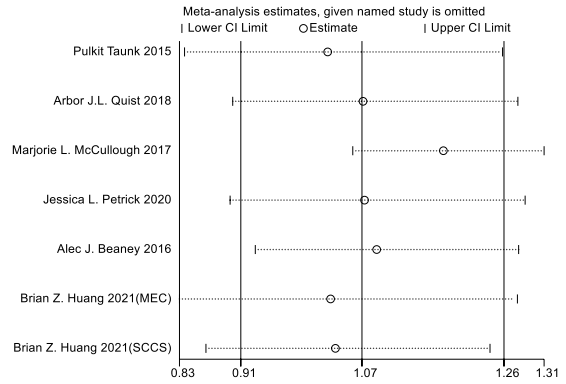

FIGURE 3
Sensitivity analyses of red meat consumption and pancreatic cancer risk.

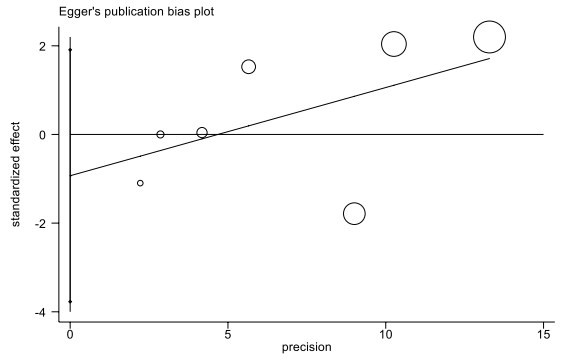

FIGURE 4
Egger's test evaluating publication bias of red meat consumption and pancreatic risk.

but no such relationship was found for processed meat. The subgroup analyses conducted in this study were unable to fully account for potential sources of interstudy heterogeneity, as statistically significant differences in histological subtype, number of samples, or study quality were not observed. In the sensitivity analysis of the literature on the relationship between pancreatic cancer and processed meat, we included one case control study due to its limited number (Supplementary Table S1) (16). After re-performing the sensitivity analysis on the remaining cohort studies, our results remained consistent and robust.

Our findings are consistent with those of numerous other meta-analyses that have reached similar conclusions regarding the association between red and processed meat consumption and pancreatic cancer risk. For instance, Farvid et al. performed a systematic review and meta-analysis of 148 prospective studies published up to December 2020 to summarize the evidence on the relationship between consumption of red meat (unprocessed), processed meat, total red meat, processed meat, and the incidence of various cancers. By utilizing random-effects models to summarize relative risks for the highest and lowest intake categories for each exposure variable, they concluded that neither intake of red meat alone (unprocessed) nor processed meat alone was associated with an increased risk of pancreatic cancer (18). Han et al. in their dose–response meta-analysis comprising 118 cohort studies reporting associations between consumption of unprocessed red meat and processed meat and mortality/incidence rates for six different cancers including pancreatic cancer since April 2019, calculated pooled relative risks (RR) along with corresponding 95% confidence intervals (CI). Their analysis demonstrated that reducing weekly intake by three servings per week had only a minimal absolute effect on cancer mortality or incidence related to both red meat and processed meat consumption (19). Zeraatkar et al., who included 14 randomized trials comparing lower vs. higher intakes of either red or processed meat among adults in terms of cardiovascular disease and cancer incidence rates found that one randomized trial indicated a low red meat diet

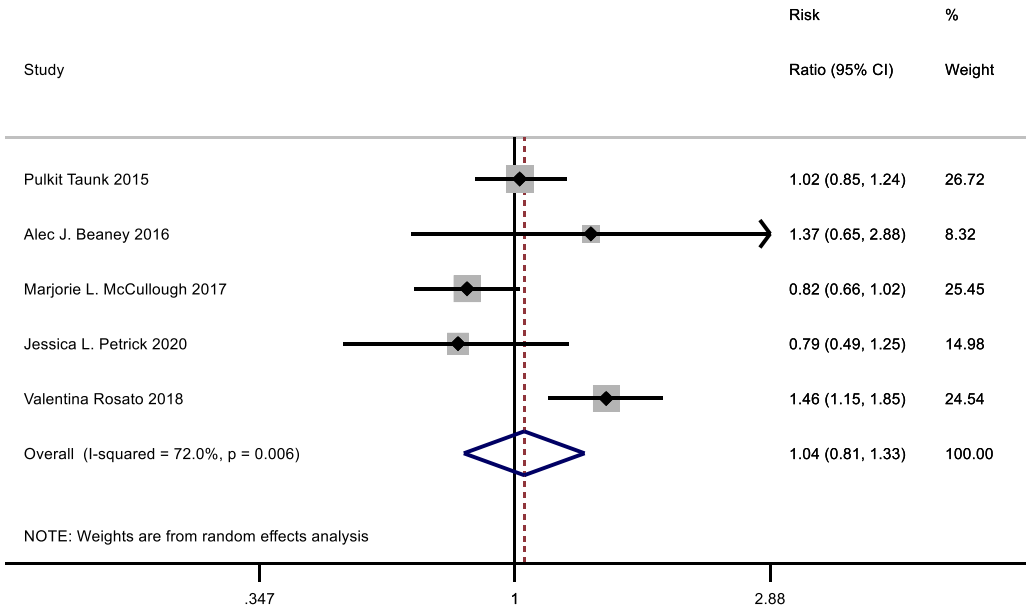

FIGURE 5
Forest plot of processed meat consumption (highest vs. lowest category) and pancreatic cancer risk.

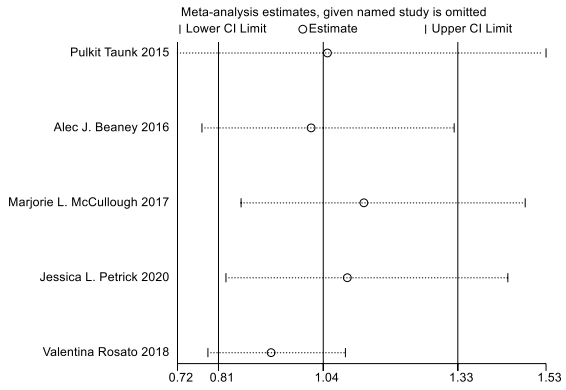

FIGURE 6
Sensitivity analyses of processed meat consumption and pancreatic cancer risk (all studies).

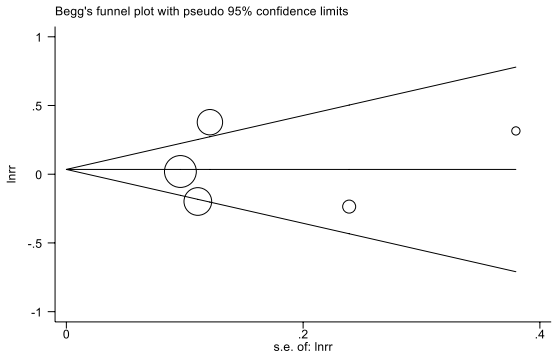

FIGURE 8
Begg's test evaluating publication bias of processed meat consumption and pancreatic risk.

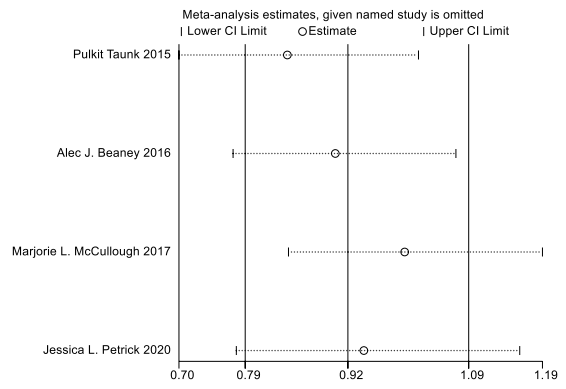

FIGURE 7
Sensitivity analyses of processed meat consumption and pancreatic cancer risk (all cohort studies).

may have limited impact on pancreatic cancer risk specifically among women (20). Additionally, Vernooij et al. found no statistically significant risk of pancreatic cancer incidence for dietary patterns with lower intake of red meat and processed meat (21).

However, most studies suggest that there is a biologically plausible positive association between the consumption of red and processed meat and pancreatic cancer. Several mechanisms have been proposed to explain the potential role played by red and processed meat in increasing pancreatic cancer risk. For instance, it is well-established that red meat contains heme iron, which stimulates the production of N-nitroso compounds (NOCs) by bacteria in the large intestine (22). Moreover, red meat consumption promotes DNA adduct formation, leading to epigenetic changes in DNA. On the other hand, processed meat contains higher levels of nitrite/nitrate and sodium compared to unprocessed meat (23), which further enhances NOCs production. Additionally, cooking methods such as high-temperature frying, grilling or smoking result in the formation of heterocyclic amines (HAAs) and

polycyclic aromatic hydrocarbons (PAHs) (24). Animal studies have demonstrated that these compounds may induce DNA adduct formation and interfere with apoptosis processes, potentially promoting carcinogenesis. Furthermore, both red and/or processed meats are rich sources of saturated fat; animal experiments have shown that rats fed a high-fat diet develop more pancreatic cancer compared to those on a low-unsaturated fat diet (25, 26). Observational studies also support a positive association between animal fat intake and pancreatic cancer incidence (27). This could be attributed to excess saturated fat inducing alterations in gut microbiota composition, thereby activating proinflammatory pathways and leading to inflammation, which is known as risk factors for cancer (28). Additionally, prolonged cooking at high temperatures enhances the formation of N- (carboxymethyl) lysine (CML) advanced glycation end products (CML AGEs) in food (29). CML AGEs may lead to insulin resistance, oxidative stress, and chronic inflammation (30–32). It is hypothesized that CML AGEs may contribute to the development of pancreatic cancer by altering the interstitial environment of tissues (33). Moreover, several persistent organic pollutants (POPs) are commonly detected in meat, which are carcinogenic. Studies suggest that consuming lamb or other POPs may increase the risk of cancer (34). Lastly, red meat contains binding forms of Nonhuman sialic acid N-glycolylneuraminic acid (Neu5Gc) and methionine that can be incorporated into human tissues through metabolism, leading to inflammation (35, 36). This mechanism could potentially explain why consumption of red meat is associated with an increased risk of pancreatic cancer.

Our study possesses several strengths. Firstly, our search strategy was meticulously detailed. Secondly, it was conducted by two independent reviewers for data selection and extraction, with consultation from a third investigator in case of disagreements after discussion, thereby minimizing bias and error. Thirdly, we have a substantial sample size that allows for more robust conclusions regarding the association between intake of red and processed meat and pancreatic cancer risk. Fourthly, the studies included in this article were predominantly cohort studies (with only one being a case–control study), which reduces the potential for recall and selection biases. Lastly, subgroup analyses were performed to investigate the sources of heterogeneity.

However, our study also has certain limitations. Firstly, the original studies encompassed both cohort studies and case–control studies; therefore recall bias, interviewer bias, and inaccurate measures of dietary consumption in case–control studies may impact the outcomes concerning processed meat consumption and pancreatic cancer risk. Secondly, there might be selection bias within the study population as it primarily focused on two high human development index (HDI) countries, the United States and Italy, where a higher incidence of pancreatic cancer is associated with a higher quality of life. Additionally, individuals in these countries tend to consume more red and processed meat compared to those in developing nations which could potentially inflate associations observed. Moreover, some participants were recruited from health care registries who generally exhibit greater attention toward healthy living practices thus reducing correlations between variables studied here. Thirdly, due to variations among original studies regarding specific daily meat consumption details, the inclusion criteria uniformly extracted highest and lowest levels of relative risk (RR) intake. Fourthly, certain studies accounted for potential confounding factors, including gender, alcohol consumption, smoking habits, and body mass index (BMI), while others did not. Fifthly, it is worth noting that our findings may have been influenced by imprecise measurements of meat intake in the original studies or variations in meat cooking methods, which could have impacted the overall relative risk estimation. Furthermore, since the original studies included in our study employed different unit categories (e.g., portion size and time), standardization was not feasible for extracting average values for red meat or processed meat from each stud; thus preventing us from conducting a dose–response analysis. We hope that future studies can provide more detailed investigations into the dose–response relationship between red/processed meat consumption and pancreatic cancer.

Conclusion

Our meta-analysis of cohort and case–control studies revealed no significant association between red meat and processed meat consumption and pancreatic cancer risk. However, considering the dietary guidelines proposed by the NutriRECS consortium in 2019 (37) and conclusions drawn by other researchers, further investigations are warranted to validate this relationship.

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.

Author contributions

YaS and YuS designed the study. YuS contributed to the literature database search, data collection, data extraction, data analysis, and writing of the manuscript. XH performed the data extraction and check of the results. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1249407/full#supplementary-material

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Dietary intake of total vegetable, fruit, cereal, soluble and insoluble fiber and risk of all-cause, cardiovascular, and cancer mortality: systematic review and dose–response meta-analysis of prospective cohort studies

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Objectives: To conduct a systematic review and meta-analysis of prospective cohort studies to investigate the association between total, vegetable, fruit, cereal, soluble and insoluble fiber intake and risk of all causes, cardiovascular disease (CVD), and cancer mortality and quantitatively assess the dose–response relation.

Methods: Eligible studies were identified by searching PubMed, Embase and Web of science before August 2023. Random effects models were used to calculate summary relative risk (RR) and 95% confidence intervals (CI) and restricted cubic splines to model the linear/non-linear association.

Results: The summary RR for all-cause, CVD and cancer mortality of dietary fiber was 0.90 (95% CI: 0.86,0.93), 0.87 (0.84,0.91), 0.91 (0.88,0.93), respectively. Significant association was observed for all-cause and CVD mortality with fruit, vegetable cereal and soluble fiber intake and cancer mortality with cereal fiber intake. No significant association was found for insoluble fiber, vegetable or fruit fiber intake and cancer mortality. Dose-response analysis showed a significant non-linear relation of dietary fiber intake with all-cause mortality, and linear relation for others.

Conclusions: Higher dietary fiber including different type and food sources of fiber intake were associated with lower risk of mortality. Our findings provide more comprehensive evidence on dietary fiber intake with mortality.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier: CRD42022338837.

KEYWORDS

dietary fiber intake, mortality, cancer, cardiovascular disease, meta-analysis

1. Introduction

Cardiovascular disease (CVD) and cancer are the leading causes of death globally (1). It has been estimated that global deaths from coronary heart disease, stroke, and cancer will reach up to 18.6 million, 12.2 million, and 10.0 million, respectively in 2019–2020 (1–3). Poor diet contributed to one of the largest risk factors for death, accounting for 8.3% of all deaths (4). The WHO recommends a daily intake of dietary fiber >25 g/day for adults (5); however, the consumption of dietary fiber remains low in many high-income countries (18.3 g/day in the United States, 14.8 g/day in the United Kingdom, 16.9 g/day in France, and 15.0 g/day in Japan) (6). Major nutrition shifts occur in developing countries with an increase in fat intake and a decrease in whole grain and fiber intake. The dietary fiber consumption level was reported to be even lower in middle-income countries (9.7 g per capita/day in China) (7, 8). Accumulating evidence indicated that dietary fiber might decrease the risks of various chronic diseases (9, 10), including obesity, diabetes, hypertension, CVD (11–14), and cancer (15–17).

Inconsistent results were found in previous studies examining the effect of dietary fiber on mortality. Most of the previous studies detected an inverse association between dietary fiber and all-cause, CVD, or cancer mortality (18–20), but no association was found in other studies (21, 22). Although few systematic reviews and meta-analyses were conducted to analyze the relationship between fiber intake and mortality, some of those meta-analyses focused on specific populations such as patients and cancer survivors (23–25) and unstable findings have been reported with controversial results in many subgroups. A most recent meta-analysis conducted in 2019 analyzed the relationship between total fiber and a series of health outcomes, which included 68,183 deaths, but did not take into consideration the specific types of dietary fiber (26). More than 10 studies (18–20, 22, 27–33) have been reported since the last meta-analysis, with approximately 424,953 participants and 30,215 deaths that could be further added in this updated meta-analysis. Therefore, it is necessary to conduct an updated meta-analysis to explore the association between dietary fiber intake and all-cause, CVD, or cancer mortality and provide evidence on their dose–response relationship.

Dietary fiber can be classified into insoluble and soluble fibers based on solubility (34). Studies on associations between insoluble or soluble fiber intake and mortality have also been inconclusive. In a cohort study of 92,924 Japanese consumption of both insoluble and soluble fibers was associated with a lower risk of all-cause mortality (20). While some observational studies have not found a significant association between soluble or insoluble fiber intake and all-cause mortality mortality (28, 35). Only one previous systematic review and meta-analysis investigated the association between soluble and insoluble fiber intake and CVD mortality (36); however, the study did not assess the association between all-cause between all-cause mortality and cancer mortality.

The levels and sources of dietary fiber intake may be substantially different among countries. For example, grain products are the main source of dietary fiber for the US population (37), while dietary fiber mainly comes from vegetables for the Japanese population (38). Bean, fruit, and vegetable fibers but not cereal fibers are associated with reduced risk of all-cause mortality in a study conducted in Japan (39), whereas others reported no associations of individual food sources of dietary fiber (including fibers from cereals, fruits, or vegetables) with the risk of ischemic heart disease mortality mortality (40). Although a previous meta-analysis investigated the association between cereal fiber intake and all-cause, cardiovascular, and cancer mortality (41), the study included general participants and people with diseases, and several cohort studies with large sample sizes have been published in recent years (20, 28). Different from previous meta-analyses, this meta-analysis explored dietary fibers from different sources and cardiovascular or cancer mortality. To the best of our knowledge, most previous meta-analyses (24, 26, 36, 41–45) did not analyze the relationship between fibers from different sources and mortality. A meta-analysis (46) was conducted on the association between dietary fibers obtained from different sources including cereal, fruit, legume, and vegetable fibers and cardiovascular mortality.

Hence, our study aimed to conduct an updated systematic review and meta-analysis of prospective cohort studies to investigate the risk of all-cause, cardiovascular, and cancer mortality associated with dietary fiber intake and different food sources and different types (soluble and insoluble fiber) of dietary fiber intake in general populations and further explore the dose–response relationship.

2. Methods

The systematic review and meta-analysis were registered in the prospective register of systematic reviews database (PROSPERO) (https://www.crd.york.ac.uk/prospero/index.asp, identifier CRD42022338837) and conducted and reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (47).

2.1. Search strategy

We systematically searched the PubMed, Embase, and Web of Science electronic databases from their inception up to 25 August 2023. We used a combination of MeSH terms and free-text terms to identify relevant publications assessing dietary fiber intake and fibers from different food sources in relation to all-cause, CVD, and cancer mortality, with restriction to the English language and without date limitation. Moreover, the reference lists from the retrieved articles, systematic reviews, and meta-analyses were searched for further relevant studies. Study authors were contacted, but non-peer-reviewed sources were not considered. Details of the search terms used for querying literature are shown in Supplementary Table 1. The literature search was conducted by two independent investigators (F. Y. and P. Q.).

2.2. Inclusion and exclusion criteria

The PICOS (participants, interventions/exposures, comparators, outcomes, and study design) criteria were used to identify studies that were eligible for inclusion: (1) the study

design was prospective cohort studies; (2) the exposure of interest was dietary fiber intake; (3) the outcome of interest included all-cause, CVD, or cancer mortality; and (4) the risk estimates, including adjusted hazard ratios (HR) or risk ratios (RR), with their corresponding 95% confidence intervals (CIs) were reported. When reports pertained to overlapping participants, we included only the study with a larger population to avoid duplication of data.

Reviews, abstracts, comments, or unpublished results were excluded. Studies on children, adolescents, or patients with chronic kidney disease, or who were undergoing hemodialysis, end-stage cancer, or critical illnesses were excluded.

2.3. Data extraction and quality assessment

The data extraction and quality assessment were conducted by F. Y. and P. Q., and any discrepancies were discussed with a third investigator (C. H.). The following characteristics from each study finally included in the meta-analysis were extracted using a standardized form: name of first author, publication year, country or region, the name of the study, sample size and number of deaths, follow-up period, types of outcomes, gender, age, types of fibers, amount of intake, measurement of fiber, assessment of interested outcomes, RRs/HRs and 95% CIs, and variables adjusted for in the analysis. When separate risk estimates for men and women were available in a study, their RRs were combined using a fixed-effects model to generate a pooled risk estimate. For dose–response meta-analysis, the risk estimates should be provided for at least three quantitative categories of fiber intake.

We assessed study quality with the Newcastle–Ottawa Scale (NOS) for cohort studies (48). A maximum score of 1 for each question in the checklist can be awarded. Scores were calculated according to three major aspects: selection of participants, adjustment for confounders, and ascertainment of outcomes and nine questions. Scores of 0–2, 3–5, 5–7, and 7–9 were considered poor, fair, good, and high quality, respectively.

2.4. Statistical methods

For studies reporting HRs for fiber consumption, we assumed that the HR was approximately equal to the RR (49). The missing number of cases in each category was calculated by using the reported RRs/HRs and the number of total cases (50). The average or midpoint of each defined quartile was used for the dose amount. If the category dose range was open-ended, we assumed the length of the open-ended interval to be the same as that of the adjacent interval. For studies reporting risk estimates compared to medium or highest dietary fiber intake, the RR was recalculated by setting the lowest category of dietary fiber intake as the reference.

We computed the highest vs. lowest estimates by using a random-effects model (51), which considered variations (heterogeneities) both within and between studies. We calculated summary RRs (95% CIs) of all-cause, CVD, and cancer mortality per 10 g/day increment. We used the generalized least squares regression to estimate study-specific dose–response associations (52) and the random-effects model to pool the study-specific dose–response RR estimates (51). To examine possible linear or non-linear associations, we used restricted cubic splines for each study with more than three categories of exposure, with three fixed knots at 25%, 50%, and 75% of the total distribution of the reported intake, and combined them using multivariable meta-analysis (53). The significance of non-linearity was calculated using null hypothesis testing (53). We combined the study-specific slopes using random-effects models.

Heterogeneity was assessed using Cochran's Q test and I^2 statistic (54), with a value of $I^2 > 50\%$ considered to represent potentially important heterogeneity, and $P < 0.1$ was considered statistically significant for the Q statistic (55). Publication bias was assessed using Egger's test and funnel plots. When Egger's test indicated bias, a trim and fill method was used to detect the effect of probable missing studies on the overall effect. We further carried out subgroup analyses stratified by study characteristics, including duration of follow-up (>10 vs. ≤10), number of cases (≤1,000 vs. >1,000), geographical location, study quality (>7 vs. ≤7), adjustment for confounding factors (physical activity (PA), comorbidity at baseline, carbohydrate, protein), and dietary assessment methods, and meta-regression to investigate potential sources of heterogeneity. We also conducted sensitivity analyses excluding each study at a time from each analysis to clarify if the results are robust. A two-tailed $P < 0.05$ was considered significant. The Stata version 15.0 software (Stata Corp., TX) was used for the analyses.

3. Results

The flowchart for the selection is presented in Figure 1. We found 7,947 studies through the database search and reference lists. After removing duplicates, 5,355 records remained. After reviewing the title and abstract of these studies, 5,053 studies were subsequently excluded, and 302 full-text studies were then assessed. After full-text screening, a total of 290 publications were excluded because of duplicated data from the same cohort studies ($n = 22$), reviews ($n = 11$), or meta-analyses ($n = 15$), not relevant exposure ($n = 110$), not relevant outcome ($n = 67$), not cohort study ($n = 16$), or not adults or general population ($n = 18$). Finally, 32 publications were included in the systematic review and meta-analysis.

3.1. Study characteristics

A total of 32 articles (18–22, 28, 29, 32, 35, 40, 56–77) were included in the systematic review and the present meta-analysis. The characteristics of the studies included in the meta-analysis are listed in Table 1. The number of participants in these studies ranged from 314 to 452,717, with a mean or median age ranging from 16 to 99 years. Ten studies were from the United States (18, 21, 35, 56, 62, 64, 65, 67, 72, 77), four from the United Kingdom (19, 70, 71, 74), three cohorts conducted in Australia (58, 61, 63), two conducted among multiple nations (40, 59), two from Spain (28, 57), one from Dutch (69), one from Finland (68), one from France (22), one from Israeli (66), three from Japan (20, 29, 60), one from Korea (32), one from China (75), one from Malaysia (76), and one from Sweden (73). The follow-up period ranged from 2 to 40 years. Notably, 22 studies assessed

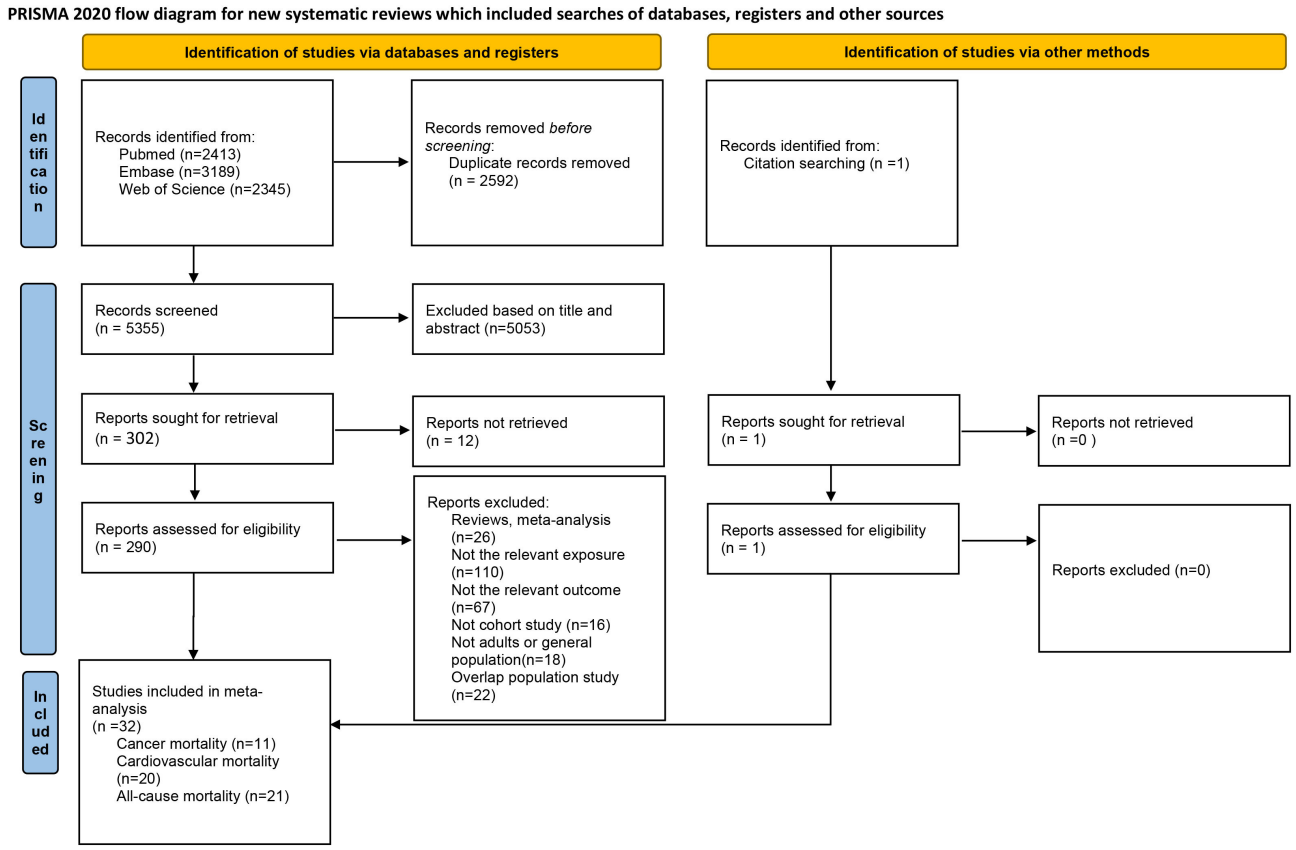

FIGURE 1
Flowchart of study selection.

dietary fiber intake using the food frequency questionnaire (FFQ) (20, 28, 32, 40, 56–63, 65–67, 70–74), and 10 using 24-h dietary records (18, 19, 21, 22, 35, 64, 69, 75–77). A total of 21 studies adjusted for physical activities (18, 20–22, 28, 32, 35, 40, 56, 57, 59, 60, 62, 65, 67, 68, 71, 72, 75), and others did not adjust for physical activities, and only one study did not adjust for age (69).

In all, 22 prospective cohort studies were summarized for meta-analysis to evaluate the possible relationships between dietary fiber consumption and mortality risk, totaling 171,751 deaths (164,183 for all-cause, 95,879 for CVD, and 107,114 for cancer mortality) among 2,567,890 participants. A total of 21 articles reported RRs of all-cause mortality (18–22, 28, 32, 35, 57, 59, 61, 62, 66, 69, 71–77), 11 reported RRs of cancer mortality (18–22, 28, 32, 35, 57, 59, 61, 62, 66, 69, 71–74, 77), 5 reported RRs of mortality from coronary heart disease (60, 63, 68–70), 14 reported RRs of mortality from CVD (18, 20, 21, 29, 32, 56–58, 60, 62, 65, 70, 72, 77), three reported RRs of mortality from ischemic heart disease (40, 64, 67), and four reported RRs of mortality from stroke (29, 60, 63, 70). Assessment of quality of the included studies for the association between dietary fiber and mortality is shown in Supplementary Table 2. By applying the NOS, the mean quality assessment score of included studies was 7.39 (range 5–8), with 28 studies assessed as high quality (more than 7 points) (18–22, 28, 29, 32, 35, 40, 56–60, 62–68, 70–73, 75, 77) and the other four (61, 69, 74, 76) as good quality.

The results of the highest vs. lowest meta-analyses on the associations between intake of dietary fiber and all-cause, CVD, and cancer mortality are shown in Table 1, Supplementary Figures 1–12.

3.2. Dose–response meta-analysis

3.2.1. Dietary fiber

A total of 14 studies (18–22, 28, 32, 57, 59, 69, 72, 75–77) with a total of 1,367,285 participants and 97,469 deaths were included in the dose–response meta-analysis of dietary fiber intake and all-cause mortality. The summary RR for a 10-g/day increment of dietary fiber intake was 0.90 (95% CI: 0.86–0.93; I^2 = 86.1%, $P_{heterogeneity}$ < 0.001; Table 2, Supplementary Figure 19). Evidence of heterogeneity between subgroups in stratified analyses was not found (Supplementary Figure 7). A non-linear dose–response association was found between dietary fiber intake and all-cause mortality ($P_{non-linearity}$ = 0.0096, Figure 2). The shape of the non-linear curve was steeper with a dietary fiber intake of <15 g/day, but the increase was more gradual after 15 g/day.

Thirteen studies (18, 20, 21, 29, 32, 40, 57, 58, 60, 64, 65, 72, 77) on the association between dietary fiber intake and CVD mortality were included in the dose–response analysis, which included 945,653 participants and 78,735 deaths. The summary

TABLE 1 Main characteristics of prospective studies examined the association of dietary fiber intake with all-cause, cardiovascular, cancer mortality.

