Research Topics

Women's health in an interdisciplinary dimension – determinants of nutritional disorders

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Published in
Frontiers in Nutrition

ISSN 1664-8714
ISBN 978-2-8325-5539-2
DOI 10.3389/978-2-8325-5539-2

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Women's health in an interdisciplinary dimension – determinants of nutritional disorders

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Citation
Krupa-Kotara, K., León Guereño, P., Uchmanowicz, I., Czapla, M., eds. (2024). *Women's health in an interdisciplinary dimension – determinants of nutritional disorders*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5539-2

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frontiers | Frontiers in Nutrition

TYPE Editorial
PUBLISHED 26 September 2024
DOI 10.3389/fnut.2024.1492625

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 07 September 2024
ACCEPTED 11 September 2024
PUBLISHED 26 September 2024

CITATION
Krupa-Kotara K, León-Guereño P, Uchmanowicz I and Czapla M (2024) Editorial: Women's health in an interdisciplinary dimension – determinants of nutritional disorders. *Front. Nutr.* 11:1492625.
doi: 10.3389/fnut.2024.1492625

Editorial: Women's health in an interdisciplinary dimension – determinants of nutritional disorders

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KEYWORDS
women's health, nutritional disorders, eating disorders, reproductive health, micronutrients

Editorial on the Research Topic
Women's health in an interdisciplinary dimension – determinants of nutritional disorders

Introduction

Women's health is a complex and multidimensional issue that requires an interdisciplinary approach that considers both biological and social determinants. In recent decades, there has been a growing interest in the study of women's health, particularly in the context of diet-related diseases. The increase in the prevalence of these diseases in the female population, starting in the second half of the 20th century, can be attributed to increasing life expectancy, as well as increasing exposure to environmental factors, including lifestyle. At the same time, the mechanisms for the development of many diet-related diseases are still incompletely understood, mainly because of their multifactorial etiology.

An important aspect of women's health is understanding how genetic and environmental factors interact to lead to the development of disease. As Judith Stern aptly put it, "*genetics loads the gun, but it's the environment that pulls the trigger*" (1). This means that disease phenotypes are not only the result of interactions between genes but also between genes and environmental factors. In the context of eating disorders in women, this approach is particularly important because a variety of factors, such as diet, physical activity, stress, and cultural differences, can influence health and disease development.

In the analysis of women's health, the role of gender as a variable that differentiates health status cannot be overlooked. Gender is a key determinant of health inequalities, which stem from both biological (sex) and socio-cultural (gender) causes. On the one hand, biological differences affect susceptibility to certain diseases, while on the other hand, social roles, different patterns of health behavior and lifestyles also have a significant impact on women's health. Although women's life expectancy has increased significantly in recent decades, there are still marked differences in health status between different populations, which can be attributed to these very different patterns of social role behavior and cultural factors.

This Research Topic focused on health promotion, disease prevention, and the diagnosis and treatment of all nutritional disorders that affect women's physical social, and emotional wellbeing. The collected research papers, reports, systematic reviews, meta-analyses provide a wide range of perspectives that contribute to understanding the complexity of women's health problems in a global context, consistent with the guidelines of evidence-based medicine and evidence-based nutrition. Among them are papers focusing on the impact of diet and supplementation on women's reproductive health, studies analyzing health and psychological behaviors related to nutrition, and papers addressing specific health problems such as micronutrient deficiencies and the effects of chronic diseases.

Each of the articles presented brings valuable insights to the interdisciplinary discussion of women's health and eating disorders, addressing a variety of health aspects that are crucial to improving women's quality of life (Figure 1).