References	Location	Follow-up (year)	Proportion of women	Age	Sample size	Outcome and cases	Exposure type	Exposure measurement	Adjustments
You et al. (76)	Malaysia	5	52.0%	>60	2,322	All-cause mortality 336	Dietary fiber	24 h recall	Age, gender, marital status and years of education
Zhang et al. (75)	China	11	52.8%	47.35 (mean)	8,307	All-cause mortality468	Dietary fiber	24 h recall	Age, sex, BMI, education, regions, physical activity, smoking status, alcohol drinking, total energy intake, total carbohydrate intake, protein intake, fatty intake, systolic blood pressure, diastolic blood pressure, Na intake, legume fiber, fruit fiber, and vegetable fiber.
Xu et al. (77)	US	17.1	45.80%	62.1 (mean)	86,642	All-cause mortality 17,536; CVD mortality 4,842; Cancer mortality 5,760	Dietary fiber; Insoluble fiber; Soluble fiber	Dietary history method	Age (continuous), sex (male vs. female), race (non-Hispanic White vs. Other), body mass index (BMI, < 25.0 kg/m2 vs. ≥ 25.0 kg/m2), education (≤ high school vs. ≥ some college), smoking status (never vs. former ≤ 15 years since quit vs. former > 15 years since quit vs. former year since quit unknown vs. current smoker ≤ 1 pack per day vs. current smoker > 1 pack per day vs. current smoker intensity unknown), marital status (married vs. not married), alcohol drinking status (never vs. former vs. current), and total energy intake (continuous)
Kwon et al. (32)	Korea	10.1 (median)	61.6%	>40	3,892	All-cause mortality 602; CVD mortality 149	Dietary fiber	FFQ	Age, sex, BMI, smoking, alcohol intake, exercise, total calorie intake, hypertension, diabetes, dyslipidemia, and baseline eGFR
Ha et al. (18)	US	9.3 (median)	51.3%	≥30	20,602	All-cause mortality 3,539; CVD mortality 798; Cancer mortality 714	Dietary fiber	1-d 24-h dietary recall	Age, sex, and race/ethnicity education, smoking, BMI, physical activity, dietary supplement use, and history of cardiovascular disease, diabetes, and hypertension, Adequate Intake;

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TABLE 1 (Continued)

References	Location	Follow-up (year)	Proportion of women	Age	Sample size	Outcome and cases	Exposure type	Exposure measurement	Adjustments
Ho et al. (19)	UK	10.6 (mean)	55.9%	37–73	195,658	All-cause mortality 4,780	Dietary fiber	24 h recall	Total energy intake and office-based risk factors: age, sex, diabetes, body mass index categories, systolic blood pressure, and smoking. Protein, saturated fatty acids, polyunsaturated fatty acid, monounsaturated fatty acid, starch, sugar
Katagiri et al. (20)	Japan	16.8 (mean)	54.0%	45–74	5,4445	Men: All-cause mortality 11,773; Women: All-cause mortality 7,627; Men: Cancer mortality 11,773; Women: Cancer mortality7627; Men: CVD mortality 11,773; Women: CVD mortality 7,627	Dietary fiber; Soluble fiber; Insoluble fiber; Cereal fiber; Vegetable fiber; Fruit fiber	FFQ	Age, area, BMI, smoking status, alcohol intake, sports or physical exercise during leisure time, hypertension with medication, self-reported diabetes with and without medication, health check-up, amount of green tea intake, coffee intake, salt intake
Miyazawa et al. (29)	Japan	24	56.12%	30–79	8,925	Men: CVD mortality 419; Women: CVD mortality 404; Men: stroke mortality 205; Women: stroke mortality 180	Dietary fiber	Modified Standards Tables for Food Composition in Japan (Third edition)	Age, smoking status, drinking status, BMI, medication of hypertension, past history of diabetes mellitus, sodium, saturated fatty acids, long-chain n-3 polyunsaturated fatty acids, available carbohydrate
Partula et al. (22)	France	5 (median)	78.7%	>18	107,377	All-cause mortality 635	Dietary fiber	Web-based 24-h dietary records	Age, sex, educational level, BMI, physical activity, smoking status, alcohol intake, energy intake, and number of 24-h dietary records. family history of cancer and CVD, and the personal history of cancer, CVD, and T2D.

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TABLE 1 (Continued)

References	Location	Follow-up (year)	Proportion of women	Age	Sample size	Outcome and cases	Exposure type	Exposure measurement	Adjustments
Dominguez et al. (28)	Spain	10.1 (mean)	61.0%	NR	19,703	All-cause mortality 323	Dietary fiber; Vegetable fiber; Fruit fiber; Legume fiber; Cereal fiber; Soluble fiber; Insoluble fiber	136-item FFQ	Age, sex, marital status, body mass index, smoking, alcohol, physical activity, hours per day spent watching television, baseline hypercholesterolemia, baseline hypertension, history of depression, history of CVD, history of cancer, history of diabetes, following special diets at baseline, snacking between meals, sugar-sweetened beverages consumption, and total energy intake
Chan et al. (35)	US	13.74 (mean)	53.4%	>20	15,740	All-cause mortality 3,164; Cancer mortality 656	Insoluble fiber	24-h dietary recall	Age, sex, race, marital status, education level, energy intake, folate intake, body mass index, alcohol consumption, smoking status and physical activity frequency per week.
Xu et al. (72)	US	14 (mean)	43.9%	61.7 (mean)	367,442	All-cause mortality 38,381; CVD mortality 9,323; Cancer mortality 16,000	Dietary fiber	Self-administered 124-item FFQ	Age, gender, smoking status, smoking dose, and time since quitting smoking, race/ethnicity, education, marital status, self-rated health status, body mass index, physical activity, use of menopausal hormone therapy, and intake of alcohol, red meat, fruits, vegetables, and total energy.
Gopinath et al. (61)	Australia	10 (total)	56.7%	>49	1,609	All-cause mortality 610	Dietary fiber	FFQ	Age, sex, marital status, living status, smoking, and weight status
Huang et al. (62)	US	14 (mean)	43.9%	50–71	36,7442	All-cause mortality 46,067; CVD mortality 11,283; Cancer mortality 19,043	Cereal fiber	A self-administered 124-item FFQ	Age, gender, the number of cigarettes smoked per day, time of smoking cessation, race or ethnicity group, alcohol intake, education level, marital status, health status, obesity, physical activity, consumption of red meat, total fruit and total vegetables, total energy intake, and hormone usage.

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TABLE 1 (Continued)

References	Location	Follow-up (year)	Proportion of women	Age	Sample size	Outcome and cases	Exposure type	Exposure measurement	Adjustments
Xu et al. (21)	US	10 (median)	0%	70–71	1,110	Men: All-cause mortality 300; Men: CVD mortality 138; Men: Cancer mortality 111	Dietary fiber	7-day dietary record	Protein intake (energy adjusted), age, BMI, smoking, physical activity, education, CVD, diabetes, hyperlipidemia, hypertension, eGFR, UAER, and CRP.
Buil-Cosiales et al. (57)	Spain	5.9	43.0%	55–75	7,216	All-cause mortality 425; CVD mortality 103; Cancer mortality 169	Dietary fiber	A 137-item validated FFQ	Age, sex, smoking status, diabetes, BMI, baseline systolic and diastolic arterial blood pressures, and intervention group and stratified by recruitment center, use of statins, alcohol intake, educational level, physical activity, and total energy intake.
Threapleton et al. (70)	UK	14.3 (median)	100%	50.4 (mean)	31036	Women: CHD mortality 113; Women: stroke mortality 117; Women: CVD mortality 230	Soluble fiber; Insoluble fiber; Cereal fiber; Fruit fiber; Vegetable fiber	Self-administered FFQ	Age, BMI, calories from carbohydrate, fat and protein, ethanol intake, METS, smoking status, socio-economic status.
Crowe et al. (40)	Eight European countries	11.5 (mean)	62.4%	53.8 (mean)	306,331	IHD deaths 2,381	Dietary fiber; Cereal fiber; Fruit fiber; Vegetable fiber	Quantitative FFQ; diet history questionnaires; semi-quantitative FFQ	Stratified by sex, centre and smoking and adjusted for age, alcohol intake, BMI, physical activity, marital status, highest education level, current employment, hypertension, hyperlipidaemia, angina pectoris, diabetes mellitus, polyunsaturated to saturated fat ratio and total energy intake.
Chuang et al. (59)	Multi-national	12.7 (mean)	71.2%	50.8 (mean)	452,717	All-cause mortality 23,582; Men: All-cause mortality 10,366; Women: All-cause mortality 13,216; Men: Cancer mortality 4,039; Women: Cancer mortality 5,575	Cereal fiber; Fruit fiber; Vegetable fiber; Dietary fiber	Extensive self-administered quantitative dietary questionnaires; semiquantitative FFQ; diet-history method; 7-d menu book	Education, smoking, alcohol consumption, BMI, physical activity, and total energy intake.

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TABLE 1 (Continued)

References	Location	Follow-up (year)	Proportion of women	Age	Sample size	Outcome and cases	Exposure type	Exposure measurement	Adjustments
Nilsson et al. (73)	Sweden	1–19	52.0%	49 (median)	21,596	Men: All-cause mortality:1460; Women: All- cause mortality:923	Dietary fiber	FFQ	BMI, sedentary lifestyle, education, current smoking, intake of alcohol and total energy, Red meat, Fatty fish, Fat, Berries, Boiled coffee, Blood dishes, Vegetables, Bread
Akbaraly et al. (74)	UK	18	30.30%	39–63	7,319	All-cause mortality: 534; Cancer mortality: 259; CVD mortality: 141	Dietary fiber	Semiquantitative FFQ	Sex, age, ethnicity, occupational grade, marital status, smoking status, total energy intake, physical activity, BMI categories, prevalent CVD, type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome, and inflammatory markers
Baer et al. (56)	US	18	100%	30–55	50,112	Women: CVD mortality: 1,026; Women: All-cause mortality: 4,893; Women: Cancer mortality: 1,430	Cereal fiber	Semiquantitative FFQ	Age, Body mass index at age 18 years, Smoking status, Physical activity, Alcohol intake, Nut consumption, Polyunsaturated fat, Glycemic load, Dietary cholesterol, Systolic blood pressure, Personal history of diabetes, Parental MI before age 60 years, Time since menopause
Buyken et al. (58)	Australia	13 (total)	54.5%	≥49	2,735	Women: CVD mortality 109; Men: CVD mortality 151	Dietary fiber; Vegetable fiber; Fruit fiber; Cereal fiber	145-item FFQ	Age, energy, dietary glycemic index residuals, alcohol consumption 20 g/d compared with 20 g/d, current smoking, and presence of diabetes at baseline;

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TABLE 1 (Continued)

References	Location	Follow-up (year)	Proportion of women	Age	Sample size	Outcome and cases	Exposure type	Exposure measurement	Adjustments
Eshak et al. (60)	Japan	14.3	60.6%	40–79	58,730	Men: CVD mortality 1,063; Women: CVD mortality 1,017; Men: CHD mortality 1,063; Women: CHD mortality 1,017; Men: stroke mortality 1,063; Women: stroke mortality 1,017	Dietary fiber; Insoluble fiber; Soluble fiber; Cereal fiber; Fruit fiber; Vegetable fiber	Self-administered FFQ	Age, BMI, history of hypertension, history of diabetes, alcohol consumption, smoking, education level, hours of exercise, hours of walking, perceived mental stress, sleep fish, SFA, n-3) fatty acids, sodium, folate, and vitamin E.
Kaushik et al. (63)	Australia	13	43.3%	>49	2,897	Stroke mortality 95; CHD mortality NR	Cereal fiber	FFQ.	Age, gender, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, body mass index, smoking status, educational qualifications, fair or poor self-rated health, history of myocardial infarction and stroke, and presence of diabetes, energy
Streppel et al. (69)	Dutch	40	0%	49 (mean)	1,373	Men: CHD mortality 348; Men: All-cause mortality 1,130	Dietary fiber; Vegetable fiber; Fruit fiber; Cereal fiber	Cross-check dietary history method	Total energy, saturated fat, trans unsaturated fatty acid, and cis polyunsaturated fat acid intakes; alcohol intake, wine use, fish intake, prescribed diet, the number of cigarettes smoked, the duration of cigarette smoking, cigar or pipe smoking, BMI, and socioeconomic status.
Lubin et al. (66)	Israeli	18	52.0%	55.2 (mean)	623	All-cause mortality 151	Dietary fiber	FFQ	Mean daily energy intake, Ethnic origin, Sex, Age, 5-y increment, Smoking status, Systolic blood pressure, Physical activity, BMI, Fatty acids, Energy intake from fat, Cholesterol

(Continued)

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TABLE 1 (Continued)

References	Location	Follow-up (year)	Proportion of women	Age	Sample size	Outcome and cases	Exposure type	Exposure measurement	Adjustments
Mozaffarian et al. (67)	US	8.6 (mean)	38.8%	>65	3,588	IHD deaths159	Cereal fiber; Fruit fiber	99-item FFQ	Age, sex, education, diabetes, ever smoking, pack-years of smoking, daily physical activity, exercise intensity, alcohol intake, and cereal, fruit, and vegetable fiber intake
Liu et al. (65)	US	6 (mean)	100%	≥45	Women: 38,480	Women: CVD mortality 570	Dietary fiber; Cereal fiber; Vegetable fiber; Fruit fiber; Soluble fiber; Insoluble fiber	A validated 131-item SFFQ	Age, randomized treatment assignment, smoking status, exercise, alcohol intake, use of postmenopausal hormone, body mass index, use of multivitamin supplements, history of hypertension, history of high cholesterol, history of diabetes, parental history of MI before age 60, dietary folate, total fat, protein, and total energy intake.
Todd et al. (71)	UK	3 (total)	100%	40–59	3,833	Women: All-cause mortality 108	Dietary fiber	Semiquantitative FFQ	Age, serum total cholesterol, systolic blood pressure, carbon monoxide, energy, previous medical diagnosis of diabetes, body mass index, the Bortner personality score, triglycerides, high density llpoproteln cholesterol, fibrinogen, a self-reported measure activity in leisure, and alcohol consumption
Pietinen et al. (68)	Finland	6.1	0%	50–60	21,930	Men: CHD mortality 1,399;	Dietary fiber; Soluble fiber; Insoluble fiber; Cereal fiber; Vegetable fiber; Fruit fiber	A self-administered modified dietary history method.	Age, treatment group, smoking; body mass index; blood pressure; intakes of energy, alcohol, and saturated fatty acids, education, and physical activity, intakes of beta-carotene, vitamin C, and vitamin E
Khaw et al. (64)	US	12 (mean)	58.6%	50–79	859	Men: IHD deaths 42; Women: IHD deaths 23; IHD deaths 356; Men: IHD deaths 42; Women: IHD deaths 23	Dietary fiber	A 24-hour dietary recall	Age, systolic blood pressure, plasma cholesterol, fasting blood glucose, obesity, cigarette smoking habit

CVD, cardiovascular disease; FFQ, food-frequency questionnaire; US, United States; eGFR, estimated glomerular filtrationrate; BMI, Body mass index; NR, Not reported; UAER, Urinary Albumin Excretion Rate; CRP, C-reactive protein; UK, United Kingdom; CHD, Coronary Heart Disease; IHD, ischemic heart disease; T2D, Type 2 Diabetes Mellitus; SFA, Saturated Fatty Acid; METS, Metabolic Equivalants; MI, myocardial infarction; SFFQ, Simplified Food Frequency Questionnaire.

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TABLE 2 Dietary fiber intake and risk of all-cause, cardiovascular, and cancer mortality for the highest versus lowest and dose-response meta-analysis.

		Highest vs. lowest fiber analysis				Dose-response analysis			
		No of studies	RR (95% CI)	I^2%	*P* value	No of studies	RR (95% CI)	I^2%	*P* value
Dietary fiber	All-cause mortality	16	0.81(0.77,0.86)	71.90	<0.001	14	0.90(0.86,0.93)	86.10	<0.001
	CVD mortality	14	0.78(0.72,0.84)	63.20	0.001	13	0.87(0.84,0.91)	77.80	<0.001
	Cancer mortality	6	0.82(0.77,0.87)	58.70	0.033	7	0.91(0.88,0.93)	27.90	0.216
Vegetable fiber	All-cause mortality	5	0.96(0.83,1.10)	69.30	0.011	4	0.88(0.73,1.05)	49.60	0.114
	CVD mortality	7	0.87 (0.81,0.94)	0.00%	0.952	7	0.91(0.78,1.06)	0.00	0.498
	Cancer mortality	-	-	-	-	2	0.89(0.79,1.01)	47.30	0.168
Fruit fiber	All-cause mortality	5	0.89(0.81,0.98)	19.00	0.294	4	0.99(0.92,1.07)	27.60	0.246
	CVD mortal ity	11	0.79(0.68,0.92)	71.90	<0.001	8	0.76(0.52,1.09)	73.30	0.001
	Cancer mortality	-	-	-	-	-	-	-	-
Cereal fiber	All-cause mortality	5	0.88(0.80,0.97)	84.70	<0.001	5	0.82(0.73,0.93)	56.00	0.059
	CVD mortality	13	0.87(0.81,0.94)	46.40	0.033	9	0.84(0.73,0.97)	47.10	0.057
	Cancer mortality	3	0.86(0.83,0.90)	0.00	0.589	2	0.77(0.56,1.06)	90.20	0.001
Insoluble fiber	All-cause mortality	5	0.85(0.78,0.93)	79.20	0.001	5	0.86(0.81,0.92)	71.30	0.008
	CVD mortality	6	0.74(0.69,0.79)	0.00	0.986	6	0.81(0.78,0.85)	0.00	0.647
	Cancer mortality	3	0.92(0.74,1.14)	82.90	0.003	3	0.93(0.81,1.07)	87.30	<0.001
Soluble fiber	All-cause mortality	5	0.91(0.85,0.97)	66.80	0.017	5	0.83(0.74,0.92)	60.90	0.037
	CVD mortality	5	0.79(0.72,0.86)	0.00	0.719	5	0.62(0.47,0.84)	63.80	0.026
	Cancer mortality	2	0.97(0.63,1.51)	88.80	0.003	2	0.97(0.55,1.70)	89.00	0.003

CVD, cardiovascular disease; RR, relative risk.

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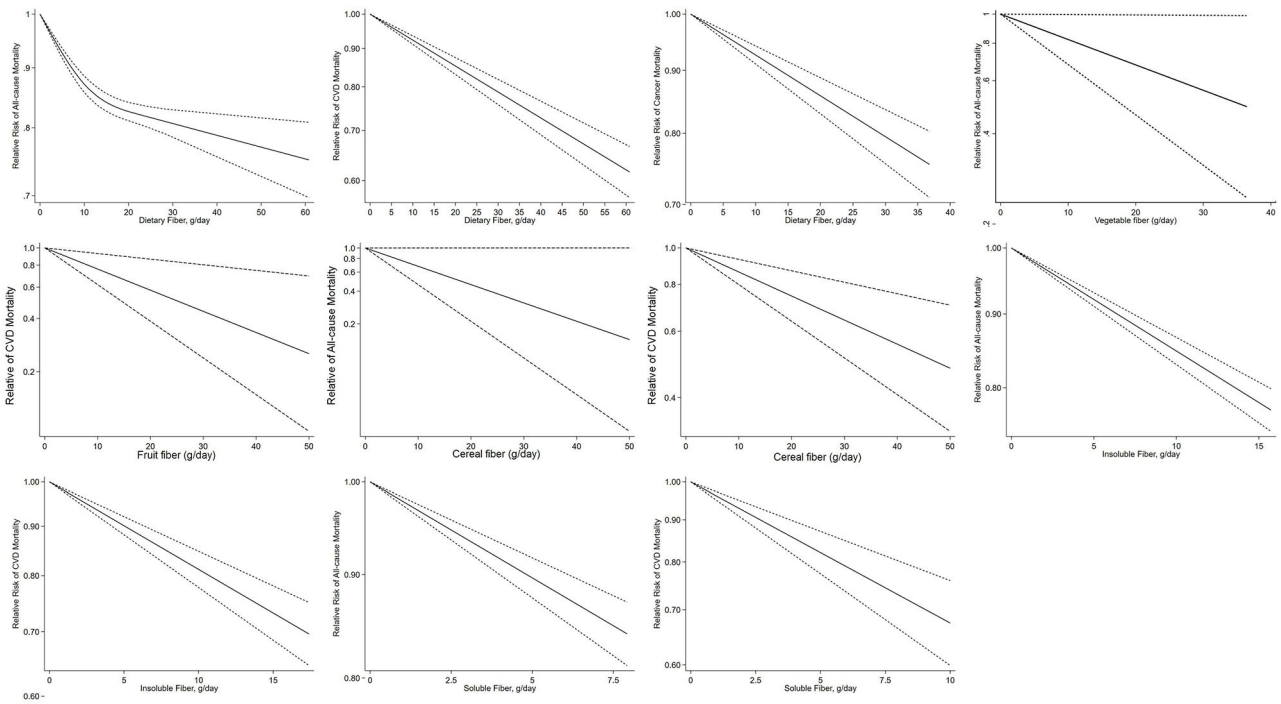

FIGURE 2
Dose–response association of per 10 g/day increase in total fiber, vegetable, fruit, cereal, soluble and insoluble fiber intake with all-cause, cardiovascular, and cancer mortality by restricted cubic splines.

RR for a 10-g/day increment of dietary fiber intake was 0.87 (95% CI: 0.84–0.91; I^2 = 79.2%, $P_{heterogeneity}$ < 0.001; Table 2, Supplementary Figure 19). Evidence of heterogeneity between subgroups was observed in the analysis stratified by adjustment for comorbidity at baseline (P = 0.032) (Supplementary Figure 7). No evidence of a non-linear dose–response association was found between dietary fiber intake and risk of CVD mortality ($P_{non-linearity}$ = 0.247, Figure 2). Dose–response analysis of six studies (18, 20, 21, 57, 59, 72) showed an inverse association between dietary fiber and cancer mortality (summary RR 0.90, 95% CI: 0.87–0.94; I^2 = 35.4%, $P_{heterogeneity}$ = 0.17; Table 2, Supplementary Figure 19). Evidence of heterogeneity between subgroups was observed in the analysis stratified by adjustment for region (P = 0.032) (Supplementary Figure 7). There was no indication of non-linearity between dietary fiber intake and risk of cancer mortality ($P_{non-linearity}$ = 0.995, Figure 2).

Sensitivity analysis showed that the exclusion of any single study from the analysis did not appreciably alter the summary effect sizes (Supplementary Table 9).

3.2.2. Vegetable fiber

Four studies (22, 28, 59, 69) were included in the dose–response meta-analysis of vegetable fiber intake and all-cause mortality. The summary RR for a 10-g/day increment of vegetable fiber intake was 0.88 (95% CI: 0.73–1.05; I^2 = 49.6%, $P_{heterogeneity}$ = 0.11; Table 2, Supplementary Figure 20). No evidence of heterogeneity between subgroups was observed (Supplementary Figure 8). The non-linearity between dietary fiber intake and risk of cancer mortality approached significance (P = 0.07, Figure 2).

No significant association was seen between vegetable fiber intake and CVD mortality based on six studies (40, 58, 65, 68–70). The summary RR for a 10-g/day increment of vegetable fiber was 0.91 (95% CI: 0.78–1.06; I^2 = 0%, $P_{heterogeneity}$ = 0.50; Table 2, Supplementary Figure 20). No evidence of heterogeneity between subgroups was observed (Supplementary Figure 8). A non-linear dose–response association was found between vegetable fiber intake and risk of cancer mortality ($P_{non-linearity}$ = 0.01, Figure 2). The association between vegetable fiber and CVD mortality has a J-shape, with the lowest estimates at 5 g/day.

In the sensitivity analysis, exclusion of the study by Partula et al. (22) and Streppel et al. (69) resulted in a change in the significant inverse association between vegetable fiber intake and all-cause mortality to a marginally significant inverse association, but the summary estimate of vegetable fiber intake and CVD mortality remained robust (Supplementary Table 10).

3.2.3. Fruit fiber

No significant association was seen between fruit fiber intake and all-cause mortality based on four studies (22, 28, 59, 69). The summary RR for a 10-g/day increment of fruit fiber intake was 0.99 (95% CI: 0.92–1.07; I^2 = 27.6%, $P_{heterogeneity}$ = 0.25; Table 2, Supplementary Figure 21). No significant association with fruit fiber intake was found in subgroup analyses, and no evidence of heterogeneity between subgroups was observed (Supplementary Figure 9). There was no indication of non-linearity

between fruit fiber intake and all-cause mortality ($P_{non-linearity}$ = 0.25, Figure 2).

No significant association was found between fruit fiber intake and CVD mortality based on seven studies studies (40, 58, 60, 65, 68–70). The summary RR for a 10-g/day increment of fruit fiber intake was 0.76 0.52–1.09; I^2 = 73.3%, $P_{heterogeneity}$ = 0.001; Table 2, Supplementary Figure 21). No evidence of heterogeneity between subgroups was observed (Supplementary Figure 9). There was no evidence of non-linearity between fruit fiber intake and CVD mortality ($P_{non-linearity}$ = 0.13, Supplementary Figure 14).

A sensitivity analysis showed that exclusion of the studies by Eshak et al. (60) or Pietinen et al. (68) resulted in a change from the non-significant association between fruit fiber intake and CVD mortality to a significant inverse association (Supplementary Table 11).

3.2.4. Cereal fiber

In the dose–response analysis of cereal fiber intake and all-cause mortality, based on five studies studies (22, 28, 56, 59, 69), a significant inverse association was found. The summary RR for a 10-g/day increment cereal fiber intake was 0.82 (95% CI: 0.73–0.93; I^2 = 56.0%, $P_{heterogeneity}$ = 0.06; Table 2, Supplementary Figure 22). No evidence of heterogeneity between subgroups was observed (Supplementary Figure 10). There was no indication of non-linearity between soluble fiber intake and CVD disease mortality (P = 0.24, Figure 2).

In the dose–response analysis of cereal fiber intake and CVD mortality, based on nine studies (40, 56, 58, 60, 63, 65, 68–70), a significant inverse association was found. The summary RR for a 10-g/day increment of cereal fiber intake was 0.84 (95% CI: 0.73–0.97; I^2 = 47.1%, $P_{heterogeneity}$ = 0.06; Table 2, Supplementary Figure 22). No evidence of heterogeneity between subgroups was observed (Supplementary Figure 10). There was no indication of non-linearity between cereal fiber intake and CVD mortality ($P_{non-linearity}$ = 0.45, Figure 2), with nine studies included (40, 56, 58, 60, 63, 65, 68–70).

Two studies (56, 59) reported data on cereal fiber intake and cancer mortality. The summary RR for a 10-g/day increment of cereal fiber intake was 0.77 (95% CI: 0.56–1.06; I^2 = 90.2%, $P_{heterogeneity}$ = 0.001; Table 2, Supplementary Figure 22).

The sensitivity analysis showed that the summary estimate is robust (Supplementary Table 12).

3.2.5. Insoluble fiber

Five studies (20, 22, 28, 35, 77) assessed the dose–response meta-analysis of insoluble fiber intake and all-cause mortality. The summary RR for a 10-g/day increment of insoluble fiber intake was 0.86 (95% CI: 0.81–0.92, I^2 = 71.3%, $P_{heterogeneity}$ = 0.008; Table 2, Supplementary Figure 23). Evidence of heterogeneity between subgroups was observed in the analysis stratified by the number of cases included in the study (0.034) and whether adjusted for region (P = 0.040) (Supplementary Figure 11). There was no indication of non-linearity between insoluble fiber intake and all-cause mortality ($P_{non-linearity}$ = 0.909, Figure 2), with five studies included (20, 22, 28, 35).

Six studies (20, 60, 65, 68, 70, 77) on the association between insoluble fiber intake and CVD mortality were included in the dose–response analysis. The summary RR for a 10-g/day increment of insoluble fiber intake was 0.81 (95% CI: 0.78–0.85; I^2 = 0.00%, $P_{heterogeneity}$ = 0.65; Table 2, Supplementary Figure 23). No evidence of heterogeneity between subgroups was observed (Supplementary Figure 11). There was no evidence of non-linear dose–response association between insoluble fiber intake and CVD mortality ($P_{non-linearity}$ = 0.52, Figure 2), with six studies included (20, 60, 65, 68, 70).

The dose–response analysis of three studies (20, 35, 77) showed no significant association between insoluble fiber and cancer mortality (summary RR: 0.93, 95% CI: 0.81–1.07), with no significant heterogeneity among the studies (I^2 = 87.3%, $P_{heterogeneity}$ < 0.001; Table 2, Supplementary Figure 23). There was no evidence of non-linear dose–response association between insoluble fiber intake and CVD mortality ($P_{non-linearity}$ = 0.699, Figure 2), with two studies included (20, 35).

In the sensitivity analysis, the summary estimate is robust for all-cause and CVD mortality. Exclusion of the study by Katagiri et al. (20) resulted in a change from the non-significant association between insoluble fiber intake and cancer mortality to a significant inverse association (Supplementary Table 13).

3.2.6. Soluble fiber

Five prospective studies (20, 22, 28, 35, 77) were included in the dose–response meta-analysis of soluble fiber intake and all-cause mortality. The summary RR for a 10-g/day increment of soluble fiber intake was 0.83 (95% CI: 0.74–0.92; I^2 = 60.9%, $P_{heterogeneity}$ = 0.037; Table 2, Supplementary Figure 24). Evidence of heterogeneity between subgroups was observed in the analysis stratified by dietary fiber measurement (P = 0.032) (Supplementary Figure 12). There was no indication of non-linearity between soluble fiber intake and all-cause mortality ($P_{non-linearity}$ = 0.785, Figure 2), with five studies included (20, 22, 28, 35).

Five studies (60, 65, 68, 70, 77) provided RRs of soluble fiber intake and CVD mortality. The summary RR for a 10-g/day increment of soluble fiber intake was 0.62 (95% CI: 0.47–0.84; I^2 = 63.8%, $P_{heterogeneity}$ = 0.026; Table 2, Supplementary Figure 24). Evidence of heterogeneity between subgroups in stratified analyses was not observed (Supplementary Figure 12). There was no indication of non-linearity between soluble fiber intake and CVD mortality ($P_{non-linearity}$ = 0.587, Figure 2).

In the sensitivity analysis, the summary estimate is robust, except that exclusion of the study by Katagiri et al. and Xu et al. (20, 77) lead to a non-significant association between soluble fiber intake and all-cause mortality (Supplemental Table 14).

3.3. Publication bias

In the highest vs. lowest meta-analysis, Egger's linear regression test and visual inspection of the funnel plots (Supplementary Figure 25) indicated possible publication bias for the association between dietary fiber intake and CVD mortality

($P = 0.001$), and vegetable fiber intake and all-cause mortality ($P = 0.038$), but no evidence of publication bias for other outcomes. In the dose–response analyses, Egger's linear regression test and visual inspection of the funnel plots indicated possible publication bias for the association between dietary fiber intake and cancer mortality ($P = 0.043$) (Supplementary Figures 31, 36). No evidence of significant publication bias was found in other analyses (Supplementary Figures 26–30, 32–35). Application of the trim and fill method did not result in a change in the average effect size, further suggesting that the results were not affected by publication bias.

4. Discussion

The present systematic review and meta-analysis investigated the association between dietary fiber intake and different sources and types of fiber intake and all-cause, CVD, and cancer mortality by applying highest vs. lowest, linear, and non-linear dose–response analyses. We found that dietary fiber intake was inversely associated with all-cause, CVD, and cancer mortality. The inverse association was also found for cereal fiber intake. All categories of fibers were inversely associated with CVD mortality. The inverse association of cancer mortality was only detected for cereal fiber and dietary fiber. Significant associations were also found for other fiber intake and all-cause mortality, except for fruit and vegetable fiber intake. Besides, a non-linear relationship was found for all-cause mortality.

A large number of longitudinal cohort studies have reported the health benefits of dietary fiber intake (78–80). Several systematic reviews and meta-analyses suggested that high dietary fiber intake was associated with a reduced risk of all-cause, CVD, and cancer mortality (42, 46), which was consistent with the findings from our systematic review and meta-analysis. The subgroup analysis also showed the stability of the findings, which was different from previous meta-analyses meta-analyses (24). This may account for the fact that our study has additionally included more than 14 related studies studies (18–22, 28, 29, 32, 35, 61, 62, 75–77) published in recent years, with than 2,614,294 participants included, compared to the previous meta-analysis. This study found a non-linear relationship between dietary fiber and all-cause mortality, showing that the protective effect of dietary fiber is relatively constant when the daily intake is >15 g. A meta-analysis including five papers concluded that risk reduction associated with all-cause mortality was greatest when the daily intake of dietary fiber was between 25 and 29 g, while the dose–response data suggested that amounts >30 g/day confer additional benefits (26). The inconsistent findings might be because of the relatively large number of studies included: publications since 2016 were not included in their dose–response analyses of dietary fiber intake and all-cause mortality (26), and ∼14 more articles updated to 2023 were included in our dose–response meta-analysis. The non-linear relationship of dietary fiber was not found among all-cause and cancer mortality because the effect of dietary fiber on different health outcomes may have different mechanisms.

Dietary fibers from different food sources have a distinctive mix of different types of compounds and may have a different effect on all-cause and CVD mortality (81, 82). The present systematic review and meta-analysis found the inverse association between vegetable and fruit fiber intake and CVD mortality as well as the significantly inverse association between cereal fiber intake and all-cause, CVD, and cancer mortality, but no association of vegetable fiber with cancer or all-cause mortality. A meta-analysis also found that cereal fiber intake was protectively associated with all-cause, CVD, and cancer mortality, although it included general participants and people with diseases (41). Our study also showed that cereal fiber but not fruit fiber or vegetable fiber was significantly associated with lower total mortality in the dose–response analysis, which was in line with an earlier meta-analysis (45). The recommended level of dietary fiber intake is 25 g for adult women and 38 g for adult men, and the public should consume adequate amounts of dietary fiber from a variety of plant foods (83). Plant foods contain more than just dietary fiber, so any protective properties of plant-based diets may be linked to other dietary components, such as vitamins, minerals, or phytochemicals, and not just isolated dietary fiber (84). The unstable findings in the subgroup analysis suggest that more studies are further needed on the association between fruit fiber and CVD mortality.

Soluble fiber is found in oat bran, barley, beans, lentils, peas, and some fruits and vegetables, while insoluble fiber is rich in foods such as wheat bran, whole grains, nuts, and seeds (77). Although mounting evidence has suggested the protective role of dietary fiber against various chronic diseases (13, 22), the health effect may depend on the dietary fiber type (85, 86), and the findings on soluble and insoluble fiber intake and mortality are contradictory (20, 22). Our study found the inverse association between both soluble and insoluble fiber intake and all-cause and CVD mortality. The finding on CVD mortality was in line with one previous systematic review and meta-analysis (87), and our study included eight additional studies (18, 20, 21, 29, 32, 57, 72, 77) after 2012 and found a linear relationship. To the best of our knowledge, this is the first study to explore soluble and insoluble fiber intake and all-cause and cancer mortality. No significant association was found between insoluble or soluble fiber intake and cancer mortality in the present study, which may be explained by the limited number of studies included. Insoluble fiber is characterized by a fecal-bulking ability, which may reduce the risk of cancer mortality (77); however, evidence regarding soluble or insoluble fiber on cancer mortality remains limited and inconsistent, and only three studies (20, 35, 77) conducted in Japan and the United States were included in our systematic review and meta-analysis. Further prospective studies on soluble and insoluble fiber intake and cancer mortality are therefore needed.

The mechanism underlying the inverse relationship between dietary fiber and mortality is unclear, but there are several plausible explanations. The protective effect of dietary fiber on cholesterol (88, 89), blood pressure (90), insulin sensitivity (85), and blood glucose (91) as well as the anti-inflammatory effects (92) may partly explain the protection from mortality. A study demonstrated that the inclusion of a practical dose of dietary fiber (11.6 g) in a bakery product significantly reduced postprandial glucose and insulin responses in healthy adults (93). Insulin is known to promote the action of the hepatic enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)

reductase (94). Inhibition of HMG-CoA reductase may result in the prevention of excess cholesterol being synthesized and released into circulation by the liver and may thereby reduce the risk of CVD (95). Moreover, alteration of intestinal microbiota composition and function may be an important reason for the potential benefits of dietary fiber (96). Experimental studies also suggested that the reduction of soluble fiber may influence the synthesis of microbial metabolites that are important for regulating metabolic, immune, behavioral, and neurobiological outcomes (97).

This review has some strengths. First, the present study was a comprehensive systematic review and meta-analysis of prospective cohort studies to investigate the association between dietary fiber intake and mortality, using high vs. low analysis and dose–response analysis. Second, the different types and food sources of dietary fiber were also considered, which can provide valuable insight into the mechanisms and evidence for strategies to derive the greatest benefit from balanced consumption of dietary fiber. Furthermore, a large number of participants and deaths have been included and allowed us to quantitatively assess the association between dietary fiber intake and risk of mortality.

In terms of study limitations, first of all, most studies did not consider other nutrients as confounding factors, such as protein, carbohydrate, or fiber from other food sources, which may affect the magnitude of the association between dietary fiber intake and mortality. Besides, comorbidity at baseline was not controlled in a few studies, which could affect the association between dietary fiber and mortality. Second, different dietary fiber assessment tools were used, which might lead to variation in the study results. Third, only three studies (20, 35, 77) reported risk estimates on soluble or insoluble fiber intake and cancer mortality, which limit us to conduct the subgroup and sensitivity analyses and suggest the necessity of further studies. Fourth, different diet assessment tools were used (FFQ, 24-h dietary recall, semiquantitative FFQ), and therefore measurement error was unavoidable. Fifth, sensitivity analyses demonstrated a profound lack of robustness among summary estimates for vegetable fiber and fruit fiber intake on mortality in the dose–response meta-analysis. Sixth, high heterogeneity exists in our meta-analysis of fruit fiber–CVD mortality and dietary fiber–all-cause mortality associations, although sensitive and subgroup analyses were conducted to show stable findings. The meta-regression analysis was also conducted, and we found that the heterogeneity may come from different levels of study quality for studies included in the meta-analysis of dietary fiber and all-cause mortality and different durations of follow-up for the studies on the association of fruit fiber and CVD mortality.

In conclusion, the present systematic review and meta-analysis found that higher dietary fiber intake was associated with a lower risk of all-cause, CVD, and cancer mortality. For different food sources of dietary fibers, fruit, vegetable, and cereal fiber intake were related to reduced risk of mortality, but there was no association of vegetable or fruit fiber with cancer mortality, showing a significant non-linear relationship between dietary fiber intake and all-cause mortality and a linear relation for other fibers. Our study incorporates different types and food sources of dietary fibers, which provide valuable insight into the mechanisms and may provide evidence for strategies to derive the greatest benefit from a balanced consumption of dietary fiber. The association between insoluble or soluble fiber intake and mortality and the difference between sources of dietary fiber and cancer mortality warrants further investigation.

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.

Author contributions

FY and PQ conceived, designed, performed the study, and drafted the manuscript. FY, JM, CH, XZ, YC, RL, and PQ extracted, analyzed, or interpreted the data. FY, JM, YC, RL, CH, XZ, FH, and PQ revised the manuscript. All authors approved the final manuscript.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1153165/full#supplementary-material

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Maternal dietary patterns and acute leukemia in infants: results from a case control study in Mexico

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Background: Childhood cancer is the leading cause of disease-related mortality among children aged 5–14 years in Mexico, with acute leukemia being the most common cancer among infants. Examining the overall dietary patterns allows for a comprehensive assessment of food and nutrient consumption, providing a more predictive measure of disease risk than individual foods or nutrients. This study aims to evaluate the association between maternal dietary patterns during pregnancy and the risk of acute leukemia in Mexican infants.

Methods: A hospital-based case–control study was conducted, comparing 109 confirmed acute leukemia cases with 152 age-matched controls. All participants (≤24 months) were identified at hospitals in Mexico City between 2010 and 2019. Data on *a posteriori* dietary patterns and other relevant variables were collected through structured interviews and dietary questionnaires. Multivariate logistic regression was employed to estimate the association between maternal dietary patterns during pregnancy and the risk of acute leukemia in infants.

Results: The "Balanced & Vegetable-Rich" pattern, characterized by a balanced consumption of various food groups and higher vegetable intake, exhibited a negative association with acute leukemia when compared to the "High Dairy & Cereals" Pattern (adjusted odds ratio [OR] = 0.51; 95% confidence interval [CI]: 0.29, 0.90). We observed that mothers who gave birth to girls and adhered to a healthy dietary pattern during pregnancy exhibited significantly lower odds of their children developing AL compared to those who gave birth to boys [OR = 0.32 (95% CI 0.11, 0.97)]. Our results underscore the significance of maternal nutrition as a modifiable factor in disease prevention and the importance of prenatal health education.

KEYWORDS

dietary patterns, pediatric cancer, acute leukemia, leukemia, maternal diet, case–control

1. Introduction

In Mexico, childhood cancer is the first cause of death by disease in children aged 5–14 years and the sixth among those under five. It represents almost 70% of the total burden of disease in these age groups (1). Acute Leukemia (AL) is the most common cancer among children and adolescents around the world. Among Hispanic children, the incidence of AL is the highest compared with other neoplasms in Caucasian and African American and is more frequent in males than among females (2). In spite that this disease represents a low proportion of cancer cases in the total population, it causes the highest number of years of life potentially lost (YLL) due to premature death.

AL etiology is largely unknown. However, experimental evidence show that translocations are initiating events that occur early *in utero* and are present in a substantial proportion of childhood AL. Clonal markers in leukemic cells and clonotypic fusion gene sequences in neonatal blood spots, have been observed in monozygotic twins, in whom only one of them develops the disease (3). These findings underscore the need to examine potential risk factors in the fetal environment, such as maternal diet. Diet may yield protective and/or negative effects leading to cancer, not only through the intake of diverse dietary components that take part in epigenetic processes such as: DNA methylation, histone modifications, noncoding RNAs in fetus but also, as a vehicle for carcinogenic compounds, like N-nitroso precursors, that cross transplacental barrier (4).

Evidence suggests that the size and growth rate of the fetus during gestation may play a role in the development of leukemia. For example, some studies have shown that children who are born small for gestational age may have a higher risk of developing leukemia (5). It is thought that a slower growth rate during gestation may increase the risk of certain genetic mutations that can lead to the development of leukemia. Some studies have reported that maternal nutrition effects

on fetal growth and development may differ between male and female fetuses (6). However, there is limited evidence on the differential effects of maternal dietary patterns on leukemia risk in boys and girls.

Early epidemiological studies focused on AL and maternal diet evaluation of a single nutrient and/or food. Further studies evidenced the role of food groups on AL development. In this way, there is available evidence regarding the negative association between maternal consumption of folic acid and protein with AL, respectively (7), as well as the consumption of fruits, vegetables, fish, shellfish, beans, and beef (8). In contrast to the observed relationship with the consumption of chocolate, wine, coffee, and processed meats, which are dietary inhibitors of the nuclear enzyme topoisomerase II, as well as sugars and syrups (9). Individual components of the diet interact with each other, so this approach of evaluating dietary components one by one has gradually evolved to the evaluation of dietary patterns.

Because of the complexity of diets, the overall effects (antagonic or synergistic) of various nutrients and foods that are consumed simultaneously, may only be assessed through the identification of dietary patterns (10), which depend on culture and availability of foods in each population and are not necessarily replicated throughout different countries. Research on dietary patterns in Latin American populations is scarce, and its possible relationship with childhood AL is null.

Our aim was to evaluate the association between maternal dietary patterns during pregnancy and AL in Mexican infants and to explore if this association differs by sex.

2. Materials and methods

During the period of 2010 to 2019, a clinical based case–control study was carried out in Mexico City and State of Mexico. The study population comprised children that were identified in 9 public secondary and tertiary public hospitals. The protocol was approved by the Mexican Institute of Social Security (IMSS) IRB with number 2010-785-064.

2.1. Cases

Eligible cases were children up to 24 months of age with acute leukemia (AL), which was confirmed with bone marrow smears and histochemical tests (myeloperoxidase, sudan black B reaction, esterases, periodic Schiff reaction (PAS) and acid phosphatase) and immunophenotype. In total, 237 eligible cases were identified and 110 accepted to participate, yielding a response rate of 47.8%. Not participating children included: 11 which denied participation and 116 did not have complete dietary information.

2.2. Controls

Cases were sex and 1:1 age matched (±12 months) with a child (control) attending to any of the ambulatory surgery services from the same health institution where the cases were gathered (IMSS, Secretary of Health, Secretary of Health of Mexico City, State of Mexico Institute of Health, Institute of Security and Social Services for State Workers). In total, 276 eligible controls were identified, of which 24 did not agree to participate (response rate of 91.3%) leaving 252 controls whose diagnoses were: circumcision (%), hernioplasty, orchiopexy, tonsillectomy, intoxication, first and second level burns.

2.3. Interviews

Mothers gave informed consent to participate in a face-to-face interview in the hospitals. Previously trained personnel gathered information regarding the family sociodemographic characteristics, child reproductive history, parents' alcohol, and tobacco consumption as well as maternal diet during pregnancy.

2.4. Maternal diet

Dietary maternal intake, during pregnancy, was obtained through a food frequency questionnaire (FFQ). This instrument contained 116 items including foods, beverages, and local dishes. The reproducibility of this questionnaire was previously evaluated in Mexican women, to whom it was applied twice at an interval of 1 year, while its validity was estimated using a 24-h diet recall at 3-month intervals as a reference. The details of this validation have been published (11).

According to the methodology suggested by Willett et al. (12) the FFQ includes 10 response options for frequency of consumption ranging from "never" to "6 or more times a day," as well as predetermined portions for each food as follows: a glass (e.g., milk and wine), cup (for yogurt, some fruits and vegetables, tea, juices, alcoholic and non-alcoholic beverages), a spoon (e.g., oils, sour cream, sauces and nuts), a slice (e.g., cheese, some fruits and meats), a plate (e.g., legumes and local dishes) and a piece (e.g., some fruits and breads).

Total energy content in foods and local dishes was obtained from nutritional composition tables of the United States Department of Agriculture (USDA 2007, 2017–2018) that include a wide variety of foods similar to those consumed in the study area. For the few foods that were not found in the USDA tables, such as tejocote (a local fruit), we used the reference tables of the National Institute of Medical Sciences and Nutrition "Salvador Zubirán" (13). Only two foods (soy juice and soy beer) were not found in neither food data sources.

Energy consumption was estimated by adding the caloric intake from foods and local dishes. Due to the fact, that some fruits and vegetables are only consumed during certain seasons of the year, their energy intake was weighted according to their availability in the market, for example, only 50% of the kcal of plums were considered, as they are available for 6 months of the year (14).

Up to this phase, one case was eliminated, because the estimated total energy intake was less than 525 kcal, which corresponds to less than 2 standard deviations of the daily intake observed in pregnant Mexican women and may not represent a valid biological value (15). Therefore, the final sample size of this report was 109 cases and 252 controls.

2.4.1. Dietary patterns

We derived dietary patterns from 22 food groups and 8 isolated foods. Food groups were created according to their similarity in the content of macro and micronutrients (e.g., fat, carbohydrates, protein, vitamins, sodium); sugar (added or not) or type of fat (saturated or vegetal); otherwise, foods were included as isolated items (atole, corn,

corn tortilla, egg, poultry, avocado, dehydrated cranberries and soy sauce).

To derive dietary patterns we used 2 different approaches: Cluster analysis and factor analysis. For cluster analysis, we used food groups and foods in portions per day and their energy percentage contribution. Through the K-means method, we ran 6 cluster solutions and selected one that contained 2 non-overlapping clusters. As a result, each individual belonged to only one cluster that we named Balanced & Vegetable-Rich or High Dairy & Cereals.

We further determined the factor loadings of each food group, using factor analysis (14). We orthogonally rotated the factors (varimax rotation) to keep them uncorrelated and to improve their interpretation. After assessment of graphic analysis and interpretability, we retained factors with eigenvalues >1.5. We defined each factor by a subset of at least 5 food groups with an absolute loading ≥0.2 (16).

We estimated each pattern by summing the personal intake of the food groups weighted by their corresponding loading factor. We derived 3 dietary patterns named High Saturated Fats & Sugars, Moderate Meat & Cereals and Balanced & Vegetable-Rich. With this analysis, each participant receives a score for each pattern identified.

2.5. Statistical analysis

Mother, father, and child characteristics were compared between cases and controls using Chi square, one-way ANOVA (Table 1).

The association between maternal dietary patterns and AL was assessed using unconditional multivariate logistic regression models. Covariates were selected based on two criteria. Firstly, we included covariates that exhibited significant differences between the cases and controls. These covariates encompassed factors such as institution, breastfeeding, age at pregnancy, education (both maternal and paternal), smoking before and during pregnancy, iron and vitamin consumption, drug use for genital infection, and the age of the father. Secondly, we incorporated covariates based on a causal directed acyclic graph (DAG) approach, which considered variables such as age at pregnancy, state of residence, person/room ratio, breastfeeding, iron and vitamin supplementation, tobacco and alcohol use, and maternal education. Detailed information regarding the covariates can be found in Supplementary Figure 1.

Using as a reference category the "High Dairy & Cereals" cluster, we estimated the odds ratio for AL among individuals belonging to the "Balanced & Vegetable-Rich" cluster. We created tertiles based on the dietary pattern score distributions among controls. We estimated the odds ratios for LA comparing tertile 3 and 2 versus tertile 1, respectively. We also stratified the adjusted models and estimated the dietary pattern x sex interaction adding the respective multiplicative term.

We performed tests for linear trends using the continuous dietary pattern scores. We used $p < 0.05$ as a cutoff for significance.

We conducted our analysis using STATA, version 13 and Daggity v3.0.

3. Results

In order to ensure comparability between the study groups, we carefully controlled for the distribution of children's age and sex, which was similar across all groups. Comparative analysis revealed that mothers of children with AL exhibited lower alcohol intake during pregnancy, lower person/room ratios and lower intakes of iron during pregnancy compared to mothers of healthy children. Moreover, children diagnosed with AL were reported to have a higher birthweight compared to controls (see Table 1).

Through cluster analysis, we identified two distinct dietary patterns, labeled as 'High Dairy & Cereals' and 'Balanced & Vegetable-Rich.' Both patterns included food groups such as 'other fruits' and 'other vegetables.' However, the 'High Dairy & Cereals' cluster stood out for its higher consumption of cereals, dairy products, and eggs, whereas the 'Balanced & Vegetable-Rich' cluster was characterized by a higher intake of allium vegetables and corn tortillas.

Additionally, factor analysis yielded three major dietary patterns: (1) 'Balanced & Vegetable-Rich,' which was characterized by high consumption of fruits, allium vegetables, other vegetables, and legumes, and low consumption of pastries and refined cereals; (2) 'High Saturated Fats & Sugars,' which exhibited high consumption of saturated fats, refined cereals, canned products, corn tortillas, and sodas, and low consumption of whole grain cereals, seafood, and dairy products; and (3) 'Moderate Meat & Cereals,' which showed high consumption of processed meat, red meat, poultry, and refined cereals, and low consumption of dairy, fruits, and legumes. The factor-loading matrixes for these dietary patterns explained a total variance of 20.3% (see Table 2).

Our analysis unveiled a notable inverse association between the 'Balanced & Vegetable-Rich' dietary pattern and the risk of developing Acute Leukemia (AL). While adjusting for various influencing factors, including institution, breastfeeding, age at pregnancy, parental education, smoking habits before and during pregnancy, iron and vitamin consumption, drug use for genital infections, age of the father, and paternal alcohol consumption, the 'Balanced & Vegetable-Rich' pattern demonstrated odds ratios (OR) of 0.51 (95% CI, 0.29, 0.90) in the cluster analysis. In the factor analysis, assessing different levels of adherence (T3 vs. T1) to the same dietary pattern ('Balanced & Vegetable-Rich'), the OR was 0.47 (95% CI, 0.24, 0.91).

We observed that mothers who gave birth to girls and adhered to the 'Balanced & Vegetable-Rich' dietary pattern had significantly lower odds of their children developing AL compared to those who gave birth to boys. This difference was evident in both cluster and factor analyses. Cluster analysis demonstrated odds ratios (OR) of 0.40 (95% CI: 0.17, 0.94) for mothers following a 'Balanced & Vegetable-Rich' pattern, while mothers of boys had OR of 0.64 (95% CI: 0.2, 1.47). There is a significant interaction between the "Balanced & Vegetable-Rich" dietary pattern and the sex of infants in relation to the risk of AL (P for interaction 0.020). Similarly, factor analysis showed OR of 0.32 (95% CI: 0.11, 0.97) for mothers of girls adhering to a 'Balanced & Vegetable-Rich' pattern, in contrast to OR of 0.49 (95% CI: 0.19, 1.23) for mothers of boys, also showing a statistical significant pattern x sex interaction (0.037).

The 'Moderate Meat & Cereals' pattern was found to have an inverse association with the development of AL, with an OR of 0.28 (95% CI: 0.11, 0.97). This suggests that a higher intake of the 'Moderate Meat & Cereals' pattern is associated with reduced odds of AL. Notably, this association was significant overall (Table 3).

TABLE 1 General characteristics of the study subjects.

Characteristics	Cases (n = 109)		Controls (n = 252)		p-value
	(n)		(n)		
Child					
Sex, boys %	52	47.7	151	60.4	0.026
Age, months [mean ± SD]	109	15.5 ± 7.3	252	18.5 ± 9.7	0.004
State of residence, %					
Mexico City	42	38.5	132	52.4	0.016
State of Mexico	67	61.5	120	47.6	
Health institution*, %					
Ministry of Health	62	56.9	164	65.08	0.139
Mexican Institute of Social Security	47	43.1	88	34.9	
Person/room ratio, [p50(p10,p90)]	109	2.5 (1.5,5.0)	252	3.00 (1.7,6.0)	0.047
Breastfeeding, yes %	96	88.1	226	89.7	0.651
Breastfeeding, months [p50(p10,p90)]	109	6.0 (0.0,15.0)	252	7.0 (0.0,18.0)	0.242
Birth weight, grams [mean ± SD]	109	3,144.8 ± 400.7	252	2,928.1 ± 610.9	0.001
Mother					
Age at pregnancy, years [mean ± SD]	109	25.9 ± 6.4	252	25.6 ± 6.3	0.615
Education, years [p50 (p10,p90)]	109	9.00 (6.0,15.0)	252	10.00 (7.0,13.6)	0.833
Smoking before pregnancy, yes %	31	28.4	77	30.6	0.687
Smoking during pregnancy, yes %	4	3.7	7	2.8	0.74
Alcohol consumption during pregnancy, yes %	4	3.7	31	12.3	0.011
Iron supplement during pregnancy, yes %	76	69.7	216	85.7	<0.001
Mineral consumption during pregnancy, yes %	4	3.67	16	6.4	0.453
Vitamins supplement during pregnancy, yes %	98	89.9	238	94.4	0.119
Drug use for genital infection, yes %	15	13.8	34	13.5	0.945
Father					
Age at pregnancy, years [mean ± SD]	105	28.8 ± 7.9	250	28.8 ± 7.4	0.944
Education, years [p50 (p10,p90)]	104	10.5 (6.0,15.0)	245	9.0 (6.0,14.0)	0.226
Smoking before pregnancy, yes %	48	47.1	141	58	0.062
Alcohol consumption before pregnancy, yes %	88	85.4	222	90.6	0.158

*Includes Secretary of Health, Secretary of Health of Mexico City, State of Mexico Institute of Health (ISEM, by its acronym in Spanish), Institute of Security and Social Services for State Workers (ISSSTE, by its acronym in Spanish).

4. Discussion

To our knowledge, this is the first study to examine childhood AL and dietary patterns in a sample of pregnant women in Mexico. Using two different approaches, we found two similar 'Balanced & Vegetable-Rich.' patterns, characterized by high consumption of foods included in the following groups: fruits, vegetables, allium, legumes, and low intake of refined sugars and cereals that were negatively associated with AL. These 'Balanced & Vegetable-Rich.' patterns were inversely and significantly associated with AL only among girls. In contrast, we found a positive but not significant relationship between AL and a pattern characterized by saturated fats and cereals.

There is no previous evidence on maternal dietary patterns and childhood leukemia, and the scarce information on food groups is inconclusive. According to a recent meta-analysis (8), a challenge in this area is to have information on comparable food groups across studies. In this context, for example, two studies included in a recent meta-analysis reported an inverse relationship between the consumption of fruits (OR: 0.81, 95% CI: 0.67–0.99),

TABLE 2 Food groups consumption (portions/day) according to dietary patterns using cluster and factor analysis in the study sample (cases = 109, controls = 252).

Food groups	Cluster		Dietary pattern						All women
	High dairy & cereals	Balanced & vegetable-rich	High saturated fat & sugars		Moderate meat & cereals		Balanced & vegetable-rich		All women
	Portions/day (mean)		Factor loadings/portions/day (mean)						Portions/day (mean)
Dairy products	1.1	1.16		1.18	0.49	1.13		1.1	1.14
Dairy with added sugar	0.43	0.47	0.33	0.39	0.55	0.4		0.41	0.46
Citrus fruits	0.81	1.03		0.9	0.34	0.9	0.41	0.97	0.96
Other fruits	1.95	2.09		1.88	0.5	1.76	0.49	1.85	2.04
Egg	0.78	0.7	0.32	0.69		0.68		0.84	0.73
Poultry	0.37	0.41		0.4	0.35	0.39		0.4	0.39
Processed meats	0.61	0.59	0.22	0.55	0.61	0.5	0.21	0.6	0.6
Red meat	0.53	0.46		0.43	0.5	0.43		0.52	0.48
Fish and shellfish	0.25	0.27	−0.21	0.23	0.51	0.21		0.26	0.26
Saturated fats	0.71	0.74		0.69	0.63	0.66		0.74	0.72
Cruciferous vegetables	0.43	0.35		0.39		0.34	0.65	0.34	0.37
Allium vegetables	1.74	1.39	0.74	1.52		1.3		1.45	1.49
Green leafy vegetables	0.6	0.67		0.62		0.56	0.73	0.51	0.64
Other vegetables	3.48	2.5	0.7	2.5		2.45	0.38	2.83	2.79
Corn	0.18	0.16		0.16		0.16	0.51	0.16	0.17
Potato	0.33	0.29	0.38	0.3		0.29	0.54	0.31	0.3
Legumes	0.81	0.73	0.34	0.73	0.21	0.69	0.51	0.71	0.75
Canned chili peppers	0.28	0.17	0.74	0.14		0.14		0.18	0.2
Corn tortilla	12.62	3.24	0.36	5.12		5.48		5.74	6.05
Cereals	2.03	2.02		2.04	0.52	1.91	0.22	1.85	2.02
Cereals high in fat and sugar	0.74	0.61	0.48	0.62	0.44	0.61		0.58	0.65
Soft drinks	0.56	0.34	0.61	0.31		0.36		0.32	0.41
Coffee and tea	0.91	0.72	0.43	0.71		0.68	−0.24	0.75	0.77
Corn-based drinks	0.17	0.22		0.16	0.29	0.17	0.37	0.19	0.21
Vegetable oils	0.88	0.64	0.62	0.6		0.61		0.7	0.71

vegetables (OR: 0.51, 95% CI: 0.28, 0.94); and legumes (OR: 0.76, 95% CI: 0.62–0.94) with AL. Our results confirmed those associations in spite that there might be some different foods within the groups.

Several biological mechanisms have been implicated, as fruits and vegetables contain micronutrients that exert a protective action against leukemogenesis. Antioxidants, in particular vitamin A (retinoid acid), C (ascorbic acid) and E, as well as carotenoids are known to protect against oxidative damage of lipids, lipoproteins and DNA (4). Carotenoids have been shown to enhance DNA repair and have a positive effect on immune function, cell transformation and differentiation (4). Ascorbic acid can inhibit the *in vitro* proliferation of leukemic cells (4), while vitamin A plays a prominent role in the induction of terminal differentiation of lymphoid and myeloid blasts and in the inhibition of their clonogenic growth (4). In addition, direct and dose–response cytotoxic effects against leukemic cells have been suggested through selective regulation of cell cycle proteins for a variety of flavonoids present in most green leafy vegetables.

The consumption of allium vegetables, mainly garlic, onion, and leeks has not been studied regarding AL. Extensive experimental

TABLE 3 Association between acute leukemia and dietary patterns.

	Total population		Girls		Boys	
Patterns	Cases/ Controls	OR (95%CI)*	Cases/ Controls	OR (95%CI)*	Cases/ Controls	OR (95%CI)*
Cluster						
High Dairy & Cereals	41/65	Ref	24/25	Ref	17/40	Ref
Balanced & Vegetable-Rich	69/181	0.51 (0.29, 0.90)	34/74	0.40 (0.17, 0.94)	35/107	0.64 (0.27, 1.47)
P for trend		0.020		0.036		0.291
P for interaction pattern x sex		0.020				
Factor						
High Saturated Fats & Sugars						
T1	42/82	Ref.	27/20	Ref.	55/22	Ref.
T2	27/82	0.52 (0.27, 0.97)	42/18	0.56 (0.22, 1.42)	40/9	0.43 (0.18, 1.16)
T3	41/82	1.07 (0.57, 2.01)	30/20	1.12 (0.39, 3.22)	52/21	1.02 (0.45, 2.35)
P for trend		0.964				
P for interaction pattern x sex		0.558		0.927		0.901
Moderate Meat & Cereals						
T1	46/82	Ref.	26/34	Ref.	20/48	Ref.
T2	31/82	0.68 (0.38, 1.22)	18/31	0.56 (0.22, 1.42)	13/51	0.56 (0.24, 1.32)
T3	33/82	0.64 (0.34, 1.20)	14/34	0.28 (0.09, 0.82)	19/48	0.96 (0.41, 2.26)
P for trend		0.149				
P for interaction pattern x sex		0.044		0.021		0.843
Balanced & Vegetable-Rich						
T1	43/82	Ref.	22/33	Ref.	21/49	Ref.
T2	41/82	0.85 (0.48, 1.52)	24/34	0.89 (0.36, 2.18)	17/48	0.76 (0.33, 1.74)
T3	26/82	0.47 (0.24, 0.91)	12/32	0.32 (0.11, 0.97)	14/50	0.49 (0.19, 1.23)
P for trend		0.029				
P for interaction pattern x sex		0.037		0.051		0.129

*Adjusted by institution, residence, person/room ratio, maternal education, breastfeeding, maternal age at pregnancy, as well as maternal tobacco and alcohol consumption and supplement use of iron and vitamins during pregnancy.

research has consistently shown the anticarcinogenic potential of allyl sulfides and flavonoids in relation to colon, gastric (particularly quercetin which is present abundantly in onion) and found that these compounds promote inhibition of mutagenesis, modulation of enzyme activities, inhibition of DNA adduct formation, free-radical scavenging, and effects on cell proliferation and tumor growth (17–22). However, epidemiological findings have not been conclusive. Previous meta-analyses have shown that high consumption of allium vegetables might be inversely associated with gastric and colorectal cancer (23, 24) Moreover a worldwide pooled analysis, reported an inverse association between allium vegetables intake and gastric cancer (25). In our sample we found an inverse relationship that warrant further attention since it could be possible that some of these mechanisms were the same for childhood AL.

Likewise, our results are consistent with the findings of studies that have suggested a positive association with sugar and refined grains, a study conducted in greek population, found that the odds of AL were higher with increased maternal intake of sugars and syrups (OR, 1.32; 95% CI, 1.05–1.67) (26). The potential mechanisms supporting the positive association between sugars and cancer, have

already been discussed and include adiposity and insulin signaling pathway disruption, hormonal imbalances, inflammation, oxidative stress, DNA damage, and alteration of gene expression (27). Nevertheless, further research is needed to elucidate the relationship between AL and sugar intake.

The study of meat and processed meat consumption related to childhood cancer has been of interest since the 1990s. A more recent study, found that children who regularly ate cured meat (more than once a week) had a 74 percent greater chance of developing acute leukemia (28). Meat contains nitrosamines which have been classified as a type 1 carcinogen (29). Consumption of cured/smoked meat leads to the formation of carcinogenic N-nitroso compounds in the acidic stomach (30). Due to the high heterogeneity among the few epidemiological studies, a conclusion of the relationship between processed meats intake and AL is not currently stated. Our results do not suggest an association between meat and AL, consistently with the study by Ross et al. and in contrast to other studies. Since lack of statistical power may be and explanation for this, this question warrants further research.

The lower OR observed for mothers of girls following the 'Balanced & Vegetable-Rich' dietary pattern and the statistically significant pattern x sex interaction suggest that this dietary regimen may have a more pronounced protective effect against AL in female offspring. While the gender-specific differences in the impact of maternal healthy dietary patterns on leukemia risk are apparent in our findings, the exact biological mechanisms underlying these distinctions remain complex and not yet fully understood. Several biological factors could contribute to these gender-specific associations. One such factor is the influence of sex hormones, which play a vital role in the development and function of the immune system. Estrogens, for example, are known to have immunomodulatory effects and may affect the immune response against leukemic cells. Epigenetic modifications represent another plausible mechanism. Maternal diet during pregnancy can influence epigenetic changes in the developing fetus. These modifications can affect gene expression and cellular function, potentially contributing to variations in leukemia risk. Moreover, the immune system and its response to dietary patterns may differ between the sexes. It's known that immune responses are inherently different in males and females due to differences in immune cell populations, immune regulatory pathways, and the expression of various immune-related genes (31).

A comprehensive review and meta-analysis, spanning 38 studies, published by Blanco-López (32) et al. in 2023, shed light on the role of maternal dietary factors in childhood acute leukemia. Notably, it highlighted a reduced risk of acute lymphoblastic leukemia with increased maternal fruit consumption, while heightened coffee intake was associated with an elevated risk. These findings are consistent with the results of our study. However, to craft effective population-level prevention strategies, further research, especially from high-quality cohort studies, is crucial for identifying causal factors in this complex landscape of childhood leukemia etiology.