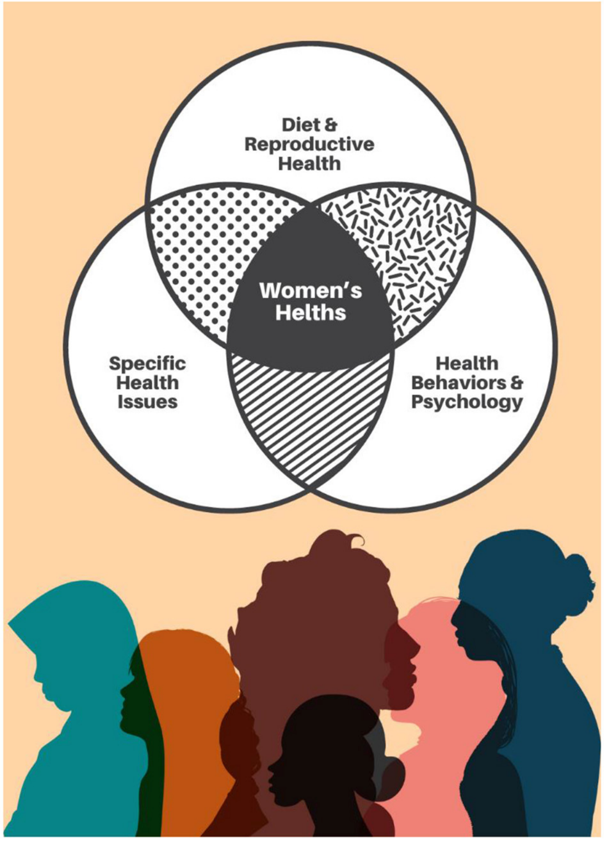

FIGURE 1
Interdisciplinary intersections in women's health research.

Effects of diet and supplementation on women's reproductive health

One of the first studies on the Research Topic to focus on the effects of diet on women's reproductive health is a paper by Tsushima et al.. This study examines the effects of a ketogenic diet on fertility in patients with polycystic ovary syndrome (PCOS). The results indicate that a ketogenic diet can significantly improve fertility-related parameters, suggesting that dietary changes may be a key element in the treatment of infertility in women with PCOS. Another study by Chen et al. examines the effect of a Mediterranean diet on blastocyst formation in women who have undergone COVID-19 infection. The findings of this study suggest that a Mediterranean diet may promote better blastocyst formation, which underscores the role of a healthy lifestyle and proper nutrition in the treatment of infertility, especially in the context of complications following viral infection.

The next study, conducted by Wang et al., analyzes the relationship between the Dietary Inflammatory Index and infertility in women. The results of this study show that diets with a high inflammatory index, characterized by a high content of processed foods, trans fats and sugars, may contribute to an increased risk of infertility. This study underscores the importance of an anti-inflammatory diet, rich in antioxidants and fiber, in the prevention and treatment of infertility, which is key to improving women's reproductive health.

The Research Topic also includes studies that focus on the impact of diet on maternal and newborn health, emphasizing the importance of proper nutrition during key periods of a woman's life. One such study is the work conducted by Sims et al., which examines the effects of the Mediterranean diet on breast milk composition in women with obesity. The results indicate that a Mediterranean diet, rich in healthy fats, fruits, vegetables, and fish, can positively affect the composition of breast milk. This is particularly important because the quality of breast milk has a direct impact on the health and development of the newborn, as well as on the child's long-term health outcomes. This study underscores the need to promote healthy dietary patterns in lactating women, especially those who are overweight or obese.

The next study, conducted by Alshwaiyat et al., focuses on the effect of diet induced weight loss on iron status and iron indices in young women with overweight or obesity and iron deficiency anemia. This study showed that controlled weight loss through diet can improve iron status in these women, which is crucial for their overall health and reproductive health. The results suggest that dietary interventions aimed at weight reduction should be planned in a way that simultaneously improves nutritional status and prevents micronutrient deficiencies.

The study, by Liu et al., addresses the effect of folic acid supplementation on perinatal mortality in China. The study found that regular folic acid supplementation, especially during the preconceptional and gestational periods, can significantly reduce the risk of perinatal mortality. Folic acid supplementation is widely recommended for the prevention of neural tube defects, but this study also underscores its key role in preventing serious perinatal complications, which is of great public health importance.

A recent study in this group, conducted by Hong et al., focuses on the relationship between maternal mineral status and the risk of preterm birth. The results of this study suggest that mineral deficiencies, including iron and calcium deficiency, may be an important risk factor for preterm birth. This study points to the need to monitor the nutritional status of pregnant women and implement appropriate dietary interventions to prevent negative health consequences for mother and child.

Health and psychological behaviors related to nutrition

The Research Topic also includes several studies that focus on psychological and behavioral aspects related to nutrition and women's health. Rozmiarek et al. analyze orthorectic behavior among female college students and their motivations for physical activity, eating habits, and restrictive eating behaviors. Orthorexia, or obsession with healthy eating, can lead to serious health disorders, including malnutrition and psychiatric disorders. The results of this study suggest that orthorexia is common among young women, especially in academia, underscoring the need for increased awareness and support for a healthy approach to diet and physical activity.

Another study, conducted by Gogojewicz et al., compared the nutritional status and health habits of women who practice yoga with those who prefer other forms of physical activity. The study found that women who practice yoga tend to have better nutritional status and more balanced eating habits. Yoga, which combines physical and mental elements, can support healthy eating habits and overall wellbeing, suggesting that its regular practice can be beneficial to women's physical and mental health.