Several limitations of this study should be considered to interpret our results. The extrapolation of our results is limited, since we had a low participation rate within the cases, and we did not have enough information from the children who did not participate to assess the representativeness of our sample. On the other hand, the maternal dietary information was not blinded to the case–control child status, however it is highly unlikely that the mothers reported, differentially between the groups, a pattern with a specific direction to be associated with AL. Nevertheless, since the collection of data on maternal nutrition during pregnancy took place around 3 years after birth, we cannot rule out the possibility of nondifferential measurement error, which translates into attenuation of the associations reported in this paper. As in all observational studies, confounding cannot be ruled out, therefore we adjusted for potentially confounding variables which were chosen after a careful analysis with the Daggity software (directed acyclic graph, Supplementary Figure 1). It's important to acknowledge that we did not have access to data on certain well-established risk factors for AL, such as exposure to pesticides or infections, which could have served as potential confounding variables.

An additional limitation of our study is that we did not explore the potential influence of genetic factors in the Mexican population. Genetic epidemiology could provide valuable insights, as the genetic architecture of Mexican individuals may play a role in the observed associations. Future research could benefit from incorporating genetic analyses to comprehensively investigate the interplay between genetic predisposition and maternal dietary patterns in childhood leukemia risk.

Our findings suggest that a dietary pattern during pregnancy characterized by the high consumption of fruits, allium vegetables, other vegetables, and legumes and low in pastries and refined cereals may be associated with reduced odds of AL, mainly in girls. Further prospective studies with more detailed diet and biomarker assessments are necessary to confirm our findings, to elucidate potential mechanisms that explain the effect of the maternal dietary patterns according to infant sex. The results of this study emphasize the importance of promoting healthy maternal dietary patterns during pregnancy for the long-term health of the offspring.

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 humans were approved by Comisión Nacional de Investigación Científica. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

PM-A: Formal analysis, Methodology, Writing – original draft. ED-G: Formal analysis, Methodology, Writing – review & editing. MP-S: Data curation, Funding acquisition, Project administration, Writing – review & editing. LE-H: Data curation, Validation, Writing

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Conflict of interest

The 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 of coffee and caffeine consumption with risk and prognosis of endometrial cancer and its subgroups: a Mendelian randomization

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Background: Previous studies have not established potential causal associations between coffee and caffeine consumption in endometrial cancer (EC) and its subgroups. Therefore, we used a two-sample MR method to assess the causal association between coffee and caffeine consumption and EC risk. We also evaluated the association between these genetically predicted exposures and EC prognosis.

Materials and methods: This study used 12 and two independent single-nucleotide polymorphisms (SNPs) associated with coffee and caffeine consumption as instrumental variables at a genome-wide significance level of $p < 5 \times 10^{-8}$. The EC Association Consortium (ECAC) performed a genome-wide association study (GWAS) analysis of 12,906 cases and 108,979 controls. FinnGen Consortium performed a GWAS analysis of 1,967 EC cases and 167,189 controls. The primary technique we employed was inverse-variance weighted, followed by the weighted median, MR-Egger regression, and MR robust adjusted profile score methods. We used the MR pleiotropy residual sum, Outlier test, and MR-Egger regression to assess Outlier and pleiotropic variants. We also conducted a sensitivity analysis through the leave-one-out method.

Results: Genetically predicted coffee consumption was not associated with EC and its subgroups in the ECAC, and the association was consistent in the FinnGen consortium. After excluding eight SNPs with confounding factors, the study performed sensitivity analyses, delivering consistent results. We also observed that caffeine consumption was not correlated with EC risk. As confirmed by MR analysis, selected SNPs determined that most do not significantly impact the likelihood of developing EC.

Conclusion: Our study indicated no convincing evidence supports coffee and caffeine consumption causing EC or impacting its prognosis. More studies are needed to validate the results.

KEYWORDS

endometrial cancer (EC), Mendelian randomization (MR), coffee consumption, caffeine consumption, endometrioid histology (EH)

1. Introduction

Endometrial cancer (EC) is one of the most common gynecologic malignancies. Its incidence was rising globally, with approximately 417,000 new cases in 2020 (1). If it continues its current trend, the number of women diagnosed with EC in the U.S. will reach 122,000 cases annually by 2030 (2).

It is recognized that Prolonged unopposed estrogen exposure is an established risk factor for EC. Metabolic factors such as obesity, insulin resistance, and dyslipidemia correlate with increased EC risk (3–6). Conversely, observational studies have shown that coffee and caffeine consumption negatively affect EC risk (7–9). Additionally, earlier research has linked higher coffee intake to lower levels of C-peptide and estrogen, two chemicals implicated in the development of endometrial cancer (10–12). However, the potential causal association of coffee and caffeine consumption with the risk of EC has yet to be established due to possible confounding factors and the lack of randomized controlled trials.

Mendelian randomization (MR) is a technique for assessing if an exposure factor has a causal effect on an outcome (13). MR strengthens causal inference by including genetic tools as exposure factors. It reduces reverse causation as alleles are randomly assigned during meiosis. The genetic tools are randomly assigned during conception and are usually not associated with confounding factors (14).

In this investigation, we evaluated the causal association of coffee and caffeine consumption with the risk of EC and its subgroups using a two-sample MR approach. We also assessed the correlation between the prognosis for EC and these genetically indicated exposures.

2. Materials and methods

2.1. Study design

Genetic variations serve as instrumental variables (IVs) in MR analyses to establish the causal link between exposure and outcome (15). MR analyses are focused on three essential hypotheses: (1) IVs are strongly associated with exposure factors; (2) IVs are not affected by any confounders; (3) IVs affect the outcome only through exposure factors, which are not related to the outcome (14). The flowchart of this MR study design is shown in **Figure 1**.

2.2. Genetic instrument selection

The 15 single-nucleotide polymorphisms (SNPs) correlated with coffee consumption, derived from a meta-analysis of four large-scale genome-wide association studies (GWASs), involved 375,833 individuals (UK Biobank and three US cohorts) of European descent (16) (**Supplementary Table 1**). The GWASs adjusted for sex, age, total energy, body mass index, and top 20 principal components. In the United Kingdom Biobank (discovery phase), a touch screen questionnaire was applied to collect coffee consumption from all participants at baseline: "How many cups of coffee do you drink each day (including decaffeinated coffee)?" In the United States cohorts (replication phase), a semi-quantitative food frequency questionnaire was used to collect the regular and decaffeinated coffee consumption (16). The effect sizes of SNP-coffee associations increased by 50% (equivalently from 1 cup to 1.5 cups). To fulfill the first MR hypothesis, we selected SNPs that were reliably genetically variables ($P < 5 \times 10^{-8}$) and independently (linkage disequilibrium; LD $r^2 < 0.001$ and cluster window > 10,000 kb) (17, 18) associated with exposures. Meanwhile, we calculated the F statistic ($F > 10$ indicates sufficient instrumental strength) (14). To fulfill the second MR hypothesis, we assessed the pleiotropic relationship between SNPs and potential confounders by searching the PhenoScanner V2 website (19, 20). Finally, to fulfill the third MR hypothesis, we excluded SNPs with $P < 0.05$ to ensure that IVs were not associated with the outcome (14). In the preliminary analysis, 11 SNPs were used as IVs for coffee consumption. Due to potential genome-wide confounders, we excluded eight SNPs and the remaining three as IVs in the sensitivity analysis (**Supplementary Table 2**).

The two variants associated with caffeine consumption came from a meta-analysis of 6 GWAS and included 9,876 individuals of European ancestry (21) (**Supplementary Table 1**). A self-reported questionnaire was used to find out how much caffeine people in coffee, tea, and cola drank. Pooled data on SNP-caffeine correlations were obtained from GWAS of 4,460 females and scaled to increase the caffeine measure by 80 mg, approximately equal to a cup of coffee (22). IVs were consistent with a $P < 5 \times 10^{-8}$, independent, and strongly correlated with the F-statistic, and were used to perform MR analyses. Detailed information on SNPs related to coffee and caffeine consumption is shown in **Table 1**.

2.3. Data sources for endometrial cancer

Endometrial cancer-related data were obtained from the Endometrial Cancer Association Consortium (ECAC) and the FinnGen Consortium. ECAC performed a GWAS analysis of 12,906 cases and 108,979 controls (23). To avoid sample size overlap in the MR analysis, we removed the UK Biobank sample from the ECAC summary statistics, resulting in 12,270 EC cases and 46,126 controls (24). Furthermore, we analyzed the association of coffee and caffeine consumption with the risk of EC (8,758 patients with endometrioid histology and 1,230 cases with non-endometrioid histology) (25). We also performed Subgroup analyses in ECAC. GWAS analysis of 1,967 EC cases and 167,189 controls at the FinnGen Consortium (26). The ninth publication of the FinnGen Consortium database includes 377,277 individuals of Finnish ancestry, consisting of genes specific to the Finnish population, with high differential complementation accuracy and phenotypes from population-based registries. It includes cases from various disease domains, adjusted for age, sex, genetic principal components, and genotyping batches.

2.4. Data sources of BMI, smoking initiation, and alcohol consumption

Analyses were adjusted for differences in genetically predicted BMI, smoking initiation, and alcohol consumption using multivariable MR. The genetic variants linked to BMI and

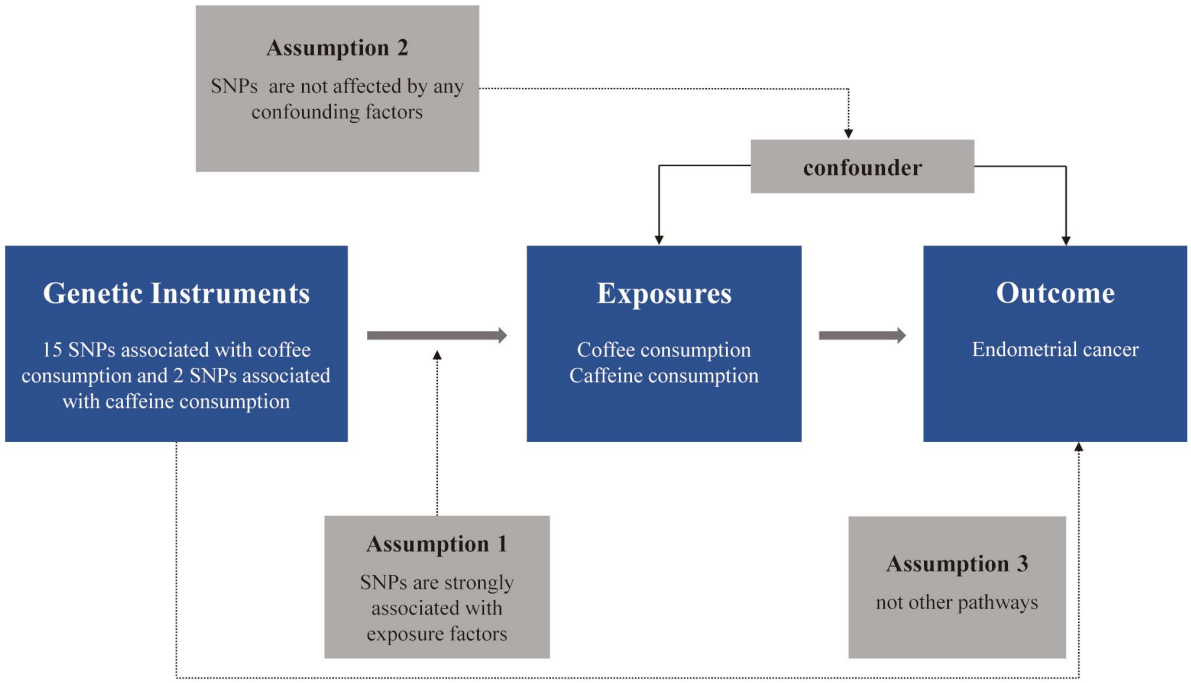

FIGURE 1
The flowchart of the Mendelian randomization (MR) study. SNP, single-nucleotide polymorphism.

exposure variables were found through a GWAS meta-analysis in the Genetic Investigation of Anthropometric Traits[1] consortium, which included 681,275 Europeans (27). GWAS data on 1,232,091 people showed summary-level information on how they started smoking (28). As was already said, GWAS data on 941,280 people showed that they drank alcohol, giving us summary-level statistics (28).

2.5. Statistical analysis

The inverse-variance weighted (IVW) was used as the primary statistical method. We used IVW with random effects to assess the relationships for genetically predicted coffee consumption. IVW fixed-effects models (analyses with several SNPs less than three) were used to estimate the interactions between genetic prediction and caffeine consumption. We also performed the weighted median (WM) and MR-Egger regression methods (29). The IVW method is applied to assume that all SNPs are valid and independent, and its meta-aggregation of multiple side effects in MR analyses of numerous SNPs (30). WM is the median obtained after weighting individual SNPs (31). The WM approach provides robust estimates, with at least 50% of the information coming from valid instrumental variables (32). The MR-Egger method allows for the inclusion of instrumental variables with a multivariate effect if the intercept P-value < 0.05 indicates the presence of horizontal multivariate validity (33). We applied the MR-pleiotropy residual sum and outlier (MR-PRESSO) methods to detect the presence of horizontal pleiotropy, and Cochran's Q statistic was used to assess heterogeneity between SNPs in each analysis (34). We also conducted a sensitivity analysis through the leave-one-out method.

Moreover, we assessed the pathogenic impact of the selected SNPs on EC prognosis by MEndelian Randomization (SUMMER[2]), by the framework of MR analysis based on the Multi-Organomics Database of SUrvival-Related Cancers (35). All analyses were performed using the "TwoSampleMR" and "MR-PROESSO" packages in R software (version 4.3.1), and all statistical tests were two-sided.

3. Results

3.1. Causal relationship between coffee and caffeine consumption with risk of EC and its subtypes

The F-statistics for coffee (the 50% increase) and caffeine (the per 80-mg increase) in this study were 159 and 67, indicating that the IVs had sufficient instrumental strength. Furthermore, MR-PRESSO did not detect abnormal SNPs in preliminary and sensitivity analyses. We did not detect heterogeneity by IVW and MR-Egger regression.

In preliminary analyses, we found pleiotropy ($p < 0.05$) in the causal relationship between two data sets and coffee consumption by MR-Egger: endometrioid endometrial carcinoma (EEC) in the ECAC consortium and EC in the FinnGen consortium (**Figure 2**).

1 https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files (accessed April 28, 2021).

2 http://njmu-edu.cn:3838/SUMMER/

TABLE 1 Association of single nucleotide polymorphisms with coffee or caffeine consumption and endometrial cancer and its subtypes.

Exposure	SNP	EA	OA	EAF	Coffee or Caffeine Consumption			Endometrial cancer and its subtypes in ECAC									Endometrial cancer in FinnGen		
					Beta	SE	*P*	EC			EH			NEH			Beta	SE	*P*
								Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*			
Coffee consumption	rs1057868	T	C	0.29	0.0197	0.0016	5.26E-33	–	–	–	0.0337	0.0198	0.09	0.0681	0.0477	0.15	0.0564	0.0333	0.09
	rs10865548	G	A	0.83	0.0154	0.0019	4.46E-15	0.0297	0.0203	0.14	0.0388	0.0239	0.10	−0.0296	0.0578	0.61	0.0386	0.0441	0.38
	rs1260326	C	T	0.61	0.0136	0.0015	2.62E-19	0.0288	0.0156	0.06	0.0293	0.0184	0.11	0.0121	0.0448	0.79	0.0294	0.0343	0.39
	rs1956218	G	A	0.56	0.0082	0.0015	3.62E-08	0.0141	0.0154	0.36	0.0273	0.0181	0.13	0.0413	0.0445	0.35	0.0225	0.0330	0.50
	rs2330783	G	T	0.99	0.0453	0.0063	1.57E-12	−0.0355	0.0654	0.59	−0.0401	0.0775	0.60	−0.1373	0.1796	0.44	−0.1951	0.1969	0.32
	rs2472297	T	C	0.27	0.0454	0.0017	5.19E-155	−0.0265	0.0181	0.14	−0.0146	0.0213	0.49	–	–	–	−0.0247	0.0379	0.51
	rs34060476	G	A	0.13	0.0189	0.0022	5.06E-18	–	–	–	0.0492	0.0285	0.08	−0.0583	0.0733	0.43	0.0897	0.0483	0.06
	rs4410790	C	T	0.63	0.0394	0.0015	5.59E-141	0.0203	0.0158	0.20	−0.0090	0.0186	0.63	−0.0242	0.0452	0.59	−0.0008	0.0345	0.98
	rs574367	T	G	0.21	0.0105	0.0018	8.06E-09	0.0030	0.0188	0.87	0.0069	0.0221	0.75	−0.0170	0.0545	0.75	0.0366	0.0422	0.39
	rs597045	A	T	0.69	0.0107	0.0015	6.62E-11	0.0009	0.0165	0.96	−0.0026	0.0199	0.90	0.0298	0.0503	0.55	–	–	–
	rs66723169	A	C	0.23	0.0147	0.0018	9.88E-17	0.0148	0.0181	0.41	0.0180	0.0213	0.40	0.0610	0.0515	0.24	0.0478	0.0428	0.26
Caffeine consumption	rs2470893	T	C	0.31	0.12	0.016	5.15E-14	−0.0241	0.0163	0.14	−0.0114	0.0192	0.55	−0.0910	0.0472	0.05	0.1356	0.1554	0.38
	rs4410790	T	C	0.62	0.15	0.017	2.36E-19	−0.0203	0.0158	0.20	0.0090	0.0186	0.63	0.0242	0.0452	0.59	−0.0547	0.1478	0.71

SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; EC, endometrial cancer; EH, endometrioid histology; NEH, non-endometrioid histology.

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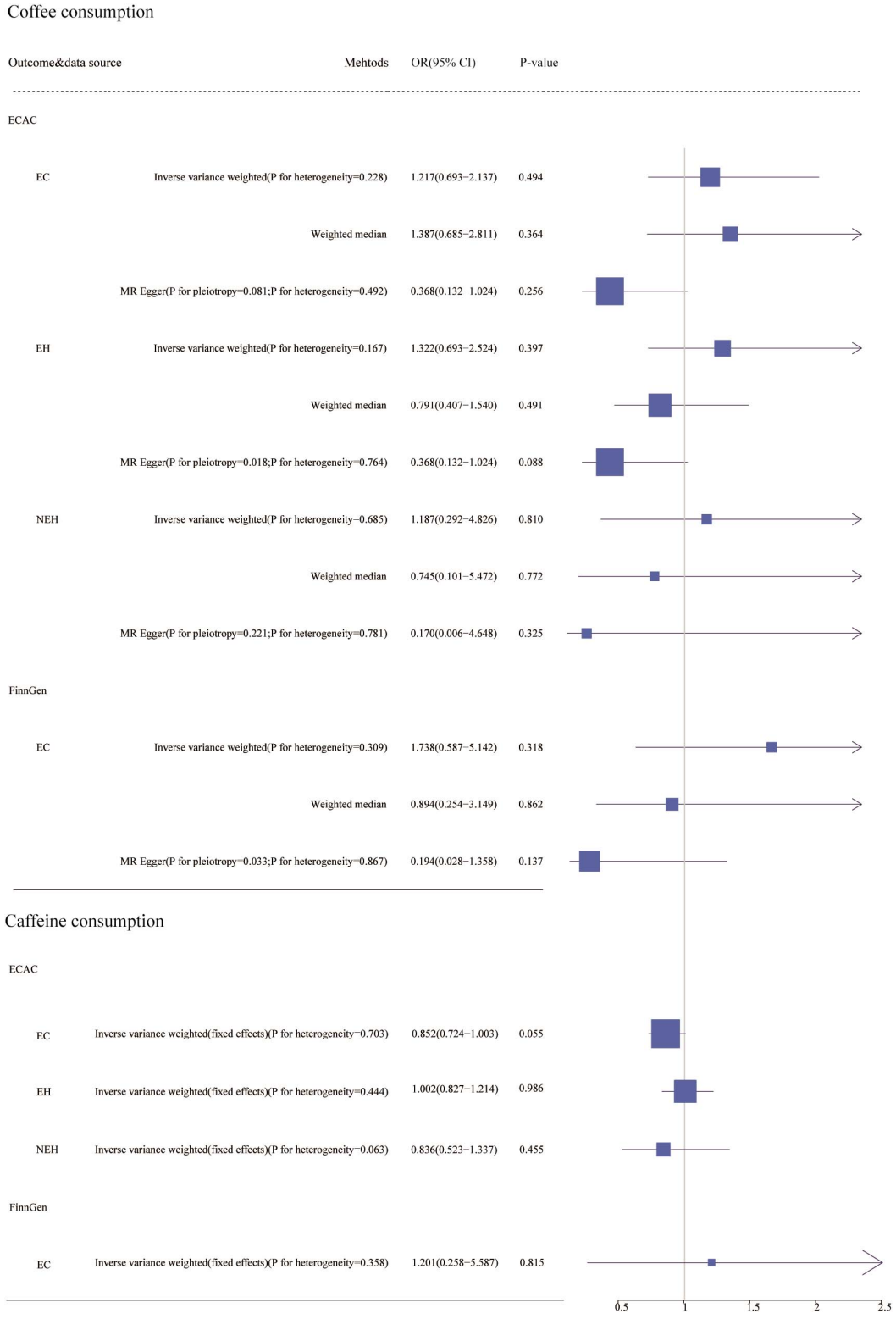

FIGURE 2
The association of genetically predicted coffee and caffeine consumption with endometrial cancer (EC) and its Subgroups. ECAC, the Endometrial Cancer Association Consortium; EH, Endometrioid histology; NEH, non-endometrioid histology; FinnGen, FinnGen Consortium; OR, odds ratio; CI, confidence interval.

To investigate the causality between coffee consumption and the risk of both EC and its subtypes, we processed the ECAC data by random-effects IVW. We found that coffee consumption was not associated with EC (OR = 1.217, 95% CI: 0.693–2.137). We also conducted a subgroup analysis of the ECAC data, which suggested that coffee consumption was not linked to non-endometrioid

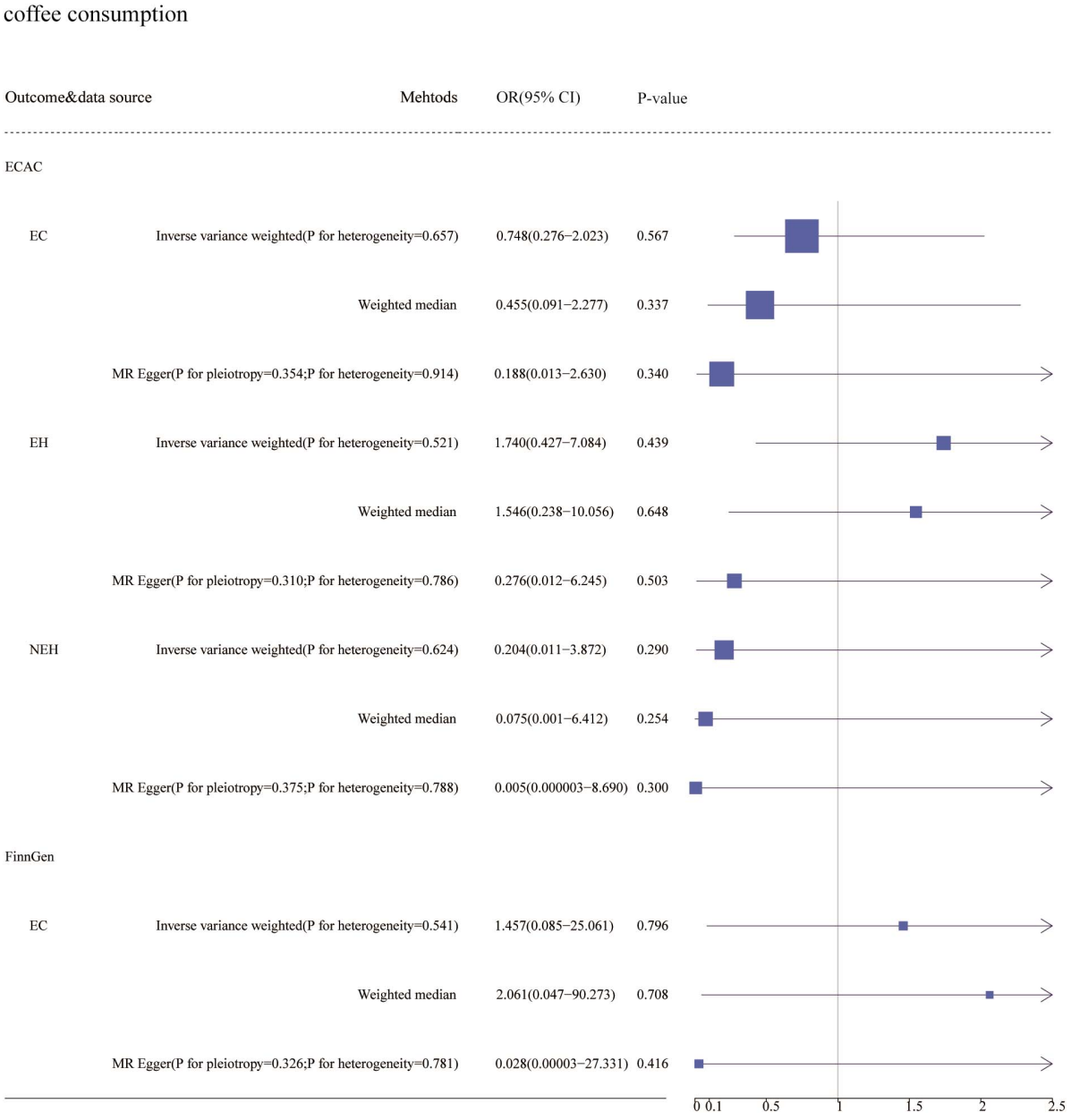

FIGURE 3
Results of sensitivity analyses association of genetically predicted coffee consumption with EC. ECAC, the Endometrial Cancer Association Consortium; EH, Endometrioid histology; NEH, non-endometrioid histology; FinnGen, FinnGen Consortium; OR, odds ratio; CI, confidence interval.

endometrial carcinoma (NEC) (OR = 1.187, 95% CI: 0.292–4.826). Furthermore, in the FinnGen consortium, coffee consumption did not affect EC (OR = 1.738, 95% CI: 0.587–5.142) (Figure 2). In sensitivity analyses, we did not find directed pleiotropy ($p > 0.05$). Additionally, we performed random-effects IVW analyses on the ECAC data and FinnGen consortium data, resulting in no significant differences from the preliminary analyses (Figure 3). Simultaneously, we adjusted pertinent variables such as body mass index, smoking initiation, and alcohol consumption and discovered that the outcomes did not deviate significantly from those of the primary analysis (Supplementary Table 3).

To investigate the causal relationship between caffeine consumption and established outcomes, we analyzed the ECAC data by fixed-effects IVW, which showed that caffeine consumption was unrelated to the risk of EC (OR = 0.852, 95% CI: 0.852–1.003). We also performed subgroup analyses, which showed that caffeine consumption was not a factor in the pathogenesis of EEC (OR = 1.002, 95% CI: 0.827–1.214) and NEC (OR = 0.836, 95% CI: 0.523–1.337). In the FinnGen Consortium data analysis, we also observed that caffeine consumption was not correlated with EC risk (OR = 1.201, 95% CI: 0.258–5.587) (Figure 2).

The study also performed a leave-one-out analysis, which excluded the effect of individual SNPs on the overall causal estimate by removing each SNP stepwise and repeating the MR analysis. The leave-one-out analysis showed relatively stable results after removing each SNP (Supplementary Figures 1–4).

TABLE 2 Effect of coffee and caffeine consumption on overall survival and cancer-specific survival in all endometrial cancers.

SNP	Exposure	HR_OS	SE_OS	P_value_OS	HR_CSS	SE_CSS	P_value_CSS
rs4410790	Caffeine consumption coffee consumption	0.702	0.154	0.022	0.632	0.182	0.012
rs2470893	Caffeine consumption	1.005	0.145	0.974	1.129	0.166	0.464
rs574367	Coffee consumption	0.908	0.168	0.565	0.991	0.189	0.960
rs10865548	Coffee consumption	1.108	0.193	0.596	1.099	0.222	0.672
rs1260326	Coffee consumption	1.112	0.147	0.471	1.067	0.172	0.708
rs73073176	Coffee consumption	0.878	0.159	0.412	0.652	0.216	0.048
rs34060476	Coffee consumption	0.869	0.181	0.438	0.800	0.228	0.329
rs1057868	Coffee consumption	0.827	0.120	0.114	0.797	0.150	0.130
rs597045	Coffee consumption	1.026	0.122	0.836	1.018	0.153	0.906
rs1956218	Coffee consumption	1.275	0.116	0.036	1.254	0.144	0.116
rs2472297	Coffee consumption	0.869	0.126	0.266	0.834	0.157	0.246
rs66723169	Coffee consumption	1.037	0.130	0.779	0.966	0.162	0.830

SNP, single-nucleotide polymorphism; HR, hazard ratio; OS, overall survival; CSS, cancer-specific survival.

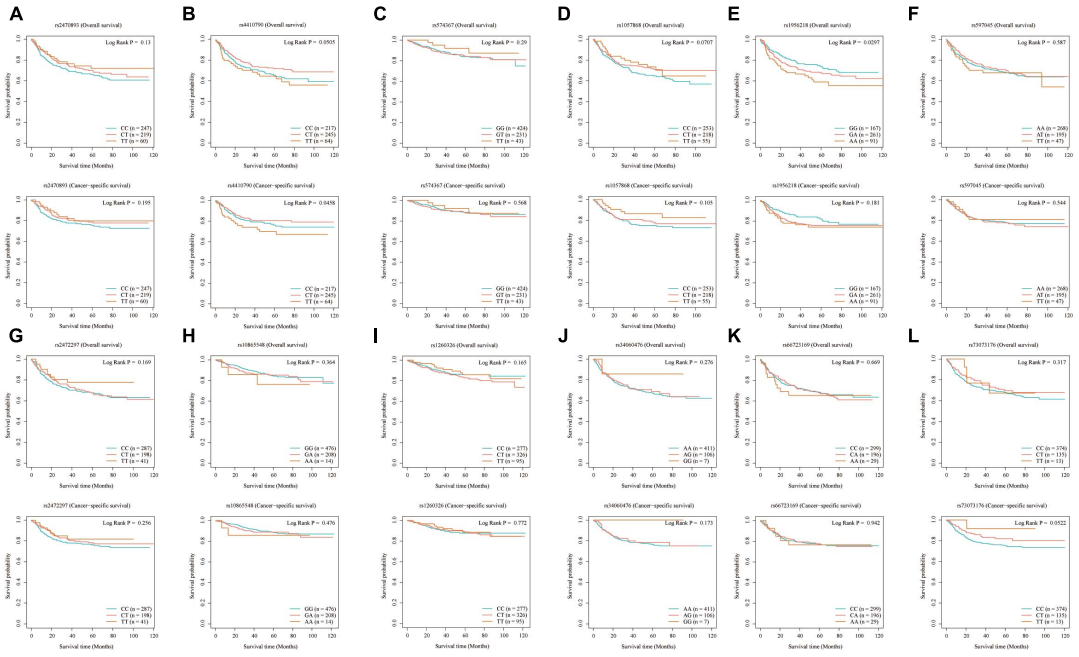

FIGURE 4
Kaplan–Meier plots of the effect of coffee and caffeine consumption on overall survival and cancer-specific survival in EC. **(A)** rs2470893; **(B)** rs4410790; **(C)** rs574367; **(D)** rs1057868; **(E)** rs1956218; **(F)** rs597045; **(G)** rs2472297; **(H)** rs10865548; **(I)** rs1260326; **(J)** rs34060476; **(K)** rs66723169; **(L)** rs73073176.

3.2. Effect of coffee and caffeine consumption on EC prognosis

Our analysis of selected SNPs has determined that most do not significantly impact the likelihood of developing EC, as confirmed by MR analysis. Shorter overall survival (OS) in EC was positively associated with the SNPs rs1956218 (HR: 1.275, $P = 0.036$) linked to coffee consumption, while the SNPs rs4410790 (HR: 0.702, $P = 0.022$) had the opposite effect. Additionally, coffee- and caffeine-consumption-associated SNPs rs4410790 (HR: 0.632, $P = 0.012$) and caffeine-consumption-associated SNPs rs73073176 (HR: 0.652, $P = 0.048$) were also identified to be associated with shorter cancer-specific survival (CSS) (Table 2; Figure 4).

4. Discussion

Our study did not find genetically predicted associations between coffee and caffeine consumption regarding the risk of EC and its subgroups. No outlier SNPs were detected, although

preliminary analyses detected pleiotropy in individual groups. Leave-one-out analyses also showed relatively stable results. After excluding SNPs with confounding factors, the study performed sensitivity analyses that did not detect pleiotropy or heterogeneity, delivering consistent results. Furthermore, we found that most SNPs were not associated with EC prognosis by MR analysis.

Previous research has been controversial regarding the association between coffee or caffeine consumption and the risk of EC. In recent times, a cross-sectional study (36) demonstrated that caffeine was not associated with the risk of EC [OR, 95% CI; 0.999 (0.996, 1.001), $P = 0.297$]. Moreover, a large prospective study (37) investigating the relationship between coffee and EC risk found that coffee intake was not significantly associated with EC risk. A published meta-analysis that resulted in this study also found a weak association between coffee consumption and EC risk. However, a meta-analysis including six cohort studies and 13 case-control studies supported coffee consumption's potentially beneficial health effects on EC, especially in women with higher BMI (38). Meanwhile, in a meta-analysis of observational studies by Je et al. (39), an increase in coffee consumption of one cup/day was negatively associated with the risk ratio of EC and similar findings were reported by Yang et al. (37), Lafranconi et al. (40) and Lukic et al. (41). Despite this, most of the results supported that coffee and caffeine consumption were associated with a reduced risk of EC. However, these findings didn't indicate that coffee and caffeine consumption was responsible for the reduced risk of EC. Due to methodological constraints and residual confounders, observational studies might only partially account for some factors influencing a result (such as the effects of a healthy lifestyle and diet).

Recently, there have been large-scale Mendelian randomization studies on coffee consumption and overall cancers, including EC, reported no causal relationship (42, 43). Nevertheless, our investigation not only examined the potential causal association of coffee and caffeine consumption with the risk of EC, but also assessed its impact on the relationship between EC progression. Confounders did not influence two-sample MR analyses, and we reduced reverse causality by using genetic variation as an instrumental variable. In this study, we assessed the association of selected SNPs with OS and CSS and produced Kaplan-Meier plots to illustrate. In terms of MR analysis, we applied two independent populations (ECAC and FinnGen consortium) separately, and the broadly consistent results ensured stability.

The study also has several disadvantages. Individual groups had horizontal pleiotropy in preliminary analyses, yet after excluding SNPs with potential confounders, we performed sensitivity analyses with generally consistent results. Second, most studies on coffee and caffeine used self-report methodologies, which were prone to bias. In addition, in this study, we did not stratify the menopausal status of EC patients, which might have led to the effect of coffee and caffeine intake on the risk of OC being influenced by menopausal status. Our studies were based on European populations and may need to be more generalizable to others.

5. Conclusion

Our MR investigation found no persuasive evidence to indicate a causal relationship between coffee and caffeine consumption and the risk of EC, and it was found to be largely irrelevant to the prognosis of EC. In the future, more clinical and basic studies are still needed to validate our results.

Data availability statement

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

Author contributions

ZC: Conceptualization, Data curation, Investigation, Methodology, Software, Validation, Writing—original draft. CL: Investigation, Methodology, Software, Supervision, Validation, Writing—original draft. JW: Conceptualization, Investigation, Validation, Visualization, Writing—original draft. FK: Formal analysis, Methodology, Project administration, Resources, Writing—review and editing.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1291355/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Leave-one-out method of studies investigating the association between EC and coffee consumption in ECAC.

SUPPLEMENTARY FIGURE 2
Leave-one-out method of studies investigating the association between EH and coffee consumption in ECAC.

SUPPLEMENTARY FIGURE 3
Leave-one-out method of studies investigating the association between NEH and coffee consumption in ECAC.

SUPPLEMENTARY FIGURE 4
Leave-one-out method of studies investigating the association between EC and coffee consumption in FinnGen Consortium.

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Associations of 10 dietary habits with breast cancer: a Mendelian randomization study

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Introduction: Epidemiological studies have revealed a link between dietary habits and the breast cancer risk. The causality of the association between food consumption and breast cancer requires further investigation.

Methods: Using Mendelian randomization, we assessed the causal effects of 10 dietary habits on the risks of breast cancer and its subtypes (estrogen receptor [ER] + and ER- breast cancer). We obtained dietary pattern data in 2018 (number of single-nucleotide polymorphisms [SNPs] = 9,851,867) and breast cancer data in 2017 (number of SNPs = 10,680,257) from IEU OpenGWAS. Rigorous sensitivity analyses were conducted to ensure that the study results were credible and robust.

Results: We identified that genetic predisposition to higher dried fruit intake was linked to a reduced risk of overall breast cancer (inverse variance-weighted [IVW] odds ratio [OR] = 0.55; 95% confidence interval [CI]: 0.43–0.70; $p = 1.75 \times 10^{-6}$), ER+ breast cancer (IVW OR = 0.62; 95% CI: 0.47–0.82; $p = 8.96 \times 10^{-4}$) and ER– breast cancer (IVW OR = 0.48; 95% CI: 0.34–0.68; $p = 3.18 \times 10^{-5}$), whereas genetic predisposition to more oily fish intake was linked to a lower risk of ER+ breast cancer (IVW OR = 0.73; 95% CI: 0.53–0.99; $p = 0.04$).

Discussion: Our findings suggest that a genetic predisposition for dried fruit and oily fish consumption may be protective against breast cancer; however, further investigation is required.

KEYWORDS

breast cancer, Mendelian randomization, dietary patterns, genome-wide association study (GWAS), nutrition

1 Introduction

Among women, breast cancer is the most common type of cancer, accounting for 11.7% of all cancer cases, and the leading cause of cancer-related deaths (1). The existing epidemiological research broadly supports a link between nutrition and the cancer risk (2, 3). Elucidating the relationship between dietary factors and the breast cancer risk can help prevent breast cancer.

Several epidemiological studies have investigated the relationship between dietary patterns and breast cancer with conflicting findings. A series of prospective cohort studies have suggested an association between a reduced breast cancer risk and diets abundant in fruits, vegetables, cereals, fish, nuts, and olive oil (4–10). However, other studies have shown that these diets are not associated with the breast cancer risk (11–13). Considering the limitations of observational studies, the validity of these findings is subject to random and systematic errors, including the

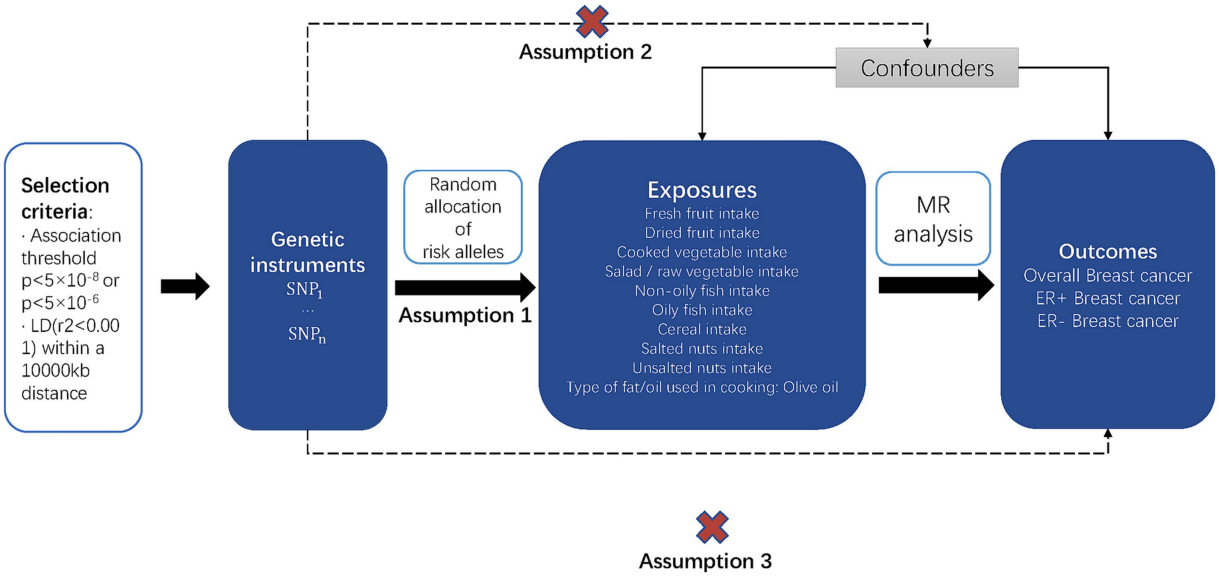

FIGURE 1
Overview of the study design and the three key assumptions of MR. Possible causal relationships between factors that might go against Mendelian randomization assumptions are shown by the dotted arrows.

effects of cohort design bias, potential selection bias, small sample size, missed follow-ups, and the presence of reverse causality between outcomes and exposure (14). Randomized controlled trials are limited by ethical issues, cost, and long follow-ups (15). Whether or not these dietary patterns play a causal role in breast cancer remains unknown.

Mendelian randomization (MR) is an emerging method that infers the causality of exposure and outcome using single-nucleotide polymorphisms (SNPs) as instrumental variables (IV) for risk factors (16, 17). Random assignment of SNPs during meiosis and recombination mimic the random grouping of the randomized controlled trial experiments. Thus, in theory, this genetic tool is less susceptible to potential reverse causality and confounding bias (e.g., potential environmental factors). Using MR techniques, we investigated the potential link between 10 dietary patterns and breast cancer susceptibility (overall breast cancer and breast cancer stratified by estrogen receptor [ER] status).

2 Materials and methods

2.1 Study design

We performed a two-sample MR analysis to investigate the causal impact of the risk factors on the outcomes. MR has the advantages of avoiding reverse causality and minimizing confounding effects in observational studies. Figure 1 shows a graphical flow of the experimental design.

As shown in Figure 1, the MR design is predicated on three key assumptions: assumption 1, IVs are strongly associated with exposure factors, indicated by the solid arrow in the figure; assumption 2, IVs are not associated with confounding factors, indicated by the dotted arrow in the figure; and assumption 3, the chosen IVs affect the outcome only via exposure, indicated by the dotted arrow in the figure (18).

2.2 GWAS summary data of 10 dietary habits and breast cancer

We collected exposure and outcome data from the IEU OpenGWAS database[1], which contains 126 billion genetic associations from 14,582 complete GWAS datasets, representing human phenotypes and disease outcomes across different populations (19, 20). Table 1 shows the data source, sample size, number of SNPs, and strength of IVs for each exposure factor.

Exposure data were obtained from the United Kingdom Biobank GWAS database and aggregated using the IEU OpenGWAS (21). The consortium collected the 2018 statistics for fresh fruit ($n = 446,462$ participants), dried fruit ($n = 421,764$ participants), cooked vegetable ($n = 448,651$ participants), salad/raw vegetable ($n = 435,435$ participants), non-oily fish ($n = 460,880$ participants), oily fish ($n = 460,443$ participants), cereal ($n = 441,640$ participants), salted nut ($n = 64,949$ participants), unsalted nut ($n = 64,949$ participants), and olive oil ($n = 64,949$ participants) intake in the European population. Data on dietary patterns were obtained from the participants by answering a touchscreen questionnaire.

Outcome data, which are publicly available GWAS summary datasets of breast cancer, were obtained from the Breast Cancer Association Consortium. The consortium pooled statistics for the overall ($n = 122,977$ cases, 105,974 non-cases), ER+ ($n = 69,501$ cases), and ER- ($n = 21,468$ cases) breast cancer populations of European ancestry and adjusted the main covariates, including country and 10 principal components (22).

1 https://gwas.mrcieu.ac=/, accessed on February 1, 2023.

TABLE 1 Brief description of each exposure factor used in our study.

Year	Trait	Consortium	Author	Sample size	Number of SNPs	Number of IVs	R^2	F
2018	Fresh fruit intake	MRC-IEU	Ben Elsworth	446,462	9,851,867	55	0.001914	15.64080
2018	Dried fruit intake	MRC-IEU	Ben Elsworth	421,764	9,851,867	43	0.002523	24.74643
2018	Cooked vegetable intake	MRC-IEU	Ben Elsworth	448,651	9,851,867	17	0.000789	20.81829
2018	Salad / raw vegetable intake	MRC-IEU	Ben Elsworth	435,435	9,851,867	22	0.000861	17.04103
2018	Non-oily fish intake	MRC-IEU	Ben Elsworth	460,880	9,851,867	11	0.000657	27.54398
2018	Oily fish intake	MRC-IEU	Ben Elsworth	460,443	9,851,867	63	0.005204	38.03898
2018	Cereal intake	MRC-IEU	Ben Elsworth	441,640	9,851,867	43	0.003103	31.87728
2018	Salted nuts intake	MRC-IEU	Ben Elsworth	64,949	9,851,867	23	0.00074511	2.1040981
2018	Unsalted nuts intake	MRC-IEU	Ben Elsworth	64,949	9,851,867	16	0.001214852	4.931687334
2018	Type of fat/oil used in cooking: Olive oil	MRC-IEU	Ben Elsworth	64,949	9,851,867	8	0.000662498	5.378855561
2017	Breast cancer (combined Oncoarray; iCOGS; GWAS meta analysis)	BCAC	Michailidou K	228,951	10,680,257	-	-	-
2017	ER+ Breast cancer (combined Oncoarray; iCOGS; GWAS meta analysis)	BCAC	Michailidou K	175,475	10,680,257	-	-	-
2017	ER- Breast cancer (combined Oncoarray; iCOGS; GWAS meta analysis)	BCAC	Michailidou K	127,442	10,680,257	-	-	-

2.3 Statistical analysis

2.3.1 IV selection

First, to extract SNPs genetically linked to the traits, we performed rigorous screening ($p < 5 \times 10^{-8}$; minor allele frequency [MAF] > 0.01) of SNPs associated with the dietary patterns. For the three dietary patterns of salted nut, unsalted nut, and olive oil intake, we did not select enough valid SNPs using the threshold of $p < 5 \times 10^{-8}$. To explore more associations between those three dietary patterns and breast cancer, we used the relatively relaxed threshold of $p < 5 \times 10^{-6}$ (23). Second, to remove linkage disequilibrium IVs, we excluded SNPs with $r^2 > 0.001$, with the most significant SNPs within a clumping distance of 10,000 kb. Third, to remove incompatible and palindromic SNPs whose direction could not be determined, we harmonized the data. Data harmonization helps avoid redundant calculations of the same allele across datasets. Palindromic variants were removed by eliminating alleles with frequencies close to 50% (24). Fourth, to exclude weak IVs, we calculate the F-values using the formula $F = \frac{(N-k-1)R^2}{k(1-R^2)}$ (25). R^2 in the formula was calculated using $R^2 = 2 \times \mathrm{MAF} \times (1-\mathrm{MAF}) \times beta^2$ (26). When the F-statistic was <10, we determined that genetic variation to be a weak IV (27). We removed one SNP with an F-value <10 for fresh fruit intake (rs586346, $F = 9.91$). Table 1 lists the F- and R^2 values for each exposure. Supplementary Table S1 shows the F and R^2 values of all SNPs. Finally, to assess the statistical power of the results, we used http://cnsgenomic.com/shiny/mRnd/ (accessed on March 2, 2023) (28). Table 2 shows the calculated statistical power estimates.

2.3.2 MR analyses

This study was guided by the Strengthening the Reporting of Observational Research in Epidemiology using MR (29). We mainly used the inverse variance-weighted (IVW) model to evaluate the causal relationship between 10 dietary patterns and the breast cancer risk (including total breast cancer, ER+ breast cancer, and ER- breast cancer). The results of the MR-Egger and weighted median (WM) methods are also presented, which help interpret the results from multiple perspectives. To evaluate the sensitivity of the results, we performed Cochran's Q, MR-Egger intercept, MR-PRESSO, and MR-Steiger filtering tests and plotted leave-one-out, scatter, and funnel plots. These plots are available in the Supplementary file. To assess the heterogeneity of the IVs, we performed Cochran's Q test using IVW and MR-Egger's methods. Heterogeneity was indicated when the p-value of the Cochran's Q test was <0.05. When heterogeneity was strong, we used a random-effects model rather than a fixed-effects model (30). To test for the presence of horizontal pleiotropy, we calculated the difference between the MR-Egger

TABLE 2 Estimation of power for Mendelian randomization analyses for breast cancer risk based on the total sample size and proportion of phenotypic variance of nutrients explained by instruments.

Outcome	Exposure	*N*	alpha	Proportion of cases	OR	R^2	power
Overall BC	Fresh fruit intake	228,951	0.05	0.537132	0.641836	0.001914	1
	Dried fruit intake	228,951	0.05	0.537132	0.540035	0.002523	1
	Cooked vegetable intake	228,951	0.05	0.537132	0.67135	0.000789	0.78
	Salad / raw vegetable intake	228,951	0.05	0.537132	0.880096	0.000861	0.15
	Non-oily fish intake	228,951	0.05	0.537132	0.430221	0.000657	1
	Oily fish intake	228,951	0.05	0.537132	0.744191	0.005204	1
	Cereal intake	228,951	0.05	0.537132	1.187451	0.003103	0.62
	Salted nuts intake	228,951	0.05	0.537132	1.246116975	0.00074511	0.30
	Unsalted nuts intake	228,951	0.05	0.537132	1.043704899	0.001214852	0.06
	Type of fat/oil used in cooking: olive oil	228,951	0.05	0.537132	0.716392316	0.000662498	0.55
ER+ Breast cancer	Fresh fruit intake	175,475	0.05	0.396074	0.650789	0.001914	0.99
	Dried fruit intake	175,475	0.05	0.396074	0.575736	0.002523	1
	Cooked vegetable intake	175,475	0.05	0.396074	0.701283	0.000789	0.62
	Salad / raw vegetable intake	175,475	0.05	0.396074	0.75149	0.000861	0.48
	Non-oily fish intake	175,475	0.05	0.396074	0.42784	0.000657	1
	Oily fish intake	175,475	0.05	0.396074	0.726119	0.005204	1
	Cereal intake	175,475	0.05	0.396074	1.285963	0.003103	0.92
	Salted nuts intake	175,475	0.05	0.396074	1.172298417	0.00074511	0.15
	Unsalted nuts intake	175,475	0.05	0.396074	1.157932392	0.001214852	0.19
	Type of fat/oil used in cooking: olive oil	175,475	0.05	0.396074	0.728121089	0.000662498	0.37
ER- Breast cancer	Fresh fruit intake	127,442	0.05	0.168453	0.550731	0.001914	0.97
	Dried fruit intake	127,442	0.05	0.168453	0.55935	0.002523	0.99
	Cooked vegetable intake	127,442	0.05	0.168453	0.504238	0.000789	0.79
	Salad / raw vegetable intake	127,442	0.05	0.168453	1.444774	0.000861	0.6
	Non-oily fish intake	127,442	0.05	0.168453	0.404211	0.000657	0.88
	Oily fish intake	127,442	0.05	0.168453	0.904957	0.005204	0.24
	Cereal intake	127,442	0.05	0.168453	0.88803	0.003103	0.21
	Salted nuts intake	127,442	0.05	0.168453	0.996131708	0.00074511	0.05
	Unsalted nuts intake	127,442	0.05	0.168453	1.179968583	0.001214852	0.13
	Type of fat/oil used in cooking: olive oil	127,442	0.05	0.168453	0.870739101	0.000662498	0.07

intercept term and 0 (Pintercept). A significant difference (Pintercept <0.05) indicated the presence of horizontal pleiotropy. Supplementary Table S2 shows the results of Cochran's Q and MR-Egger intercept tests. The MR-PRESSO method was used to exclude the influential outliers. To assess the direction of the effects of IV on the exposure and outcomes, we performed the MR-Steiger filtering test (31). Table 3 lists the outliers excluded by the MR-PRESSO and MR-Steiger filtering tests. To assess the robustness of the results, we constructed scatter plots and leave-one-out analyses.

Statistical analyses were performed using R 4.2.1 software using the "Two-sample MR" and "MR-PRESSO" packages. We adopted a Bonferroni-corrected threshold of $p = 0.00167$ (0.05/30) as a sign of

TABLE 3 Outliers excluded by the MR-PRESSO and MR-Steiger filtering tests.

Trait	GWAS ID	Outcome	Outcome GWAS ID	Outliers	
				Steiger filtering	Mr-presso
Fresh fruit intake	ukb-b-3881	Overall BC	ieu-a-1126	NA	rs10828266, rs2143081, rs2867113, rs9919429
Dried fruit intake	ukb-b-16576	Overall BC	ieu-a-1126	NA	rs10740991, rs2328887
Cooked vegetable intake	ukb-b-8089	Overall BC	ieu-a-1126	rs1421085	rs1421085
Salad / raw vegetable intake	ukb-b-1996	Overall BC	ieu-a-1126	rs6482190	rs6482190, rs34186148
Non-oily fish intake	ukb-b-17627	Overall BC	ieu-a-1126	rs56094641	rs56094641, rs7148387
Oily fish intake	ukb-b-2209	Overall BC	ieu-a-1126	rs1421085	rs1421085, rs10828250, rs16891727, rs1876245, rs4510068
Cereal intake	ukb-b-15926	Overall BC	ieu-a-1126	rs9846396	rs9846396, rs1853931
Salted nuts intake	ukb-b-15960	Overall BC	ieu-a-1126	NA	NA
Unsalted nuts intake	ukb-b-12217	Overall BC	ieu-a-1126	NA	NA
Type of fat/oil used in cooking: olive oil	ukb-b-3875	Overall BC	ieu-a-1126	NA	NA
Fresh fruit intake	ukb-b-3881	ER+ Breast cancer	ieu-1-1127	rs10828266, rs9919429	rs10828266, rs9919429
Dried fruit intake	ukb-b-16576	ER+ Breast cancer	ieu-a-1127	rs7916868, rs10740991	rs7916868, rs10740991, rs2328887
Cooked vegetable intake	ukb-b-8089	ER+ Breast cancer	ieu-a-1127	rs1421085	rs1421085
Salad / raw vegetable intake	ukb-b-1996	ER+ Breast cancer	ieu-1-1127	rs6482190	rs6482190, rs34186148
Non-oily fish intake	ukb-b-17627	ER+ Breast cancer	ieu-a-1127	rs56094641	rs56094641
Oily fish intake	ukb-b-2209	ER+ Breast cancer	ieu-a-1127	rs1876245, rs1421085, rs10828250	rs1421085, rs10828250, rs16891727, rs1876245, rs4510068
Cereal intake	ukb-b-15926	ER+ Breast cancer	ieu-1-1127	rs9846396	rs9846396
Salted nuts intake	ukb-b-15960	ER+ Breast cancer	ieu-1-1127	NA	NA
Unsalted nuts intake	ukb-b-12217	ER+ Breast cancer	ieu-1-1127	NA	NA
Type of fat/oil used in cooking: olive oil	ukb-b-3875	ER+ Breast cancer	ieu-1-1127	NA	NA
Fresh fruit intake	ukb-b-3881	ER- Breast cancer	ieu-1-1128	rs12044599, rs1375566, rs149449, rs2867113, rs7818437	rs10828266, rs149449, rs2867113
Dried fruit intake	ukb-b-16576	ER- Breast cancer	ieu-a-1128	NA	rs10740991
Cooked vegetable intake	ukb-b-8089	ER- Breast cancer	ieu-1-1128	rs1421085	rs1421085
Salad / raw vegetable intake	ukb-b-1996	ER- Breast cancer	ieu-a-1128	NA	NA
Non-oily fish intake	ukb-b-17627	ER- Breast cancer	ieu-1-1128	rs56094641	rs56094641
Oily fish intake	ukb-b-2209	ER- Breast cancer	ieu-a-1128	rs1421085	rs10828250, rs1421085, rs45501495
Cereal intake	ukb-b-15926	ER- Breast cancer	ieu-1-1128	NA	NA
Salted nuts intake	ukb-b-15960	ER- Breast cancer	ieu-1-1128	NA	NA
Unsalted nuts intake	ukb-b-12217	ER- Breast cancer	ieu-a-1128	NA	NA
Type of fat/oil used in cooking: olive oil	ukb-b-3875	ER- Breast cancer	ieu-1-1128	NA	NA

GWAS ID is the id from open GWAS.

a significant effect and $0.00167 < p < 0.05$, as a sign of a suggestive association.

3 Results

Supplementary Table S1 shows the SNPs screened for strong associations with the 10 dietary factors. Table 3 shows the outliers excluded by the MR-PRESSO and MR-Steiger analyses. Heterogeneity was detected in all studies except for the dried fruit intake and ER- breast cancer study, salad/raw vegetable intake and ER- breast cancer study, and cereal intake and ER- breast cancer study; therefore, we applied a random-effects model in the IVW analysis. From the results of the pleiotropy test, we can assume the presence of no horizontal pleiotropy in terms of statistical significance because the *p*-values of the MR-Egger intercept were > 0.05. Figures 2–4 show

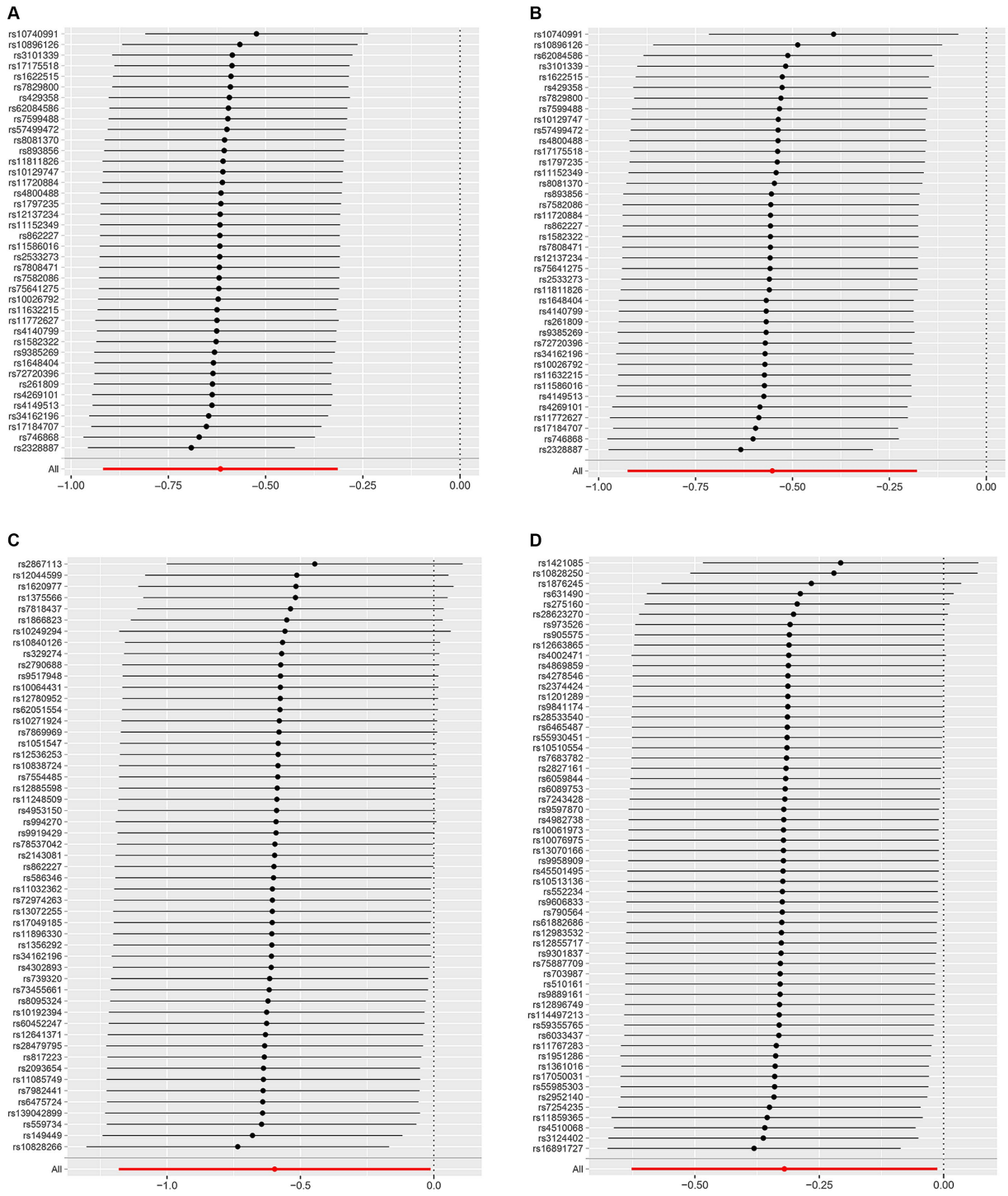

FIGURE 2
Leave-one-out plots of the MR results of **(A)** genetically predicted dried fruit intake with overall breast cancer; **(B)** genetically predicted dried fruit intake with ER+ breast cancer; **(C)** genetically predicted dried fruit intake with ER– breast cancer; **(D)** genetically predicted oily fish intake with ER+ breast cancer.

leave-one-out, scatter, and funnel plots of MR for dietary patterns associated with the breast cancer risk based on the IVW analysis.

As shown in Table 4 and Figure 5, after eliminating outliers based on MR-PRESSO and MR-Steiger filtering test results, of all dietary factors studied, only genetic tendency to intake dried fruit was found to be significantly associated with a reduced overall breast cancer risk (IVW odds ratio [OR] = 0.55; 95% confidence interval [CI]: 0.43–0.70; $p = 1.75 \times 10^{-6}$), ER+ breast cancer (IVW OR = 0.62; 95% CI: 0.47–0.82; $p = 8.96 \times 10^{-4}$) and ER- breast cancer (IVW OR = 0.48; 95% CI: 0.34–0.68; $p = 3.18 \times 10^{-5}$). In the WM model, dried fruit intake was associated with the overall breast cancer risk (WM OR = 0.59; 95% CI: 0.44–0.80; $p = 6.68 \times 10^{-4}$), and ER- breast cancer (WM OR = 0.50; 95% CI: 0.31–0.82; $p = 6.22 \times 10^{-3}$). However, in the WM model, dried fruit intake was not associated with ER+ breast cancer (WM OR = 0.74; 95% CI: 0.53–1.05; $p = 0.09$). Genetic tendency to intake oily fish, failing to pass the Bonferroni correction, was suggestive to be associated with a reduced risk of ER+ breast cancer (IVW OR = 0.73; 95% CI: 0.53–0.99; $p = 0.04$). In the WM model, oily fish intake was not associated with ER+ breast cancer (WM OR = 0.84; 95% CI: 0.65–1.07; $p = 0.16$).

Fresh fruit (IVW OR = 0.77; 95% CI: 0.58–1.00; $p = 0.05$), cooked vegetable (IVW OR = 0.67; 95% CI: 0.28–1.59; $p = 0.36$), salad/raw vegetable (IVW OR = 1.08; 95% CI: 0.70–1.69; $p = 0.72$), non-oily fish (IVW OR = 0.71; 95% CI: 0.41–1.23; $p = 0.22$), oily fish (IVW OR = 0.85; 95% CI: 0.71–1.03; $p = 0.09$), cereal (IVW OR = 1.02; 95% CI: 0.82–1.29; $p = 0.83$), salted nut (IVW OR = 1.24; 95% CI: 0.87–1.77; $p = 0.21$), unsalted nut (IVW OR = 1.04; 95% CI: 0.74–1.45; $p = 0.79$),

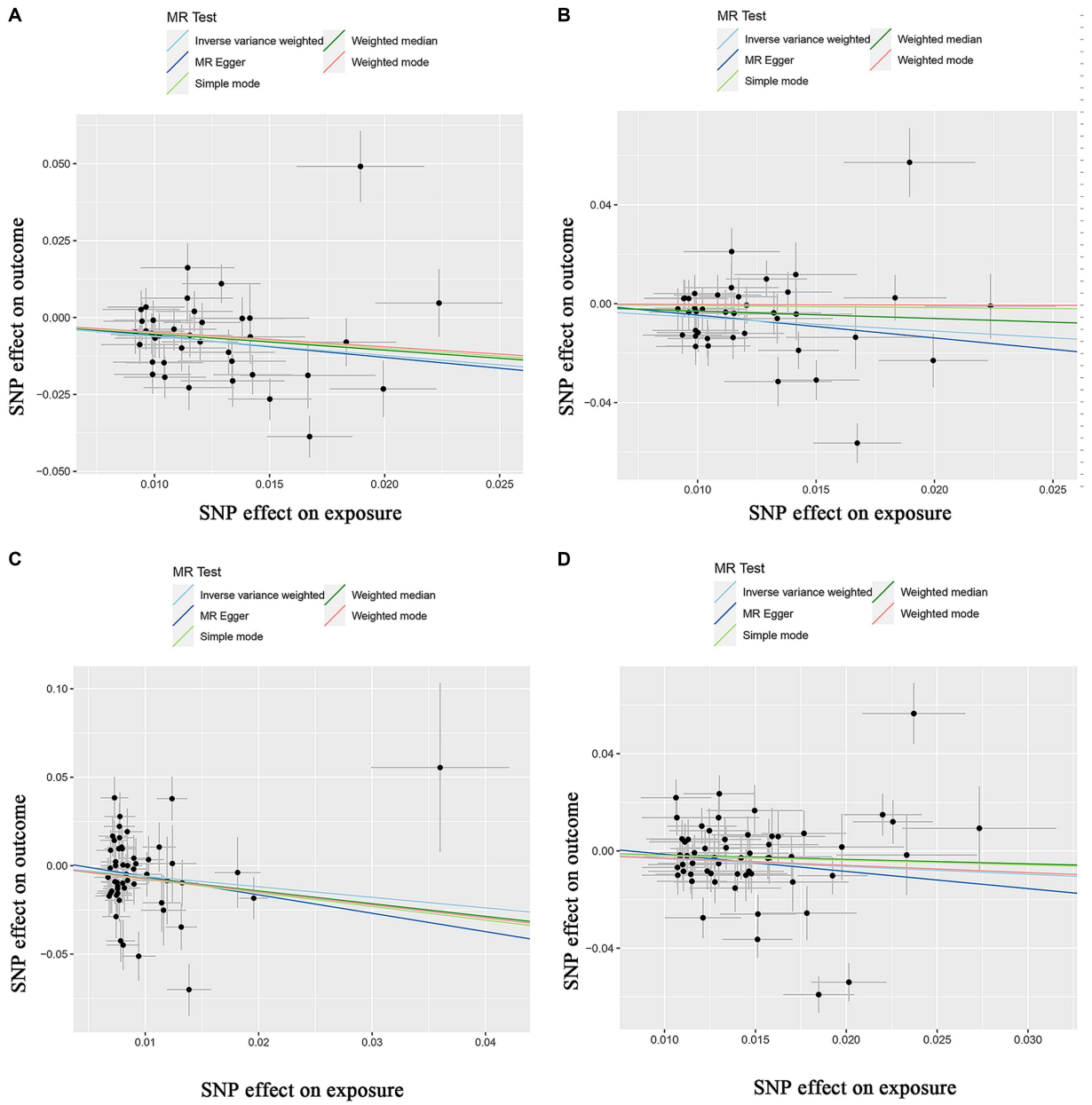

FIGURE 3
Scatter plots of the MR results of **(A)** genetically predicted dried fruit intake with overall breast cancer; **(B)** genetically predicted dried fruit intake with ER+ breast cancer; **(C)** genetically predicted dried fruit intake with ER– breast cancer; **(D)** genetically predicted oily fish intake with ER+ breast cancer.

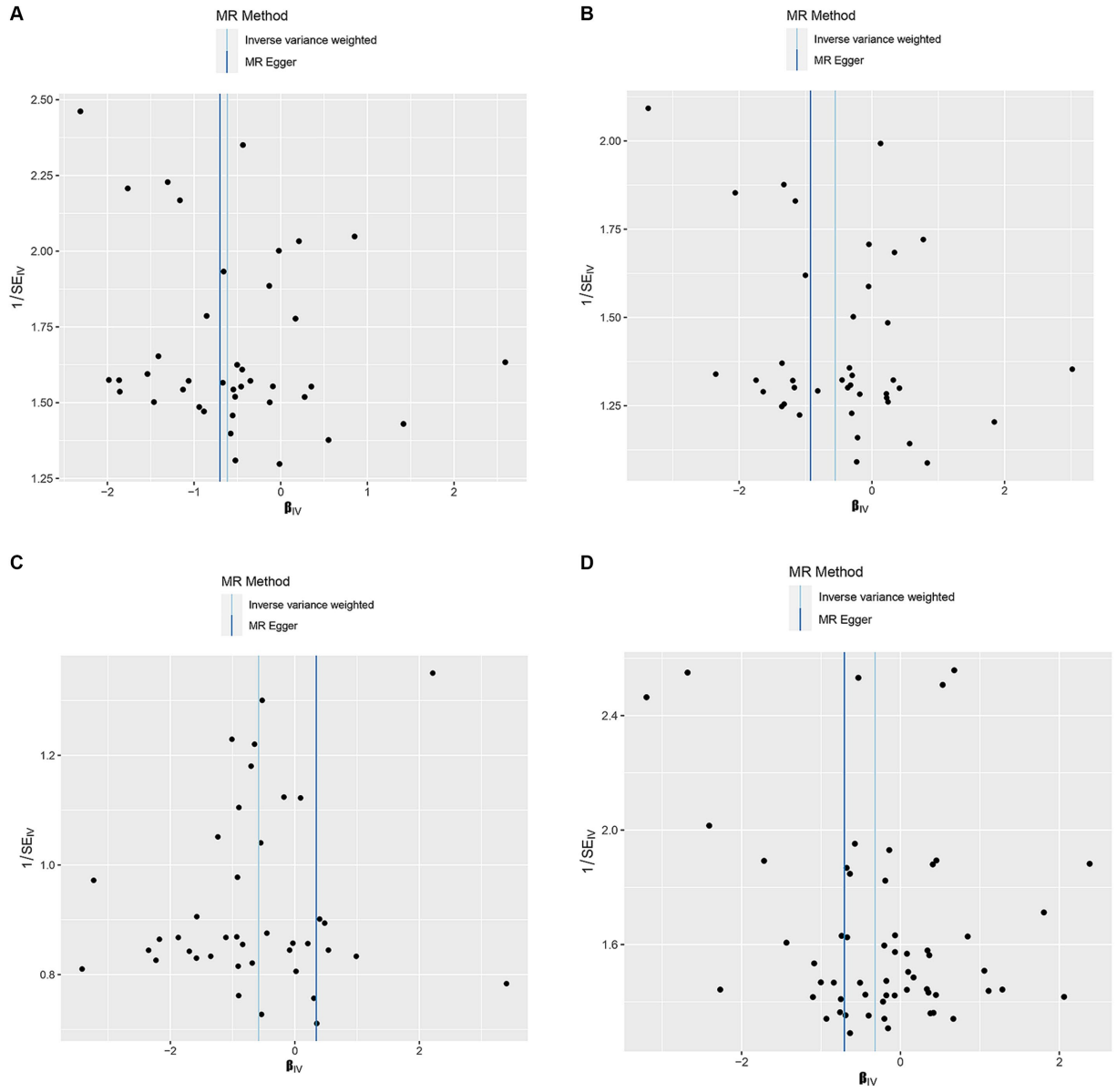

FIGURE 4
Funnel plots of the MR results of **(A)** genetically predicted dried fruit intake with overall breast cancer; **(B)** genetically predicted dried fruit intake with ER+ breast cancer; **(C)** genetically predicted dried fruit intake with ER− breast cancer; **(D)** genetically predicted oily fish intake with ER+ breast cancer.

or olive oil (IVW OR = 0.71; 95% CI: 0.47–1.08; $p = 0.11$) was not associated with the overall breast cancer risk (Figure 6).

Fresh fruit (IVW OR = 0.80; 95% CI: 0.59–1.08; $p = 0.15$), cooked vegetable (IVW OR = 0.70; 95% CI: 0.30–1.63; $p = 0.41$), salad/raw vegetable (IVW OR = 1.02; 95% CI: 0.63–1.66; $p = 0.90$), non-oily fish (IVW OR = 0.78; 95% CI: 0.43–1.40; $p = 0.41$), cereal (IVW OR = 1.13; 95% CI: 0.87–1.47; $p = 0.32$), salted nut (IVW OR = 1.17; 95% CI: 0.76–1.80; $p = 0.46$), unsalted nut (IVW OR = 1.15; 95% CI: 0.72–1.84; $p = 0.53$), or olive oil (IVW OR = 0.72; 95% CI: 0.45–1.17; $p = 0.19$) intake was not associated with ER+ breast cancer.

Fresh fruit (IVW OR = 0.65; 95% CI: 0.42–1.00; $p = 0.05$), cooked vegetable (IVW OR = 0.84; 95% CI: 0.42–1.66; $p = 0.62$), salad/raw vegetable (IVW OR = 1.44; 95% CI: 0.74–2.78; $p = 0.27$), non-oily fish (IVW OR = 0.93; 95% CI: 0.45–1.90; $p = 0.84$), oily fish (IVW OR = 1.04; 95% CI: 0.76–1.41; $p = 0.79$), cereal (IVW OR = 0.88; 95% CI: 0.64–1.22; $p = 0.46$), salted nut (IVW OR = 0.99; 95% CI: 0.47–2.09; $p = 0.99$), unsalted nut (IVW OR = 1.17; 95% CI: 0.67–2.06; $p = 0.56$), or olive oil (IVW OR = 0.87; 95% CI: 0.45–1.67; $p = 0.67$) intake was not associated with ER- breast cancer.

The full MR results for the 10 dietary habits and overall, ER+, and ER- breast cancer risks, including results of the MR-Egger, WM, IVW, simple model, and WM methods, can be viewed in Supplementary Tables S3–S5, respectively.

4 Discussion

Observational studies lack correction for risk factors and have a range of biases, such as study design and population, which may lead

TABLE 4 Association between genetic tendencies for 10 dietary habits and the breast cancer risk.

Exposure phenotypes		Number of SNPs	Overall breast cancer		Number of SNPs	ER+ Breast cancer		Number of SNPs	ER– Breast cancer	
			OR (95% CI)	*p*-value		OR (95% CI)	*p*-value		OR (95% CI)	*p*-value
Fruit	Fresh fruit intake	48	0.77 (0.58–1.01)	0.057242197	51	0.80 (0.59–1.09)	0.159731	47	0.65 (0.42–1.00)	0.050251382
	Dried fruit intake	38	0.55 (0.43–0.70)	1.75408×10^{-6}	38	0.62 (0.47–0.82)	0.000896	39	0.48 (0.34–0.68)	3.18216×10^{-5}
Vegetable	Cooked vegetable intake	17	0.67 (0.28–1.59)	0.363679601	17	0.70 (0.30–1.63)	0.410992	16	0.84 (0.43–1.67)	0.625276642
	Salad / raw vegetable intake	16	1.08 (0.70–1.69)	0.719768892	16	1.03 (0.64–1.67)	0.906074	18	1.44 (0.75–2.79)	0.27296844
Fish	Non-oily fish intake	8	0.71 (0.41–1.23)	0.223795105	9	0.79 (0.44–1.40)	0.414988	9	0.93 (0.46–1.91)	0.849043459
	Oily fish intake	53	0.85 (0.71–1.03)	0.091243395	58	0.73 (0.53–0.99)	0.04118	55	1.04 (0.77–1.41)	0.798353229
Cereal	Cereal intake	37	1.02 (0.82–1.29)	0.836510368	38	1.14 (0.88–1.48)	0.327498	39	0.89 (0.64–1.22)	0.468410676
Nuts	Salted nuts intake	22	1.25 (0.88–1.77)	0.219658057	22	1.17 (0.76–1.80)	0.467556675	22	1.00 (0.47–2.09)	0.991821678
	Unsalted nuts intake	15	1.04 (0.75–1.45)	0.799956254	15	1.16 (0.73–1.84)	0.537031221	15	1.18 (0.67–2.07)	0.562322459
Olive oil	Type of fat/oil used in cooking: olive oil	8	0.72 (0.48–1.08)	0.11128447	8	0.73 (0.45–1.18)	0.195888885	8	0.87 (0.45–1.68)	0.67906221

to inconsistent conclusions. In a previous study, the causal relationship between dietary patterns and the breast cancer risk was not fully elucidated. Previous studies have not been uniformly conclusive regarding the association between fruit intake and the breast cancer risk in European populations. A subset of observational studies showed no significant association between fruit intake and the breast cancer risk (4, 5, 32). A European Prospective Investigation into Cancer and Nutrition study involving 285,526 women showed no significant association between fruit intake (including dried and canned fruits) and the breast cancer risk (33). However, a prospective nurses' health study involving 182,145 women with >20 years of follow-up showed that a higher total fruit intake was associated with a reduced breast cancer risk (34). Clinical observational evidence is limited on the effect of dried fruit intake on the breast cancer risk. A prospective cohort study involving women in the United Kingdom found no association between dried fruit consumption and breast cancer incidence (35). The relationship between vegetable intake and the breast cancer risk has been controversial in previous observational studies. Previous epidemiological studies suggested that vegetable intake is not associated with the breast cancer risk (12, 36), whereas traditional studies have shown that vegetable intake is associated with the breast cancer risk (4, 5, 34, 37). The results of previous conventional studies on the relationship between grain intake and the breast cancer risk were conflicting. Some studies have found a negative association (38–42), while others have found no clear association (11, 43–45). Xiao et al. (6) previously conducted a meta-analysis of four cohort studies and seven case–control studies and observed a negative association between cereal intake and breast cancer only in the case–control study, while no negative association was observed in the cohort studies.

In this study, we used a large-scale GWAS database for a two-sample MR analysis and found that genetically predicted dried

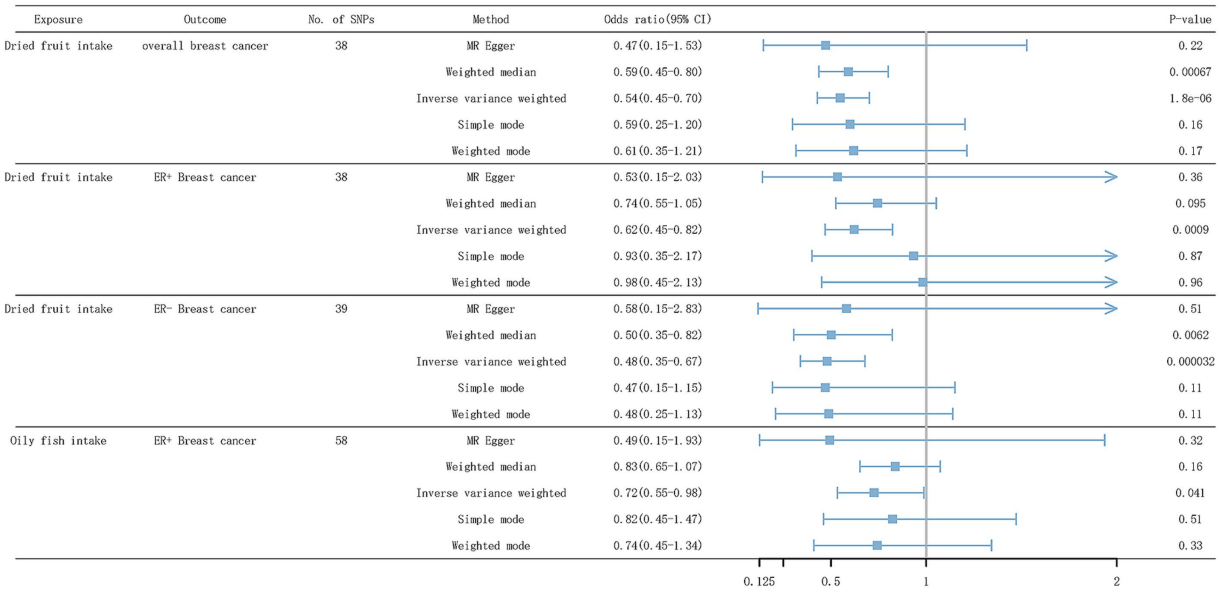

FIGURE 5
Forest plot of IVW results for dietary patterns associated with BC risk. SNP, single nucleotide polymorphism; ER+ breast cancer, Estrogen receptor-positive breast cancer; ER– breast cancer, Estrogen receptor-negative breast cancer.

fruit intake plays a critical role in breast cancer susceptibility. In addition to dried fruit intake, we found evidence that genetic predisposition to greater intake of oily fish may reduce the risk of ER+ breast cancer. Our study had several strengths. First, we used a large-scale GWAS database, which allowed us to use a much larger sample size compared to traditional studies, thus minimizing bias. Second, our study population was from Europe, effectively limiting population heterogeneity bias. Third, using genetic variables associated with a single phenotype as IVs, we largely reduced the bias caused by common genetic effects between phenotypes. Fourth, we performed rigorous sensitivity analyses to assess the effects of outliers and pleiotropy. Fifth, our MR analysis assessed the causal effects of exposure and outcomes, thus reducing the reverse causality associated with the outcome. Sixth, the MR study allowed us to identify risk factors at the genetic level, and thus, early identification of high-risk groups, which had implications for disease screening. However, our study had certain limitations. First, all samples were from Europe, thus reducing the generalizability to other populations. Second, this study relied heavily on self-reporting and may have been subject to a reporting bias. Third, the MR results only suggest possible genetic correlations and causal associations at the genetic level, and more mechanism-based experiments are required to further confirm this biological plausibility (46). Although our findings clarify a causal relationship between some dietary patterns and the breast cancer risk, the causal relationships derived from the MR experiments cannot be fully equated to the expected impact of risk factors on outcomes in a clinical setting (47). Causal relationships in MR reflect a genetic-level predisposition to risk factors, which makes interventions for risk factors potentially clinically meaningful (46). Although guiding clinical interventions for risk factors based on MR results is not appropriate, causal inferences using MR designs may be useful for screening specific populations susceptible to disease and could provide some guidance for conducting randomized controlled trials. Fourth, for the three dietary patterns of salted nut, unsalted nut, and olive oil intake, we used relatively more relaxed threshold of $p < 5 \times 10^{-6}$, and the *F*-values of the SNPs were < 10, which may led to conclusions that would be relatively weakly IV biased, i.e., genetic variants may not be strongly correlated with exposure factors. This is due to the limited sample size of the exposures. In future studies, databases with larger sample sizes could help screen for more representative IVs. Fifth, the GWAS data on dietary patterns, particularly complex dietary patterns like the Mediterranean diet, are relatively limited. This represents a valuable direction for future GWAS databases and Mendelian randomization studies.

The potential mechanisms by which dried fruit and oily fish intake were associated with the breast cancer risk in this study should be discussed. Owing to thermal degradation and oxidation reactions, dried fruits contain higher amounts of nutrients and phytochemicals compared to fresh fruits. 5-hydroxymethylfurfural, a compound commonly found in dried fruits, exhibits beneficial biological properties including *in vitro* antioxidant activity (48) and anti-hypoxic effects (49). The processing of dried fruit may also reduce the cancer risk. Mycotoxins are exogenous toxins that may be generated during the processing of dried fruits. Low-dose mycotoxin consumption can activate physiological responses, thereby counteracting chronic inflammation (50). A recent review suggested that dried fruits can reduce the impact of carcinogens by inducing the detoxification of enzymes (51). Dried fruit was prepared by removing water from the fruit and had a nutrient profile similar to that of the equivalent fresh fruit but at higher concentrations. A comparative study on raisins and grapes showed that drying concentrated polyphenol content and thus increased antioxidant activity (52). Thus, microbiome metabolites of polyphenols and other phytonutrients may be beneficial to health (53). Polyphenols exert antioxidant effects that reduce the proliferation of cancer cells and protect the DNA from damage caused by carcinogens (54). In conclusion, dried fruit intake prevents breast cancer; however, the mechanism requires further investigation. Contrary to the relationship between fish intake and the breast cancer risk, previous studies have shown that fish intake was not associated with the breast cancer risk (13), unlike the findings of this experiment. A possible explanation is that although fish are rich in omega-3 polyunsaturated fatty

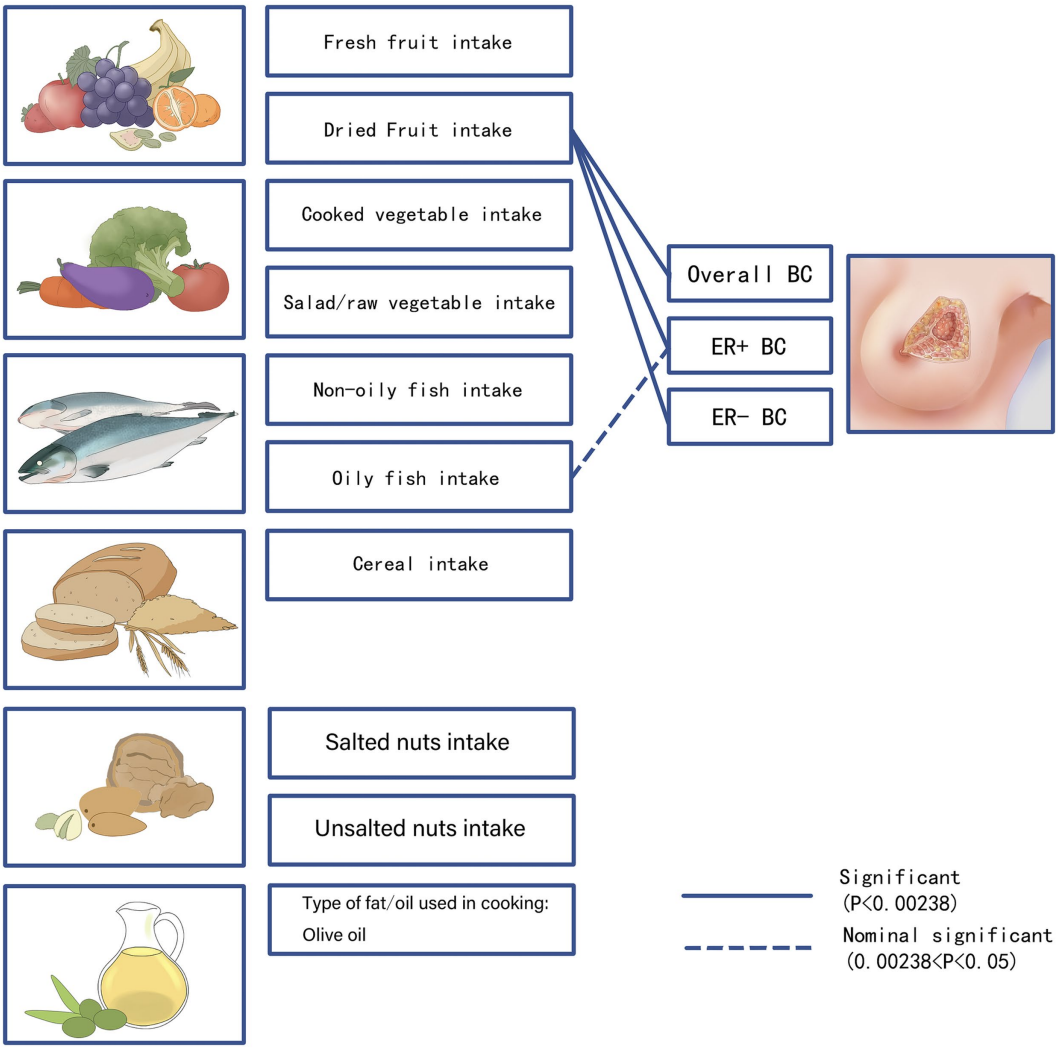

FIGURE 6
We visualized the association of 10 dietary patterns with breast cancer risk. *p*-values <0.00238 for the IVW method were considered as significant results, which we show as solid lines in the figure. 0.00238 <*p*-value<0.05 for the IVW method were considered as potentially significant results, which we show as dashed lines in the figure. BC, breast cancer; ER+ BC, Estrogen receptor-positive breast cancer; ER– BC, Estrogen receptor-negative breast cancer.

acids, which retard breast cancer growth according to *in vitro* and animal studies (55). They may also be contaminated with dioxins, methylmercury, and PCBs (56, 57). The possible dangers of dioxins or other contaminants were outweighed by the health risks of not eating fish (58).

5 Conclusion

Our study revealed that distinct histological subtypes of breast cancer are affected by the genetic propensity to dry fruit and oily fish intake to varying degrees. These findings suggest that individuals who do not include dried fruits and oily fish in their diets may benefit from considering earlier or more frequent breast cancer screenings, such as breast ultrasound and mammography, to facilitate early breast cancer detection. Additionally, at the genetic level, our results indicate an association between dietary habits involving dried fruit and oily fish intake and a reduced breast cancer risk, thereby contributing to the value of dietary recommendations for breast cancer prevention.

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.

Author contributions

XW and YD: conceptualization. XW: formal analysis and writing–original draft. YD: funding acquisition and supervision. XW and LC: software. LC, RC, RM, YL, and QZ: validation. XW, RC, RM, YL, and QZ: visualization. LC and YD: writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1215220/full#supplementary-material

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The PG-SGA outperforms the NRS 2002 for nutritional risk screening in cancer patients: a retrospective study from China

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Background and aims: As a chronic wasting disease, cancer can lead to metabolic and physiological changes in patients, resulting in severe malnutrition. Therefore, accurate assessment of nutritional status and adoption of scientifically sound nutritional interventions are of great importance for patients with cancer. This study aimed to assess the necessity of implementing the Nutrition Risk Screening 2002 (NRS 2002) tool in conjunction with the Patient-Generated Subjective Global Assessment (PG-SGA) in patients with cancer.

Methods: This retrospective study collected the clinical data of cancer patients from November 2011 to December 2018 in the Department of Oncology, Cancer Center, First Hospital of Jilin University. The NRS 2002 and the PG-SGA were used as screening tools for malnutrition. Clinical characteristics and laboratory results were detected. Anthropometric indices including hand-grip strength (HGS), visceral fat area (VFA), calf circumstance (CC), and appendicular skeletal muscle mass index (ASMI) were also collected. The diagnostic results from the NRS 2002 were compared to the malnutrition diagnosis using the PG-SGA.

Results: Of the 2,645 patients included in this retrospective study, the nutritional risk was found in 1763 (66.6%) patients based on the PG-SGA, and in 240 (9.1%) patients based on the NRS 2002, respectively. Among the 240 patients evaluated by the NRS 2002 for risk of malnutrition, 230 were also assessed by the PG-SGA as malnourished. There were no significant differences observed in the clinical characteristics and laboratory parameters between the two groups.

Conclusion: The PG-SGA is effective and had a higher positive rate in screening malnutrition for patients with cancer. The NRS 2002 is not necessary for patients who are to be assessed with the PG-SGA.

KEYWORDS

nutritional risk screening, PG-SGA, cancer patients, retrospective study, NRS 2002

1 Introduction

Cancer can lead to metabolic and physiological changes that result in severe malnutrition (1). The prevalence of malnutrition in patients with cancer has been reported more than 20% in worldwide studies (2–4). Accurate assessment and scientifically-guided nutritional intervention are critical for cancer patients (1). However, there is no consensus on the

optimal approach to nutritional screening and assessment in this population (5). The Nutrition Risk Screening 2002 (NRS 2002) and the Patient-Generated Subjective Global Assessment (PG-SGA) are two commonly used nutritional screening tools in cancer settings, but they differ substantially in components and derivation (6, 7). The NRS 2002 was recommended by the Global Leadership Initiative on Malnutrition (GLIM) for initial screening (8). It considers disease severity, nutritional status, and age (9). In contrast, the PG-SGA was designed specifically for cancer populations. The PG-SGA consists of a patient self-assessment on weight, intake, symptoms, function, and a professional evaluation of metabolic needs, and a physical exam (10). It not only screens risk but also assesses current nutritional status and predicts clinical outcomes (11–13). Given the distinct nature of the tools, there is uncertainty regarding the necessity and added value of using the NRS 2002 together with the PG-SGA for nutritional screening in cancer patients (5). Some guidelines advocate adopting the PG-SGA as the singular approach (14, 15), while others recommend utilizing both (8). This study aimed to evaluate whether the PG-SGA alone can replace combined use with the NRS 2002 in cancer patients. Clarifying the optimal strategies for nutritional screening will enable targeted, effective interventions to improve patient nutrition and outcomes.

2 Materials and methods

2.1 Patients

This retrospective study collected data on cancer patients admitted from 2011 to 2018 at the First Affiliated Hospital of Jilin University. The NRS 2002 and the PG-SGA were performed within 48 h of admission. The NRS 2002 combines disease severity, nutritional score, and age adjustment, with a total score ≥3 indicating risk (4). The PG-SGA has patient-reported intake, symptoms, function, weight loss scores and professional-rated disease, stress, and exam scores. Total score ≥2 defined risk (16). Clinical characteristics, labs, handgrip strength (HGS), and appendicular skeletal muscle mass index (ASMI) were collected. Nutritional risk by the NRS 2002 and the PG-SGA were compared. The prognosis of non-risk groups was analyzed. No specific selection criteria were established for cancer type or demographic characteristics, except for patients who declined to participate in the study. The inclusion criteria were as follow:

1. Patients>65 y of age;
2. Pathologically diagnosed with malignant tumor; and
3. The Nutrition Risk Screening 2002 and the Patient-Generated Subjective Global Assessment completed within 48 h after admission.
4. No nutritional support treatment prior to nutritional assessment and laboratory testing.

Exclusion criteria included the following:

1. Patients who had two or more coexisting types of tumors;
2. Those who had incomplete records of necessary indexes.
3. Patients who died within 3 d after admission.

2.2 Measurements

Clinical-pathological variables include age, sex, weight, height, BMI, tumor types, TNM stages (AJCC 7th edition), and Karnofsky Performance Status (KPS). Laboratory examination results including total protein (TP), albumin, prealbumin (PAB), transferrin (TFN), C-reaction protein (CRP), neutrophil to lymphocyte ratio (NLR) and platelets to lymphocyte ratio (PLR) were collected. Anthropometric indices including hand-grip strength (HGS) and appendicular skeletal muscle mass index (ASMI) were measured by bioelectrical impedance analysis.

HGS was examined in all subjects using a Jamar hydraulic grip dynamometer (Sammons Preston Rolyan, Illinois, United States). Patients were comfortably seated in an upright position with the shoulders tucked in, neutral rotation, 90° elbow flexion, and the forearms and wrists in a neutral position. The patient gripped the dynamometer with maximum strength. The test is performed three times in a row, with a 1-min rest at the end of each set, and the maximum grip strength is recorded.

The skeletal muscle mass (SMM) was examined by the multifrequency bioelectrical impedance body composition analyzer InbodyS10 (Biospace Co., Seoul, Korea). Patients were required to empty their bladder, fast for 2 h, and rest before the measurement. Patients were asked to wear light clothes and were contacted with eight electrodes during the measurements. ASM was the sum of SMM in four limbs according to the formula of InbodyS10. The appendicular skeletal muscle mass index was calculated by ASM/height(m).

2.3 Nutritional risk assessment

The NRS 2002 and the PG-SGA nutritional assessments were completed within 48 h of patient admission.

In particular, the NRS 2002 total score consisted of the sum of three components, i.e., Disease Severity Score + Nutritional Status Hypoplasia Score + Age Score. A total score of ≥3 indicates that the patient is at nutritional risk (5). The scoring criteria are shown in Figure 1.

The PG-SGA begins with a self-assessment form (A score) completed by the patient, which includes four dimensions: body mass, feeding status, symptoms, activity, and physical function. Among them, the highest score option was selected for this score for feeding situation, and the symptoms were cumulative scores. The relationship between disease and nutritional requirements, metabolic needs and physical examination were then assessed by the medical staff. Patients' disease status (B score) and stress status (C score) were cumulative scores, and physical examination (D score) determined patients' fat, muscle, and fluid sub-item scores according to most parts of the body, and the muscle loss score was used as the final score for the physical examination items. The total A-D 4-item scores were summed, and a score of ≥2 was defined as being at nutritional risk. The scoring criteria are shown in Figure 2.

2.4 Statistical analysis

Analysis was performed using SPSS 26.0 statistical software. Data normality and chi-squareness were verified by the one-sample

Initial Screening		
Is BMI <20.5kg/m²	Yes	No
Has the patient lost weight in the last 3 months?	Yes	No
Has the patient had a reduced dietary intake in the last week?	Yes	No
Is the patient severely ill? (e.g., in intensive therapy)	Yes	No

If the answer is "Yes" to any of the questions, perform the full screening.
If the answer is "No" to all the questions, the patient is re-screened at weekly intervals.

Impaired nutritional status		Severity of disease (≈stress metabolism)	
Absent Score 0	Normal nutritional status	**Absent Score 0**	Normal nutritional requirements
Mild (Score 1)	Weight loss >5% in 3 months Or Food intake below 50–75% of normal requirement in preceding week	**Mild (Score 1)**	Hip fracture Chronic patients, in particular with acute complications: cirrhosis, COPD Chronic hemodialysis, diabetes, oncology
Moderate (Score 2)	Weight loss >5% in 2 months Or BMI 18.5 – 20.5+impaired general condition Or Food intake 25–50% of normal requirement in preceding week	**Moderate (Score 2)**	Major abdominal surgery Stroke Severe pneumonia, hematologic malignancy
Severe (Score 3)	Weight loss >5% in 1 month (≈>15% in 3 months) Or BMI <18.5+impaired general condition Or Food intake 0–25% of normal requirement in preceding week in preceding week.	**Severe (Score 3)**	Head injury Bone marrow transplantation Intensive care patients (APACHE score>10)
Score:	**+**	**Score:**	**=total score**

Calculate the total score:

1. Find score (0–3) for Impaired nutritional status (only one: choose the variable with highest score) and Severity of disease (≈stress metabolism, i.e. increase in nutritional requirements).

2. Add the two scores (→ total score)

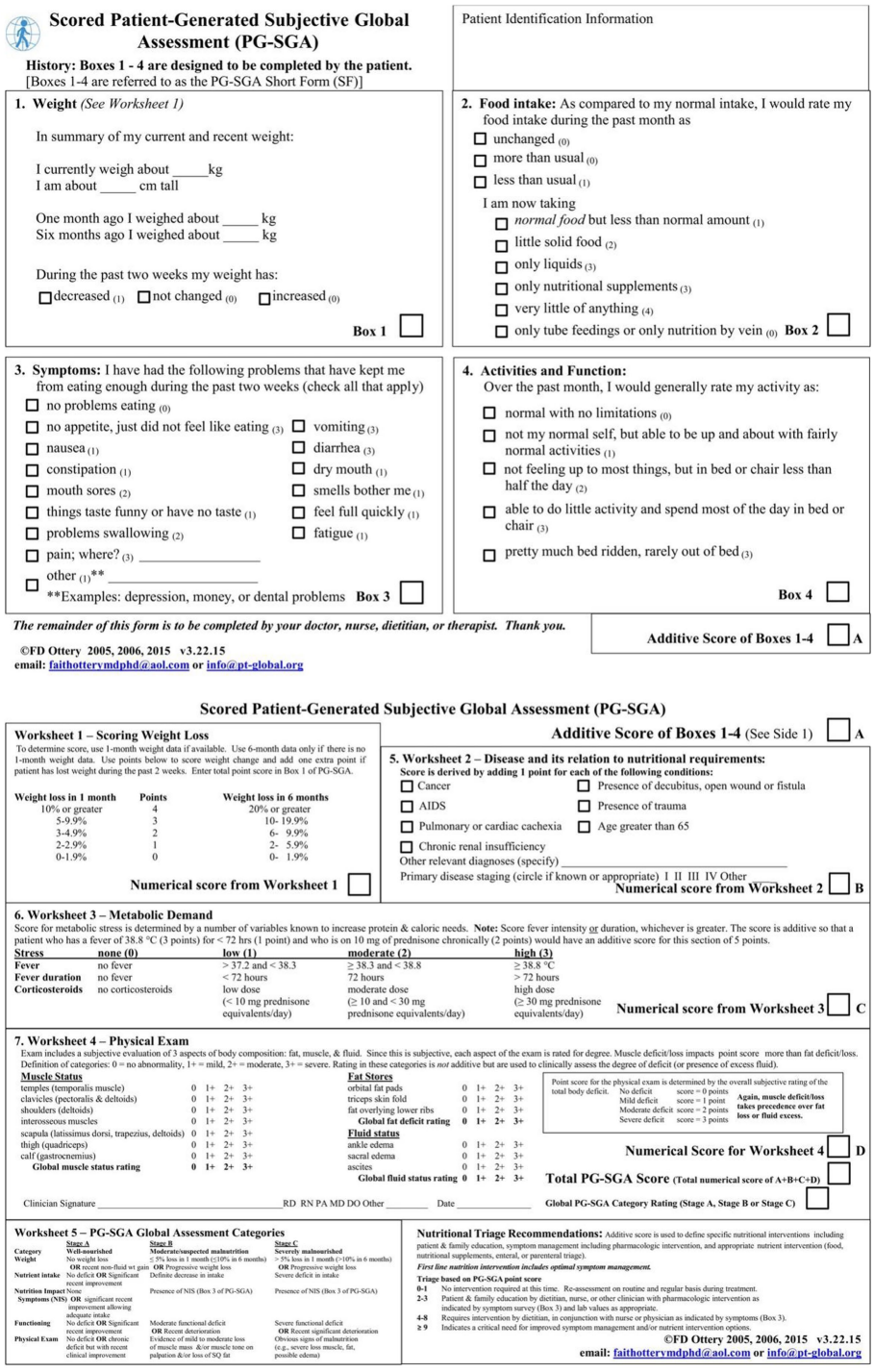
3. If age ≥70 years: add 1 to the total score to correct for frailty of elderly

4. If age-corrected total score ≥3: → the patient is nutritionally at risk and a nutritional care plan is initiated

If age-corrected total score <3: weekly re-screening of the patient.

FIGURE 1
The NRS 2002 rating form.

Kolmogorov - Smirnov test. Continuous variables that were normally distributed were expressed as mean ± standard deviation (x bar ± s), and comparisons between groups were made using independent samples *t*-tests. Continuous variables that did not follow a normal distribution after data transformation were expressed as median (interquartile range) and compared between groups using the two-sample Kolmogorov–Smirnov test. Categorical variables were expressed as percentages, and two or more groups of unordered categorical variables were tested using the χ^2 test. $p < 0.05$ was regarded as statistically significant.



Scored Patient-Generated Subjective Global Assessment (PG-SGA)

History: Boxes 1 - 4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

Patient Identification Information

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____kg
I am about _____ cm tall

One month ago I weighed about _____ kg
Six months ago I weighed about _____ kg

During the past two weeks my weight has:
☐decreased (1) ☐not changed (0) ☐increased (0)

Box 1 ☐

2. Food intake: As compared to my normal intake, I would rate my food intake during the past month as
☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)

I am now taking
☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritional supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0) **Box 2** ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply)
☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3) _____
☐ other (1)** _____
☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)
☐ fatigue (1)
Examples: depression, money, or dental problems **Box 3 ☐

4. Activities and Function:
Over the past month, I would generally rate my activity as:
☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bed ridden, rarely out of bed (3)

Box 4 ☐

The remainder of this form is to be completed by your doctor, nurse, dietitian, or therapist. Thank you.

Additive Score of Boxes 1-4 ☐ **A**

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Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Worksheet 1 – Scoring Weight Loss
To determine score, use 1-month weight data if available. Use 6-month data only if there is no 1-month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of PG-SGA.

Weight loss in 1 month	Points	Weight loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10- 19.9%
3-4.9%	2	6- 9.9%
2-2.9%	1	2- 5.9%
0-1.9%	0	0- 1.9%

Numerical score from Worksheet 1 ☐

Additive Score of Boxes 1-4 (See Side 1) ☐ **A**

5. Worksheet 2 – Disease and its relation to nutritional requirements:
Score is derived by adding 1 point for each of the following conditions:
☐ Cancer
☐ AIDS
☐ Pulmonary or cardiac cachexia
☐ Chronic renal insufficiency
☐ Presence of decubitus, open wound or fistula
☐ Presence of trauma
☐ Age greater than 65
Other relevant diagnoses (specify) _____
Primary disease staging (circle if known or appropriate) I II III IV Other ____
Numerical score from Worksheet 2 ☐ **B**

6. Worksheet 3 – Metabolic Demand
Score for metabolic stress is determined by a number of variables known to increase protein & caloric needs. **Note:** Score fever intensity or duration, whichever is greater. The score is additive so that a patient who has a fever of 38.8 °C (3 points) for < 72 hrs (1 point) and who is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	> 37.2 and < 38.3	≥ 38.3 and < 38.8	≥ 38.8 °C
Fever duration	no fever	< 72 hours	72 hours	> 72 hours
Corticosteroids	no corticosteroids	low dose (< 10 mg prednisone equivalents/day)	moderate dose (≥ 10 and < 30 mg prednisone equivalents/day)	high dose (≥ 30 mg prednisone equivalents/day)

Numerical score from Worksheet 3 ☐ **C**

7. Worksheet 4 – Physical Exam
Exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid. Since this is subjective, each aspect of the exam is rated for degree. Muscle deficit/loss impacts point score more than fat deficit/loss. Definition of categories: 0 = no abnormality, 1+ = mild, 2+ = moderate, 3+ = severe. Rating in these categories is *not* additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Muscle Status		Fat Stores	
temples (temporalis muscle)	0 1+ 2+ 3+	orbital fat pads	0 1+ 2+ 3+
clavicles (pectoralis & deltoids)	0 1+ 2+ 3+	triceps skin fold	0 1+ 2+ 3+
shoulders (deltoids)	0 1+ 2+ 3+	fat overlying lower ribs	0 1+ 2+ 3+
interosseous muscles	0 1+ 2+ 3+	**Global fat deficit rating**	**0 1+ 2+ 3+**
scapula (latissimus dorsi, trapezius, deltoids)	0 1+ 2+ 3+	**Fluid status**	
thigh (quadriceps)	0 1+ 2+ 3+	ankle edema	0 1+ 2+ 3+
calf (gastrocnemius)	0 1+ 2+ 3+	sacral edema	0 1+ 2+ 3+
Global muscle status rating	**0 1+ 2+ 3+**	ascites	0 1+ 2+ 3+
		Global fluid status rating	**0 1+ 2+ 3+**

Point score for the physical exam is determined by the overall subjective rating of the total body deficit.
No deficit score = 0 points
Mild deficit score = 1 point
Moderate deficit score = 2 points
Severe deficit score = 3 points
Again, muscle deficit/loss takes precedence over fat loss or fluid excess.

Numerical Score for Worksheet 4 ☐ **D**

Total PG-SGA Score (Total numerical score of A+B+C+D) ☐

Clinician Signature _____ RD RN PA MD DO Other _____ Date _____

Global PG-SGA Category Rating (Stage A, Stage B or Stage C) ☐

Worksheet 5 – PG-SGA Global Assessment Categories

Category	Stage A Well-nourished	Stage B Moderate/suspected malnutrition	Stage C Severely malnourished
Weight	No weight loss OR recent non-fluid wt gain	≤ 5% loss in 1 month (≥10% in 6 months) OR Progressive weight loss	> 5% loss in 1 month (>10% in 6 months) OR Progressive weight loss
Nutrient intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms (NIS)	None OR significant recent improvement allowing adequate intake	Presence of NIS (Box 3 of PG-SGA)	Presence of NIS (Box 3 of PG-SGA)
Functioning	No deficit OR Significant recent improvement	Moderate functional deficit OR Recent deterioration	Severe functional deficit OR Recent significant deterioration
Physical Exam	No deficit OR chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of muscle mass &/or muscle tone on palpation &/or loss of SQ fat	Obvious signs of malnutrition (e.g., severe loss muscle, fat, possible edema)

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage).
First line nutrition intervention includes optimal symptom management.

Triage based on PG-SGA point score
0-1 No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3 Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.
4-8 Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).
≥ 9 Indicates a critical need for improved symptom management and/or nutrient intervention options.

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FIGURE 2
The PG-SGA rating form.

3 Results

3.1 Incidence of nutritional risk

A total of 2,645 patients with cancer were included in the analysis. Two hundred and forty cases were screened with nutritional risk by the NRS 2002 (NRS ≥ 3 points) and 1993 cases were screened with nutritional risk by the PG-SGA (PG-SGA ≥ 2 points), and the incidence rates of malnutrition risk were 9.1 and 66.6%, respectively, as shown in Figure 3. The incidence rates of nutritional risk for different genders, ages, tumor types, and tumor stages screened by the two screening methods had a statistically significant ($p < 0.05$). The malnutrition incidence was higher in older patients and patients with advanced tumors, and patients with digestive tumors were more likely to be screened for nutritional risk ($p < 0.05$), as shown in Table 1.

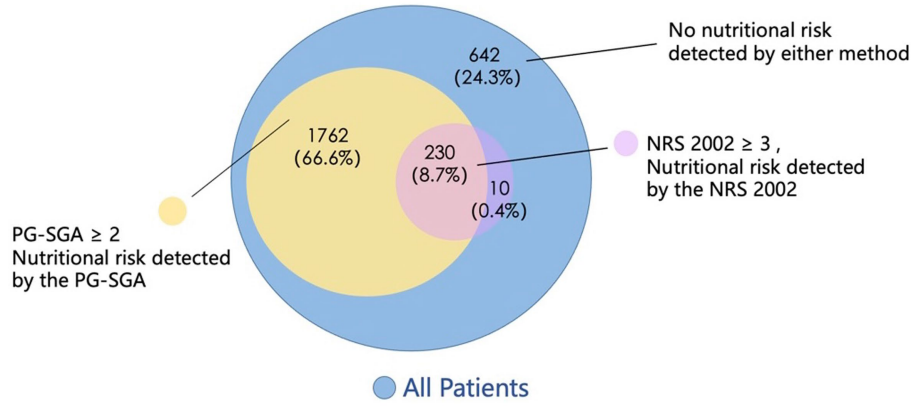

FIGURE 3
Patients' nutritional risk detected by the NRS 2002 and the PG-SGA.

TABLE 1 Comparison of the incidence of nutritional risk in different general conditions tumor patients.

Item	Number of patients	Nutritional risk screened by NRS 2002	Nutritional risk screened by PG-SGA	Chi-square value of NRS 2002	*p* value of NRS 2002	Chi-square value of PG-SGA	*p* value of PG-SGA
Gender				6.170	0.013	15.095	<0.001
Male	1,155	123 (10.7%)	913 (79.1%)				
Female	1,490	117 (7.9%)	1,080 (72.5%)				
Age							
<65	2,120	172 (8.1%)	1,469 (69.3%)	11.944	0.001	209.345	<0.001
>65	525	68 (12.9%)	524 (99.8%)				
Tumor type				59.100	<0.001	110.227	<0.001
Lung cancer	828	74 (8.9%)	618 (74.6%)				
Cancer of the digestive system	687	101 (14.7%)	605 (88.1%)				
Hematological malignancy	290	22 (7.6%)	200 (69.0%)				
Breast cancer	624	19 (3.0%)	400 (64.1%)				
Gynecological cancer	157	14 (8.9%)	123 (78.3%)				
Others	59	10 (16.9%)	47 (79.7%)				
Tumor staging				15.752	0.001	9.396	0.024
I	455	23 (5.1%)	326 (71.6%)				
II	580	51 (8.8%)	433 (74.7)				
III	659	79 (12.0%)	523 (79.4%)				
IV	951	87 (9.1%)	711 (74.8%)				

3.2 Comparison of the NRS-2002 and the PG-SGA screening results

Nutrition-related indicators of patients screened for malnutrition risk by both the NRS-2002 and the PG-SGA and those screened for malnutrition risk by the NRS-2002 were analyzed, and there were no statistically significant differences between the two populations in terms of grip strength, albumin, and muscle index, as shown in Table 2.

3.3 Prognosis of patients screened for malnutrition by the NRS-2002 vs. the PG-SGA

Prognostic analyses of those not screened for nutritional risk by the NRS-2002 and those not screened for nutritional risk by the PG-SGA were performed, and the results of the survival analyses showed that the prognosis of those not screened for nutritional risk

TABLE 2 Basic clinical information for all the NRS 2002 positive patients stratified by the PG-SGA positive.

Factors	PG-SGA, NRS 2002 positive ($N = 230$)	NRS 2002 positive ($N = 240$)	p value
KPS	87.63	88.00	0.748
TP (g/L)	64.58	64.65	0.901
Albumin (g/L)	36.82	36.95	0.993
PAB (g/L)	0.185	0.188	0.838
TFN (g/L)	2.22	2.24	0.811
HGS (kg)	22.44	22.73	0.791
ASMI (kg/m^2)	5.98	5.98	0.837

KPS, karnofsky performance status; TP, total protein; PAB, prealbumin; TFN, transferrin; HGS, hand-grip strength; ASMI, appendicular skeletal muscle mass index.

by the PG-SGA was better than that of those not screened for nutritional risk by the NRS 2002 ($p < 0.05$), as shown in Figure 4.

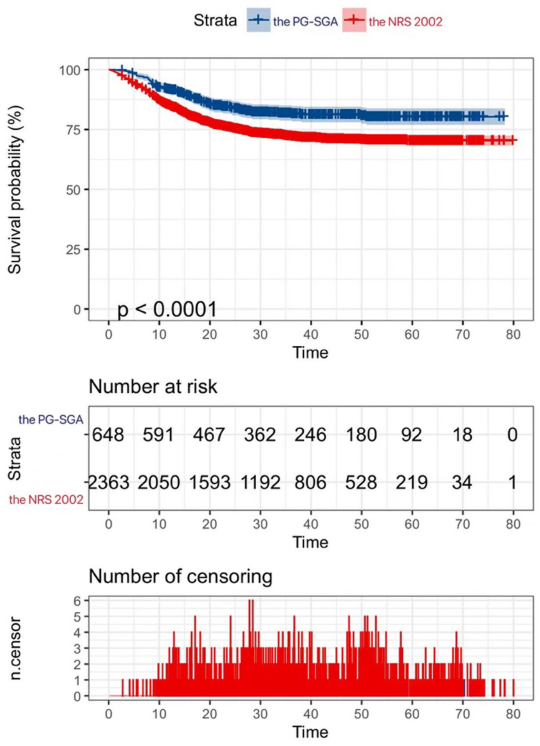

FIGURE 4
|Kaplan–Meier curves for patients without nutritional risk.

4 Discussion

Many patients with cancer are at risk for malnutrition and nutritional assessment is a vital aspect of cancer care (17). While nutrition risk screening tools contribute to the early recognition of malnutrition, nutritional screening and assessment are established in many oncological clinical settings. The NRS 2002 is recommended as the screening tool before malnutrition diagnosis according to the global leadership initiative on malnutrition (5), while the PG-SGA is recommended in various national guidelines for nutrition in patients with cancer (15). Studies showed that the PG-SGA is not only an assessment that identifies existing malnutrition, but it can also be used as a screening instrument for nutritional risk or deficit (10).

The PG-SGA identified more patients at nutritional risk than the NRS 2002 in this study. Among patients not classified as high risk by the NRS 2002, those additionally identified as malnourished by the PG-SGA had poorer survival. The PG-SGA non-risk group had a better prognosis than the NRS 2002 non-risk, suggesting the NRS 2002 may miss patients with risk. Our study indicates the PG-SGA screens cancer patients more comprehensively for nutritional risk than the NRS 2002.

4.1 Key findings and significance

The much higher prevalence of nutritional risk by the PG-SGA implies it is more sensitive than the NRS 2002 in this population (12, 18). This aligns with prior studies demonstrating higher detection rates of malnutrition by the PG-SGA vs. other single-item screening methods (19). The PG-SGA's detailed capture of reduced intake and aggravated cancer symptoms underpins its greater sensitivity over the NRS 2002's reliance on primarily weight loss and disease severity (20, 21). Though the NRS 2002 is recommended for initial screening, it appears insufficient on its own based on the poorer outcomes of patients not identified as at-risk. This finding indicates sole use of the NRS 2002 risks overlooking some patients who need and could benefit from early nutritional intervention (6, 22). Using the PG-SGA additionally would allow more complete detection of patients requiring intervention. This highlights the necessity of multi-modal nutritional screening in cancer patients to avoid overlooking opportunities for important nutritional support (7, 15).

This study confirms the high sensitivity of the PG-SGA as a nutritional risk screening tool optimized specifically for cancer patients. Its cancer-specific derivations such as patient-reported symptom impact likely underlie its superior prognostic utility over the generic NRS 2002, supporting its preferential use for prospectively assessing malnutrition risk in this population (10, 14). Thorough nutritional screening is crucial for providing appropriate supportive care to improve patient nutrition and outcomes.

4.2 Possible reasons for differences in screening tools

The NRS 2002 was designed for hospital inpatients generally, while the PG-SGA was optimized specifically for cancer populations. The PG-SGA's cancer-specific design underlies its superior sensitivity in detecting nutritional risk over the more generic NRS 2002. The PG-SGA captures extensive information about reduced oral intake and symptom impacts like anorexia, nausea, vomiting, and dysphagia that are highly prevalent in cancer patients but not addressed in the NRS 2002 (14, 15). The inclusion of patient self-assessment also enhances its sensitivity, which provides unique subjective data on changes in weight, food intake, and functional capacity that clinicians cannot observe as accurately (10). These key components enhance early identification of malnutrition before severe manifestations appear. Furthermore, the PG-SGA categorizes risk level of malnutrition severity rather than just presence/absence (23). This differentiation allows nutrition interventions to be personalized and

scaled based on the grade of malnutrition. The multidimensional nature of the PG-SGA makes it better suited to the complex etiology of cancer cachexia compared to the NRS 2002.

4.3 Limitations and future research

As a single-center retrospective study, the results may not generalize to other cancer populations. Additional studies should validate findings in other geographical and ethnic groups (24). Future research could also compare the PG-SGA to other cancer-specific tools like the Malnutrition Screening Tool (MST) to determine optimal approaches for different oncology settings (25). Incorporating nutritional biomarkers may provide further objective insight into differences between patients classified as non-risk by each tool (26). Most importantly, future research should investigate the impacts of PG-SGA screening on clinically meaningful outcomes like treatment response, quality of life, and survival with nutritional interventions (27). Cost-effectiveness analyses will also inform implementation. Ultimately, determining optimal nutritional assessment strategies will require investigations into the impacts on patient-important outcomes with nutritional interventions through high-quality randomized controlled trials (28).

5 Conclusion

In cancer patients, the PG-SGA provides more comprehensive nutritional risk detection than the NRS 2002, with prognostic utility. Relying solely on the NRS 2002 risks overlooking at-risk patients who may benefit from nutrition support. The high sensitivity of the PG-SGA underscores its value for identifying malnourishment requiring intervention in cancer populations. Clinicians should be aware that patients classified as non-risk by the NRS 2002 may still be at nutrition-related risk detectable by the in-depth PG-SGA. Implementing the PG-SGA's cancer-specific approach is vital for optimal nutritional risk screening and assessment in oncology settings. The NRS 2002 is not necessary for patients who are to be assessed with the PG-SGA.

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 humans were approved by First affiliated hospital of Jilin University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XC: Formal analysis, Investigation, Methodology, Writing – original draft. XL: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – review & editing. WJ: Conceptualization, Data curation, Investigation, Writing – review & editing. YZ: Data curation, Formal analysis, Methodology, Writing – review & editing. YH: Data curation, Formal analysis, Methodology, Writing – review & editing. YL: Data curation, Investigation, Software, Writing – review & editing. QL: Data curation, Formal analysis, Software, Writing – review & editing. HS: Project administration, Supervision, Writing – review & editing. JC: Project administration, Resources, Supervision, Writing – review & editing.

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Association between oxidative stress exposure and colorectal cancer risk in 98,395 participants: results from a prospective study

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Background: The intricate role of oxidative stress (OS) in colorectal cancer (CRC) initiation is underscored by an imbalance between pro-oxidants and antioxidants. Utilizing the Oxidative Balance Score (OBS) as a metric, this study aims to investigate the association between OS exposure and CRC risk, while also examining potential sex-specific differences in a large U.S. cohort.

Methods: The study included 98,395 adults from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. To construct the OBS, 14 dietary and lifestyle factors intricately associated with oxidative stress were quantified. A higher OBS value indicated a more favorable oxidative balance pattern or diminished OS exposure. Due to sex-specific differences in OBS, associations were evaluated separately for men and women based on Cox regression analysis. Subgroup analyses were conducted to elucidate potential modifiers.

Results: During 867,963.4 person-years of follow-up, 1,054 CRCs occurred. The mean (SD) age and OBS were 65.52 (5.73) years and 14.09 (3.95) points, respectively. In the fully adjusted Cox model, we observed an inverse association between OBS and CRC incidence in women (HR_{Q5vsQ1}: 0.72; 95% CI: 0.52, 0.99; P for trend = 0.018) but not men. Subgroup analyses revealed the inverse association was more pronounced among women without versus with a family history of CRC ($HR_{Q5\ vsQ1}$: 0.66, 95% CI: 0.47–0.93; P for trend = 0.001; P for interaction = 0.001). The results remained robust after several sensitivity analyses.

Conclusion: Higher OBS was associated with lower CRC risk in women but not men; this inverse association was stronger among women without a family history of CRC. These findings suggest exposure to OS may confer sex-specific CRC risk effects, especially for women without a family history of CRC.

KEYWORDS

oxidative stress exposure, colorectal cancer, epidemiology, sex-specific cohort studies, oxidative balance score

Introduction

Colorectal cancer (CRC) is a multifaceted disease that ranks third in new cancer cases yet second in cancer mortality. In 2020, over 1.9 million incident CRCs and 935,000 deaths were estimated globally (1). The majority of CRC malignancies arise sporadically, with modifiable lifestyle factors including obesity, physical inactivity, poor diet, alcohol use, and smoking constituting the primary environmental risk factors (2). Numerous investigations have demonstrated that dietary and lifestyle factors play a significant role in the development and progression of CRC, underscoring opportunities for prevention through diet or lifestyle modifications (3, 4). Research into diet and health has shown that nutrients rarely operate in isolation; rather, the combined effects of various dietary and lifestyle factors on CRC risk may be greater than any single element considered individually (5, 6).

Oxidative stress (OS), defined as an imbalance between pro-oxidants and antioxidants favoring the former, is the primary cause of reactive oxygen species and is hypothesized to be involved in colorectal carcinogenesis (7, 8). The oxidative balance score (OBS) allows assessment of an individual's antioxidant status by accounting for both pro-oxidant and antioxidant components of dietary and lifestyle factors (9–11). As a key metric of cellular metabolism, OBS has been linked to several major human diseases related to health, including cardiovascular disease (9), diabetes (12, 13), and cancer (14). However, current evidence regarding the association between OBS and CRC risk remains inconclusive, with conflicting findings reported. One previous study in 80,063 participants found an increased risk of CRC associated with higher oxidative stress levels (15), while another study using the Health Professionals Follow-up Cohort showed no clear association between overall antioxidant capacity and CRC risk (16). Notably, the components comprising OBS differ between males and females; however, previous investigations have not considered potential sex differences (15). To provide additional epidemiological evidence clarifying these controversial associations while accounting for potential sex disparities, we performed a retrospective analysis stratified by sex in a large U.S. population.

Materials and methods

Study design and cohort

The present analysis utilized data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. The PLCO trial enrolled 154,887 participants aged 55–74 years at 10 U.S. centers from 1993 to 2001. The trial primarily aimed to evaluate whether screening could reduce mortality for the aforementioned cancers (17). Questionnaires completed by participants included a baseline questionnaire (BQ) capturing demographics and medical history, a dietary history questionnaire (DHQ) using a 137-item food frequency questionnaire (FFQ) to assess dietary intake, and a supplemental questionnaire (SQX). Prior studies have validated the FFQ as a nutritional evaluation tool (18, 19). The PLCO trial was approved by institutional review boards at National Cancer Institute (NCI) and participating centers, and all participants provided informed consent. Specific trial details are published elsewhere (17).

Our present study aimed to examine the association between OS exposure and CRC risk based on PLCO trial. OS exposure was assessed using the OBS, composed of 14 dietary and lifestyle factors closely related to OS (9). The outcome was incidence of CRC. Follow-up time was defined as the interval between completion of the dietary questionnaire and the date of CRC diagnosis, death, loss to follow-up, or end of follow-up (i.e., December 31, 2009) (**Figure 1**). Exclusion criteria eliminated the following participants: (I) unreturned BQ (n = 4,918); (II) invalid DHQ, defined as ≥ 8 missing responses, extreme caloric intake (gender-specific 1st and 99th percentiles), and DHQ completion date preceding death (n = 38,463); (III) personal cancer history before DHQ (n = 9,683); (IV) missing smoking status (n = 20); (V) outcome event between randomization and DHQ completion (n = 114); and (VI) potentially unreliable caloric intake (<800 or > 4,200 kcal/day for males; < 600 or > 3,500 kcal/day for females) (20) (n = 3,294). After applying exclusions, 98,395 participants remained eligible (**Figure 2**).

Assessment of OBS

We calculated the OBS based on the computational method proposed by Lakkur et al. (9) in 2015. The OBS comprised 14 components selected based on their known associations with OS. In brief, we categorized continuous dietary factors related to antioxidant exposure according to sex-specific tertile cutpoints. Individuals with lower antioxidant exposure (first tertile) for particular dietary antioxidants (e.g., vitamin C, α-carotene, β–carotene, β-Cryptoxanthin, vitamin E, Lutein, Lycopene, selenium) received 0 points, while those with moderate (second tertile) or higher (third tertile) exposure were assigned 1 or 2 points, respectively. Similarly, we classified continuous dietary factors associated with pro-oxidant exposure (polyunsaturated fats and iron) into tertiles, awarding 2 points for low exposure, 1 point for moderate exposure, and 0 points for high exposure. Smoking status was coded as 2 points for never smokers, 1 point for former smokers, and 0 points for current smokers. For aspirin and other NSAIDs use, non-regular use received 0 points, missing responses received 1 point, and regular use received 2 points. Due to sex differences in alcohol intake, we used separate cutoffs to categorize alcohol intake for men versus women. For men, alcohol intake > 14 drinks/week was classified as heavy drinking (0 points), 1–14 drinks/week as moderate drinking (1 point), and no alcohol intake (2 points). For women, alcohol intake > 7 drinks/week was considered heavy drinking (0 points), 1–7 drinks/week as moderate drinking (1 point), and no alcohol intake (2 points). Summing the points for each component produced the total OBS (range 0–28), which we divided into quintiles. A higher OBS indicates a potentially favorable balance between pro-oxidants

Abbreviations: BMI, body mass index; BQ, baseline questionnaire; CIs, confidence intervals; CRC, colorectal cancer; DHQ, dietary history questionnaire; FFQ, food frequency questionnaire; HRs, hazard ratios; ICD-O, International Classification of Diseases for Oncology; NCI, national cancer institute; OBS, oxidative balance score; OS, oxidative stress; PLCO, prostate lung colorectal and ovarian; SD, standard deviation; SQX, supplemental questionnaire.

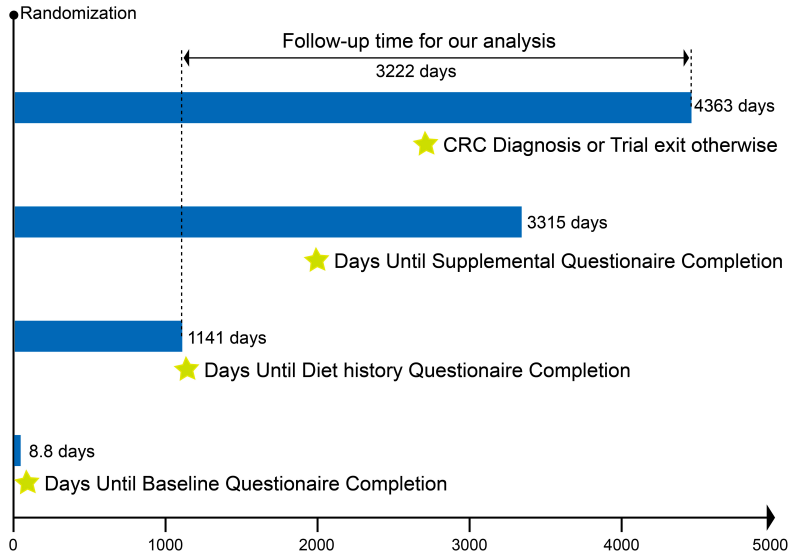

FIGURE 1
Timeline and follow-up scheme of the study. The mean time from randomization in the PLCO trial to completion of the baseline questionnaire, diet history questionnaire, and supplementary questionnaire was 8.8 days, 1,141 days, and 3,315 days, respectively. The follow-up period for our study was defined as the interval between completion of the diet history questionnaire and the date of CRC diagnosis, death, loss to follow-up, or end of follow-up, whichever came first. The mean follow-up time for our study was 3,222 days.

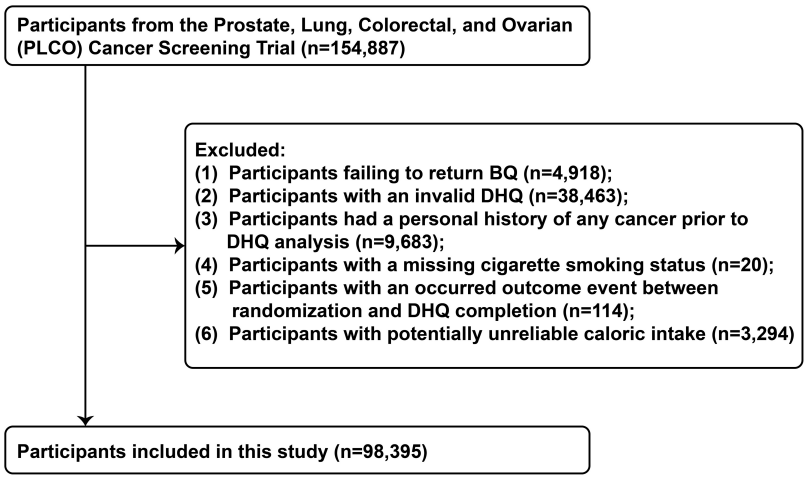

FIGURE 2
The flow chart of identifying eligible participants. PLCO, Prostate, Lung, Colorectal, and Ovarian; BQ, baseline questionnaire; DHQ, diet history questionnaire.

and antioxidants or lower OS exposure. Supplementary Table 1 summarizes the components comprising the OBS and displays the detailed scoring pattern.

Identification of CRC cases

In the PLCO trial, all participants were sent an annual health update questionnaire asking them to disclose any new cancer diagnoses, including the cancer site and diagnosis date. Research staff followed-up via phone or email with non-respondents to complete the questionnaire. Separately, death certificates and reports from family members were reviewed to capture additional cancer cases. For self-reported CRC cases, diagnostic verification involved retrieving the medical records to confirm the diagnosis and collect relevant clinical details about CRC. CRC cases were defined using the International Classification of Diseases for Oncology (ICD-O) codes for colon cancer (C18) and rectal cancer (C19–C20).

Assessment of covariates

Participant demographics, health behaviors, and medical history were obtained at baseline using self-administered questionnaires (including BQ, DHQ and SQX). Demographic variables included race and education level. Lifestyle factors encompassed smoking history and physical activity. Disease

history covered family history of CRC, personal history of diabetes, colorectal polyps, colon-related comorbidities, diverticulitis/diverticulosis, and colonoscopy screening. Age at DHQ completion, drinking status and food energy from diet were assessed with the DHQ. Physical activity level was collected through the SQX and defined as the total minutes per week of self-reported moderate to vigorous physical activity. Body mass index (BMI) calculated as weight in kg divided by height squared in m^2.

Statistical analysis

For categorical and continuous covariates missing < 5% of data, modal and median imputation was utilized, respectively. Due to a large proportion (up to 25.3%) of missing data, the physical activity level covariate was imputed using multiple imputation methods (21). Further details regarding the imputed datasets are provided in **Supplementary Table 2**. All statistical analyses were conducted using the imputed datasets.

We utilized Cox proportional hazards regression to evaluate the sex-specific association between the OBS and CRC risk, with follow-up time as the time metric. To test for linear trends, participants were assigned the median OBS value of their quintile, treated as a continuous predictor with the lowest quintile as reference. In the Cox regression analyses, two multivariable Cox models were constructed based on potential confounding variables. Model 1 adjusted for age and race. Model 2 further adjusted for education level, BMI, smoking pack-years, alcohol intake, food energy intake, physical activity level, family history of CRC, history of diabetes, colorectal polyps, colon-related comorbidities, diverticulitis/diverticulosis, and colonoscopy screening.

We conducted stratified analyses across categories of age, BMI, diabetes history, family history of CRC, smoking pack-years, alcohol use, physical activity level, energy intake, and colonoscopy screening history. For continuous subgroup variables, subgroups were defined by dichotomizing at the median based on clinical relevance. Interaction tests were conducted by incorporating OBS-by-subgroup product terms in multivariate Cox models, comparing models with and without the interaction terms.

We performed several sensitivity analyses to evaluate the robustness of the findings: (1) participants with a family history of CRC were excluded, as they may be predisposed to develop CRC. (2) participants with a history of diabetes were excluded, as they may have been required to follow stricter dietary control (22). (3) CRC cases diagnosed within the first 2 and 4 years of follow-up were excluded to minimize reverse causation.

All statistical analyses were performed using R software version 4.3.1. A two-tailed *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The detailed baseline characteristics of the study population across OBS quintiles are presented in **Table 1**. Among the 98,395 included participants, the mean (standard deviation) OBS was 14.09 (3.95). Participants were categorized into quintiles based on OBS [Quintile 1 (OBS ≤ 10), *n* = 20,125; Quintile 2 (OBS 11–13), *n* = 23,620; Quintile 3 (OBS 14–15), *n* = 17,265; Quintile 4 (OBS 16–18), *n* = 23,042; Quintile 5 (OBS > 18), *n* = 14,343]. Higher quintiles indicated adherence to an antioxidant pattern or lower OS exposure. Compared to the lowest quintile (Quintile 1), those in the highest quintile (Quintile 5) were more likely to be female, have higher educational level, undergo colonoscopy screening, and have greater total energy intake. In the gender baseline characteristics (**Supplementary Table 3**), compared to males, females had lower BMI, smoking history and intensity, alcohol drinking history and intensity, aspirin use, and higher intakes of dietary antioxidants (e.g., vitamin C, α-carotene, β–carotene, β-cryptoxanthin, vitamin E, lutein). Females also had lower intakes of pro-oxidant dietary components (polyunsaturated fats and iron). Overall, females had higher OBS scores than males.

Association between OBS and CRC incidence

Over a mean (SD) follow-up time of 8.82 (1.95) years totaling 867,963.4 person-years, 1054 CRC cases (571 female and 483 male) were documented among 98,395 participants (51,226 women and 47,169 men), reflecting an overall CRC incidence rate of 12 cases per 10,000 person-years, with incidence rates of 10.6 and 13.9 cases per 10,000 person-years in women and men, respectively. Compared to women, the CRC incidence rate in men was 31.1% higher (95% CI: 30.1% to 32.2%). In this study, we identified an inverse association between OBS and CRC incidence in women but not men. In women, the unadjusted model showed a lower CRC risk for those in the highest OBS quintile compared to the lowest quintile ($HR_{Q5vs.Q1}$: 0.66; 95% CI: 0.49, 0.89; P for trend = 0.001) (**Table 2**). This inverse association persisted after full adjustment for potential confounders (HR_{Q5vsQ1}: 0.72; 95% CI: 0.52, 0.99; P for trend = 0.018) (**Table 2**). However, no significant association was observed in men in either the crude or fully adjusted models (**Table 2**).

Additional analyses

As shown in **Table 3**, subgroup analyses revealed no modification by age, BMI, history of diabetes, pack-years of smoking, drinking status, physical activity level, food energy from diet or history of colonoscopy screening on the OBS-CRC risk association in women (all P for interaction > 0.05). Interestingly, the inverse OBS-CRC risk association was more pronounced among women without a family history of CRC (HR_{Q5vsQ1}: 0.66, 95% CI: 0.47–0.93; P for trend = 0.001), with a significant interaction by family history of CRC (P for interaction = 0.001). In sensitivity analyses excluding those with family history of CRC, history of diabetes, or early follow-up, the inverse OBS-CRC risk association persisted among women (**Table 4**).

Discussion

In this study, higher OBS were associated with a lower risk of CRC in women. However, no significant association was observed

TABLE 1 Baseline characteristics of study population according to quintiles of OBS.

Characteristics	Overall	Quintiles of OBS					*P*-value
		Quintile 1(≤ 10)	Quintile 2(11–13)	Quintile 3(14–15)	Quintile 4(16–18)	Quintile 5(> 18)	
Number of participants	98395	20125	23620	17265	23042	14343	
OBS	14.09 ± 3.95	8.54 ± 1.41	12.04 ± 0.81	14.50 ± 0.50	16.94 ± 0.81	20.15 ± 1.24	< 0.001
Age	65.52 ± 5.73	65.17 ± 5.70	65.45 ± 5.72	65.51 ± 5.73	65.67 ± 5.71	65.88 ± 5.78	< 0.001
Sex							< 0.001
Male	47169 (47.94%)	10754 (53.44%)	11730 (49.66%)	8125 (47.06%)	10453 (45.36%)	6107 (42.58%)	
Female	51226 (52.06%)	9371 (46.56%)	11890 (50.34%)	9140 (52.94%)	12589 (54.64%)	8236 (57.42%)	
Race							0.139
White	91159 (92.65%)	18656 (92.70%)	21948 (92.92%)	16015 (92.76%)	21302 (92.45%)	13238 (92.30%)	
Non-white	7236 (7.35%)	1469 (7.30%)	1672 (7.08%)	1250 (7.24%)	1740 (7.55%)	1105 (7.70%)	
Education level							< 0.001
College below	62550 (63.57%)	14191 (70.51%)	15505 (65.64%)	10794 (62.52%)	13781 (59.81%)	8279 (57.72%)	
College graduate	17348 (17.63%)	3188 (15.84%)	4130 (17.49%)	3136 (18.16%)	4241 (18.41%)	2653 (18.50%)	
Post-graduate	18497 (18.80%)	2746 (13.64%)	3985 (16.87%)	3335 (19.32%)	5020 (21.79%)	3411 (23.78%)	
Body mass index (kg/m^2)	27.20 ± 4.79	27.11 ± 4.59	27.25 ± 4.76	27.18 ± 4.78	27.22 ± 4.85	27.25 ± 5.01	0.021
Smoking Pack Years	17.66 ± 26.49	25.39 ± 29.37	19.09 ± 27.11	16.58 ± 25.34	14.59 ± 24.68	10.76 ± 22.18	< 0.001
Drink Alcohol							< 0.001
No	26659 (27.09%)	4417 (21.95%)	6091 (25.79%)	4482 (25.96%)	6654 (28.88%)	5015 (34.96%)	
Yes	71736 (72.91%)	15708 (78.05%)	17529 (74.21%)	12783 (74.04%)	16388 (71.12%)	9328 (65.04%)	
Family history of CRC							0.131
No	85990 (87.39%)	17509 (87.00%)	20641 (87.39%)	15108 (87.51%)	20230 (87.80%)	12502 (87.16%)	
Yes/Possibly	12405 (12.61%)	2616 (13.00%)	2979 (12.61%)	2157 (12.49%)	2812 (12.20%)	1841 (12.84%)	
History of diabetes							< 0.001
No	91932 (93.43%)	19043 (94.62%)	22073 (93.45%)	16148 (93.53%)	21393 (92.84%)	13275 (92.55%)	
Yes	6463 (6.57%)	1082 (5.38%)	1547 (6.55%)	1117 (6.47%)	1649 (7.16%)	1068 (7.45%)	
History of Colonoscopy Screening							< 0.001
No	51878 (54.46%)	11530 (59.16%)	12777 (56.10%)	8872 (53.09%)	11675 (52.24%)	7024 (50.38%)	
Yes	43388 (45.54%)	7959 (40.84%)	9998 (43.90%)	7840 (46.91%)	10674 (47.76%)	6917 (49.62%)	
Food Energy from Diet (kcal/day)	1728.52 ± 657.95	1482.70 ± 578.84	1610.12 ± 615.74	1728.54 ± 635.40	1884.21 ± 668.31	2018.29 ± 664.17	< 0.001
OBS Components							
Total vitamin C (mg/day)	377.99 ± 387.72	152.96 ± 200.86	285.29 ± 304.72	386.72 ± 363.76	482.05 ± 402.66	668.71 ± 463.52	< 0.001
α-Carotene (mcg/day)	845.57 ± 913.09	308.05 ± 241.52	531.45 ± 500.30	790.31 ± 728.45	1169.91 ± 1009.93	1662.56 ± 1241.07	< 0.001
Total β–carotene (mcg/day)	4673.45 ± 3850.87	1978.51 ± 1092.36	3163.31 ± 2048.18	4470.62 ± 2862.10	6243.27 ± 3850.30	8663.87 ± 5059.26	< 0.001
β-Cryptoxanthin (g/day)	172.16 ± 138.43	83.76 ± 57.99	127.74 ± 88.40	167.46 ± 112.45	219.87 ± 142.50	298.39 ± 179.47	< 0.001
Total vitamin E (mg/day)	153.00 ± 176.08	66.32 ± 122.41	124.28 ± 161.28	160.94 ± 176.40	187.65 ± 181.64	256.73 ± 183.62	< 0.001
Lutein (mcg/day)	2633.30 ± 2593.67	1207.82 ± 729.95	1817.68 ± 1318.22	2500.71 ± 2002.23	3510.53 ± 2921.49	4726.89 ± 3796.97	< 0.001
Lycopene (mcg/day)	6447.77 ± 6825.38	3687.23 ± 2552.38	4933.19 ± 3762.14	6188.45 ± 5073.10	8038.54 ± 8457.18	10571.94 ± 10278.19	< 0.001
Total selenium (mcg/day)	89.38 ± 39.64	71.62 ± 31.23	81.17 ± 34.88	89.66 ± 37.92	99.65 ± 40.94	110.98 ± 42.40	< 0.001
PUFA (g/day)	14.05 ± 7.15	12.21 ± 6.18	13.28 ± 6.74	14.17 ± 7.00	15.33 ± 7.60	15.72 ± 7.72	< 0.001
Total iron (mg/day)	23.74 ± 11.40	18.36 ± 10.17	21.74 ± 10.44	24.31 ± 10.64	26.90 ± 11.10	28.84 ± 11.97	< 0.001

(Continued)

TABLE 1 (Continued)

Characteristics	Overall	Quintiles of OBS					*P*-value
		Quintile 1(≤ 10)	Quintile 2(11–13)	Quintile 3(14–15)	Quintile 4(16–18)	Quintile 5(> 18)	
Smoking history							< 0.001
never smoker	47196 (47.97%)	6577 (32.68%)	10430 (44.16%)	8465 (49.03%)	12435 (53.97%)	9289 (64.76%)	
current smoker	8987 (9.13%)	3883 (19.29%)	2354 (9.97%)	1241 (7.19%)	1175 (5.10%)	334 (2.33%)	
former smoker	42212 (42.90%)	9665 (48.02%)	10836 (45.88%)	7559 (43.78%)	9432 (40.93%)	4720 (32.91%)	
Aspirin							< 0.001
never	51787 (52.63%)	14638 (72.74%)	13387 (56.68%)	9140 (52.94%)	10605 (46.02%)	4017 (28.01%)	
regular user	46190 (46.94%)	5392 (26.79%)	10120 (42.85%)	8050 (46.63%)	12350 (53.60%)	10278 (71.66%)	
missing	418 (0.42%)	95 (0.47%)	113 (0.48%)	75 (0.43%)	87 (0.38%)	48 (0.33%)	
Other NSAIDs							< 0.001
never	68070 (69.18%)	15212 (75.59%)	16832 (71.26%)	12081 (69.97%)	15681 (68.05%)	8264 (57.62%)	
regular user	3922 (3.99%)	332 (1.65%)	727 (3.08%)	668 (3.87%)	1042 (4.52%)	1153 (8.04%)	
missing	26403 (26.83%)	4581 (22.76%)	6061 (25.66%)	4516 (26.16%)	6319 (27.42%)	4926 (34.34%)	
Alcohol (drinks/week)	0.65 ± 1.41	0.93 ± 1.85	0.70 ± 1.49	0.64 ± 1.32	0.55 ± 1.19	0.35 ± 0.83	< 0.001

Values are means (standard deviation) for continuous variables and percentages for categorical variables. Group comparisons of continuous variables utilized analysis of variance (ANOVA). Categorical variables employed chi-squared tests to assess differences across quartiles.

TABLE 2 Association of OBS with the risk of colorectal cancer by sex in the PLCO cohort[a].

Quintiles of OBS score	No. of Participants	No. of Cases	Person-years	Hazard ratio (95% confidence interval)		
				Unadjusted	Model 1 [b]	Model 2 [c]
Male						
Quintile 1 (≤ 10)	10219	131	88415.35	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quintile 2 (11–13)	11389	125	99258.22	0.85(0.66,1.09)	0.84(0.65,1.07)	0.89(0.69,1.13)
Quintile 3 (14–15)	8117	100	71010.12	0.95(0.73,1.23)	0.93(0.72,1.21)	1.03(0.79,1.34)
Quintile 4 (16–18)	10807	127	94659.44	0.90(0.71,1.16)	0.88(0.69,1.12)	1.01(0.78,1.31)
Quintile 5 (> 18)	6637	88	58028.89	1.02(0.78,1.34)	0.98(0.74,1.28)	1.20(0.89,1.61)
P for trend				0.863	0.865	0.199
Female						
Quintile 1 (≤ 11)	13833	155	122621.94	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quintile 2 (12–13)	8307	92	73672.52	0.99(0.76,1.28)	0.97(0.75,1.26)	1.01(0.78,1.31)
Quintile 3 (14–15)	9057	71	80816.36	0.70(0.53,0.92)	0.68(0.51,0.90)	0.72(0.54,0.96)
Quintile 4 (16–18)	12118	106	108488.79	0.77(0.61,0.99)	0.76(0.59,0.97)	0.83(0.64,1.08)
Quintile 5 (> 18)	7911	59	70991.78	0.66(0.49,0.89)	0.64(0.47,0.86)	0.72(0.52,0.99)
P for trend				**0.001**	**< 0.001**	**0.018**

[a]Hazard ratio was calculated using Cox proportional hazard regression models, *P*-values were calculated from significance testing for the underlying linear trend in Cox models.
[b]Adjusted for age (years) and race (white, non-white).
[c]Adjusted for model 1 plus educational level (college below, college graduate, post-graduate), body mass index (kg/m^2), family history of colorectal cancer (no, yes/possibly), pack-years (continuous), drinker (no, yes), history of diabetes (no, yes), physical activity (min/week), history of colon screen (no, yes), history of colorectal polyps (no, yes), history of colon related co-morbidity (no, yes), history of diverticulitis or diverticulosis (no, yes) and food energy from diet (kcal/day).

in men. Subgroup analyses showed that the inverse association was stronger in women with no family history compared to those with a family history of CRC. The inverse association remained robust in sensitivity analyses excluding participants with potential confounding characteristics, lending strength to the conclusions.

CRC has been demonstrated to be closely related to dietary and lifestyle factors. For example, adherence to the Mediterranean diet (MD) and Dietary Approaches to Stop Hypertension (DASH) dietary patterns have been associated with lower incidence of colorectal cancer in several studies (23, 24). The OBS constructed in this study incorporated 14 dietary and lifestyle indicators with established links to OS exposures. While the OBS has been linked with several major chronic human diseases related to health, including cardiovascular disease (9), diabetes (12,

TABLE 3 Subgroup analyses on the association of OBS with the risk of colorectal cancer in females[a].

Subgroup variable	No. of cases	Person-years	Hazard Ratio (95% Confidence Interval) by OBS [b]					P_{trend}	$P_{interaction}$
			Quintile 1 (≤ 11)	Quintile 2 (12–13)	Quintile 3 (14–15)	Quintile 4 (16–18)	Quintile 5 (> 18)		
Age (years)									0.089
≤ 65	190	246467.46	1.00(reference)	1.04 (0.71, 1.54)	0.55(0.34, 0.89)	0.52(0.33, 0.82)	0.65(0.39, 1.07)	0.004	
> 65	293	210123.93	1.00(reference)	0.98(0.69, 1.39)	0.85(0.59, 1.22)	1.09(0.78, 1.51)	0.78(0.51, 1.20)	0.531	
BMI(kg/m^2)									0.692
≤ 30	360	352305.45	1.00(reference)	0.93(0.69, 1.26)	0.63(0.45, 0.90)	0.80(0.59, 1.08)	0.69(0.47, 1.00)	0.021	
> 30	123	104285.94	1.00(reference)	1.27(0.76, 2.11)	1.03(0.60, 1.78)	0.95(0.55, 1.63)	0.86(0.45, 1.65)	0.486	
History of Diabetes									0.519
No	438	433569.64	1.00(reference)	0.93(0.71, 1.23)	0.72(0.54, 0.97)	0.82(0.62, 1.07)	0.70(0.49, 0.98)	0.019	
Yes	45	23021.75	1.00(reference)	1.89(0.85, 4.19)	0.67(0.23, 1.95)	0.99(0.40, 2.44)	0.91(0.32, 2.64)	0.592	
Family History of Colorectal Cancer									0.001
No	419	397607.4	1.00(reference)	0.95(0.72, 1.25)	0.64(0.47, 0.87)	0.66(0.49, 0.88)	0.66(0.47, 0.93)	0.001	
Yes/possibly	64	58984.02	1.00(reference)	1.82(0.76, 4.40)	1.87(0.78, 4.45)	3.47(1.61, 7.48)	1.53(0.55, 4.26)	0.040	
Smoking Pack Years									0.162
< = median	272	267605.57	1.00(reference)	1.14(0.80, 1.61)	0.76(0.52, 1.11)	0.76(0.53, 1.09)	0.65(0.42, 0.99)	0.014	
>median	211	188985.82	1.00(reference)	0.84(0.56, 1.26)	0.67(0.43, 1.04)	0.94(0.64, 1.38)	0.93(0.56, 1.53)	0.612	
Drink Alcohol									0.192
no	151	138737.56	1.00(reference)	1.31(0.83, 2.07)	0.99(0.61, 1.63)	0.86(0.53, 1.40)	0.62(0.34, 1.14)	0.094	
yes	332	317853.83	1.00(reference)	0.89(0.64, 1.22)	0.62(0.43, 0.88)	0.82(0.60, 1.13)	0.78(0.53, 1.14)	0.120	
Physical Activity Level (min/week)									0.603
< = median	287	229171.81	1.00(reference)	1.12(0.81, 1.54)	0.74(0.51, 1.07)	0.87(0.62, 1.22)	0.61(0.38, 0.98)	0.056	
>median	196	227419.58	1.00(reference)	0.79(0.51, 1.24)	0.66(0.42, 1.04)	0.74(0.49, 1.12)	0.78(0.49, 1.24)	0.207	
Food Energy from Diet (kcal/day)									0.947
< = median	261	228187.90	1.00(reference)	1.05(0.76, 1.45)	0.73(0.50, 1.05)	0.75(0.52, 1.09)	0.67(0.39, 1.14)	0.030	
>median	222	228403.49	1.00(reference)	0.91(0.58, 1.42)	0.69(0.44, 1.08)	0.85(0.58, 1.25)	0.72(0.46, 1.10)	0.152	
History of Colonoscopy Screening									0.458
no	265	243502.74	1.00(reference)	1.08(0.77, 1.52)	0.78(0.54, 1.14)	0.74(0.51, 1.07)	0.82(0.53, 1.26)	0.139	
yes	218	213088.65	1.00(reference)	0.92(0.61, 1.37)	0.65(0.42, 1.00)	0.92(0.63, 1.34)	0.61(0.37, 1.00)	0.080	

[a]Hazard ratio was calculated using Cox proportional hazard regression models, P trend was calculated from significance testing for the underlying linear trend in Cox models, P interaction for likelihood ratio tests was calculated from significance testing of interaction terms in Cox models.

[b]Hazard ratios were adjusted for age (years), race (white, non-white), educational level (college below, college graduate, post-graduate), body mass index (kg/m2), family history of colorectal cancer (no, yes/possibly), pack-years (continuous), drinker (no, yes), history of diabetes (no, yes), physical activity (min/week), history of colon screen (no, yes), history of colorectal polyps (no, yes), history of colon related co-morbidity (no, yes), history of diverticulitis or diverticulosis (no, yes) and food energy from diet (kcal/day).

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TABLE 4 Sensitivity analyses on the association of OBS with the risk of colorectal cancer in female [a].

Categories	No. of Participants	No. of Cases	Hazard Ratio (95% Confidence Interval) by OBS [b]					P_{trend}
			Quintile 1 (≤ 11)	Quintile 2 (12–13)	Quintile 3 (14–15)	Quintile 4 (16–18)	Quintile 5 (> 18)	
Excluded participants with family history of colorectal cancer [c]	44597	419	1.00 (reference)	0.95 (0.72,1.25)	0.64 (0.47,0.87)	0.66 (0.49,0.88)	0.66 (0.47,0.93)	0.001
Excluded participants with a history of diabetes [d]	48474	438	1.00 (reference)	0.93 (0.71,1.23)	0.72 (0.54,0.97)	0.82 (0.62,1.07)	0.70 (0.49,0.98)	0.019
Excluded cases observed within the first 2 years of follow-up	51113	370	1.00 (reference)	0.89 (0.66,1.20)	0.66 (0.48,0.92)	0.79 (0.59,1.07)	0.64 (0.44,0.94)	0.011
Excluded cases observed within the first 4 years of follow-up	50995	252	1.00 (reference)	1.04 (0.73,1.49)	0.69 (0.46,1.04)	0.90 (0.63,1.29)	0.71 (0.45,1.12)	0.041

[a]Hazard ratio was calculated using Cox proportional hazard regression models, P trend was calculated from significance testing for the underlying linear trend in Cox models.
[b]Hazard ratios were adjusted for age (years), race (white, non-white), educational level (college below, college graduate, post-graduate), body mass index (kg/m2), family history of colorectal cancer (no, yes/possibly), pack-years (continuous), drinker (no, yes), history of diabetes (no, yes), physical activity (min/week), history of colon screen (no, yes), history of colorectal polyps (no, yes), history of colon related co-morbidity (no, yes), history of diverticulitis or diverticulosis (no, yes) and food energy from diet (kcal/day).
[c]Hazard ratio was not adjusted for history of colorectal cancer.
[d]Hazard ratio was not adjusted for history of diabetes.

13), and cancer (14). It should be noted that although prior studies have explored OBS in relation to CRC (15), the overall linkage between OS exposure and CRC risk remains ambiguous with inconsistent literature findings (16). The pathogenesis of CRC is intimately connected with factors that heighten OS and impair antioxidant defenses. For instance, lifestyle factors of OBS like smoking and alcohol enlarge reactive oxygen species production, whereas reduced antioxidant enzyme activity and DNA repair capacity attenuate antioxidant protection (25, 26). Conversely, sufficient intakes of antioxidant nutrients such as vitamins E and carotenoids can remove excess reactive oxygen species, boost antioxidant enzyme activity, safeguard DNA from oxidative damage, and thus mitigate CRC occurrence (27–30). In addition, it has been demonstrated that reactive oxygen species (ROS) generated by OS can disrupt critical cellular functions by interacting with cellular macromolecules, including proteins, nucleic acids, and lipids (31). For instance, oxidative damage to DNA may result in base oxidation, single- and double-strand breaks, or the creation of non-basic sites (32). Furthermore, unrepaired oxidative DNA damage enhances the risk of mutagenesis. If these mutations occur in genes imperative for regulating cell growth, such as tumor suppressor genes and proto-oncogenes, they may engender CRC (33). The body's response to injury of intestinal mucosal cells exposed to oxidative stress is inflammation. Repeated exposure to inflammatory sites can elicit chronic inflammation and activation of autoimmune processes (34). Inflammation instigates epigenetic alterations that promote colorectal carcinogenesis through increased production of growth factors and proinflammatory cytokines (35). Animal and clinical investigations have delineated the primary mechanism by which free radicals contribute to colorectal carcinogenesis; specifically, free radicals intercede in inflammation and carcinogenesis via the transcription factor NRF2 (36–38). Therefore, OBS as an integrative indicator of *in vivo* redox balance exhibits clear biological relevance to CRC risk, although the exact associations and gender differences warrant further investigation.

A unique finding of this study was the effect modification by sex on the association between OBS and CRC risk. The potential reasons may relate to the following points: (I) Several studies indicate lower NADPH oxidase activity and function in females, attributable to direct estrogen-mediated reduction of NADPH oxidase activity as well as lower expression of the essential assembly factor p47 and superoxide production, independent of estrogen effects, culminating in lower superoxide levels in females with lower oxidative stress (39–42). (II) Clinical and experimental studies have indicated that women have stronger antioxidant potential than men (43). This may be because estrogen has antioxidant qualities, making women less vulnerable to oxidative stress (44). (III) In our present analysis, the CRC incidence rate is lower in women and the gender baseline characteristics showed that relative to men, women often adopt healthier lifestyles, such as limited smoking and alcohol consumption, that may reduce oxidative damage and inflammation (45). Additionally, **Supplementary Table 3** also showed that women had higher intakes of antioxidant nutrients and higher OBS score, which may minimize oxidative damage and preserve oxidative balance, thereby lowering CRC risk (46).

This study has several notable strengths. It was a well-designed observational study in a large population, and the extensive follow-up period of up to 8 years allowed sufficient time for outcome events to occur. Moreover, we extensively adjusted for potential demographic, lifestyle, and disease history confounders, thereby minimizing residual confounding of the observed associations. Importantly, we identified a gender difference in the association between OBS and colorectal cancer risk. Furthermore, the inverse association demonstrated good robustness across multiple sensitivity analyses.

Some limitations should be acknowledged. Firstly, multiple variants of the OBS scoring system have been developed in prior studies (11, 47, 48). The present study developed an OBS scoring system using the framework proposed by Lakkur et al. (9), which integrated 14 dietary and lifestyle factors into the score calculation. Given the controversial role of PUFAs, aspirin, and NSAIDs on OS (49, 50), we reconstructed the OBS score after removing these 3 components. This reconstructed score was associated with the occurrence of CRC in the unadjusted and demographic-adjusted models, but no statistically significant association was observed in the fully adjusted model (**Supplementary Table 4**). Therefore, caution must be taken when examining the relationship between

OS and CRC, as differing OBS scoring systems may lead to disparate results. In addition, incorporating direct biomarkers of OS, such as markers of DNA damage or lipid peroxidation, could have provided more objective measures of OBS. Unfortunately, such biomarkers were not available in the database used for this analysis. Secondly, dietary data was solely gathered at the baseline. Any shifts in dietary habits during the follow-up period could introduce non-differential misclassification bias. Thirdly, our study cohort exclusively comprised American adults aged 55–74. Therefore, the generalizability of the conclusions remains subject to further investigation. Fourthly, as detailed genetic data and important blood markers (e.g., hormones and estrogen) were not available in the PLCO cohort, which limits our ability to explore the impacts of genetic predispositions, molecular subtypes, and familial predispositions on the association between OBS and CRC risk as well as its gender difference. This is an important limitation of our study. In future research, we will utilize data from databases with genomic information and biological blood markers (e.g., UK Biobank) to further explore these factors in OBS-related CRC development and distinguish the associations in different sex and CRC subtypes. Finally, while this large, observational study with lengthy follow-up identified an association between OBS and CRC in female, the lack of genomic data is a limitation to establish causal relationships through Mendelian randomization approaches.

Conclusion

In this study of U.S. adults, higher OBS were associated with lower CRC risk among women but not men. This suggests that adherence to an antioxidant diet and lifestyle pattern may aid in CRC prevention, particularly for women without a family history of CRC. Further research is warranted to confirm these findings and should consider potential sex-specific mechanisms.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://cdas.cancer.gov/.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the National Cancer Institute. The patients/participants provided their written informed consent to participate in the PLCO study.

Author contributions

LX: Conceptualization, Formal analysis, Resources, Visualization, Writing-original draft. BL: Writing-original draft, Data curation, Methodology. HG: Methodology, Funding acquisition, Writing-review and editing. ZX: Methodology, Writing-review and editing. YT: Methodology, Writing-review and editing. ZZ: Methodology, Writing-review and editing. YJ: Methodology, Writing-review and editing. LP: Methodology, Formal analysis, Funding acquisition, Writing-review and editing. HH: Writing-review and editing, Conceptualization, Supervision. YW: Conceptualization, Supervision, Writing-review and editing, Funding acquisition.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1284066/full#supplementary-material

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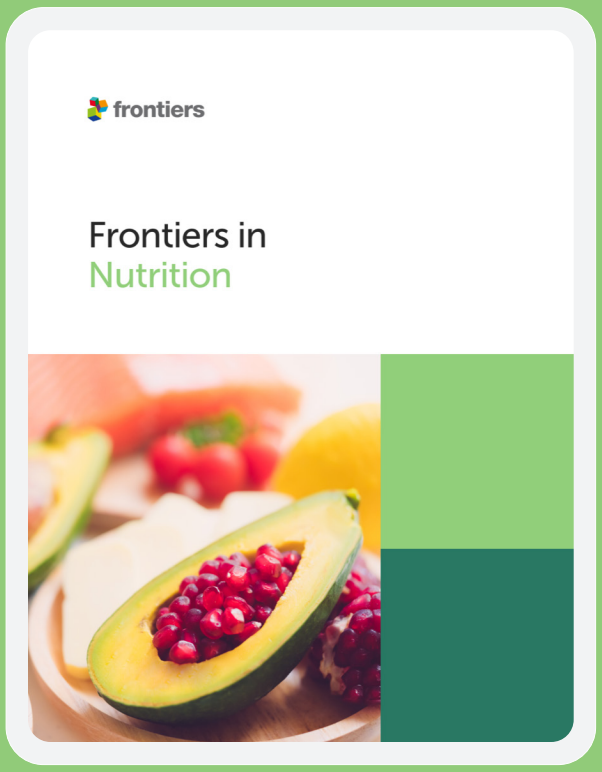

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