The next study, conducted by Mislu et al., focuses on breastfeeding techniques and related factors in northeastern Ethiopia. The results of this study show that proper breastfeeding techniques and maternal education can have a key impact on child and maternal health, especially in terms of improving health indicators and reducing the risk of malnutrition. Breastfeeding education, especially in regions with limited access to health care, is essential for promoting the health and wellbeing of women and their children.

A recent study in this category by Egele and Stark examines how specific health beliefs influence gender differences in dietary choices. The results of the study indicate that men and women differ in their dietary decisions, in part due to different health beliefs. Women, for example, are more likely to choose foods considered "healthier," such as vegetables and fruits, based on beliefs about their health benefits, while men may prefer protein-rich foods due to beliefs about building muscle mass. This study underscores the importance of incorporating gender differences into health education and dietary interventions to more effectively promote healthy eating habits among both sexes.

Specific health problems: micronutrients and chronic diseases

Another group of studies on the Research Topic focuses on specific health problems, such as micronutrient deficiencies and the effects of chronic diseases. A study by Hu et al. examines the relationship between micronutrient intake and pelvic inflammatory disease (PID). The results of this study indicate that deficiencies in certain micronutrients, such as zinc and magnesium, may increase the risk of PID, highlighting the importance of adequate nutrition in the prevention of pelvic inflammatory disease. In the context of women's reproductive health, attention to adequate levels of micronutrients in the diet is crucial for the prevention and treatment of such conditions.

The next study, conducted by Sulhariza et al., analyzes changes in hemoglobin levels during pregnancy and their relationship to the risk of gestational diabetes. This study found that a decrease in hemoglobin levels during the first trimester of pregnancy may be associated with a higher risk of developing gestational diabetes. These findings suggest the need for early diagnosis and intervention to improve health outcomes for mothers and their babies, underscoring the importance of monitoring and managing hemoglobin levels during pregnancy.

The study by Białek-Dratwa et al. analyzed dietary trends among Polish women between 2011 and 2022, focusing on the frequency of consumption of different food groups in the Silesia region. The results of this study indicate significant changes in dietary habits that may have a direct impact on population health, including the incidence of diet-related chronic diseases such as obesity, type 2 diabetes, and cardiovascular disease. This study underscores the need for ongoing monitoring of dietary habits in the population and education on healthy eating to counteract the negative health effects of poor eating habits.

A recent study in this group, conducted by Mazza et al., examines the impact of endometriosis on women's dietary choices and daily living activities. Endometriosis, which is a chronic disease that can cause severe pain and fertility disorders, also has a significant impact on women's daily functioning and dietary decisions. The results of this study point to the need for a holistic approach to endometriosis treatment, considering both medical and dietary aspects, to improve patients' quality of life.

Summary

An interdisciplinary approach to women's health, especially in the context of eating disorders, is essential to understanding the complexity of health problems that affect women at different stages of their lives. The studies and research gathered in this Research Topic highlight how a variety of factors—from genetic to social—affect women's health. Each of the featured articles brings new insights into key aspects of women's health, from diet and lifestyle to psychological and social factors.

These studies show that effective prevention and treatment of eating disorders require an understanding of both the biological and socio-cultural determinants of women's health. Work such as an analysis of the effects of the ketogenic diet on fertility, studies of the inflammatory index of diet vs. infertility, and the role of the Mediterranean diet after COVID-19 provide valuable clues for future health interventions.

In addition, publications on orthorexia, breastfeeding, mineral status in pregnancy, and endometriosis demonstrate the importance of addressing women's specific health needs in the context of their individual experiences and challenges. Ultimately, these studies underscore the need to continue and deepen research on women's health to create more effective health promotion and treatment strategies that address the diverse needs of women around the world.

The research presented here represents an important step toward a more integrated and individualized approach to women's health, considering both the biological and social contexts of health. Findings from this research can contribute to better strategies for preventing and treating eating disorders, ultimately improving the quality of life for women around the world.

Author contributions

KK-K: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. PL-G: Writing – original draft. IU: Writing – original draft. MC: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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TYPE Original Research
PUBLISHED 22 May 2023
DOI 10.3389/fnut.2023.1155947

Check for updates

OPEN ACCESS

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RECEIVED 01 February 2023
ACCEPTED 27 April 2023
PUBLISHED 22 May 2023

CITATION
Alshwaiyat NM, Ahmad A and Al-Jamal HAN (2023) Effect of diet-induced weight loss on iron status and its markers among young women with overweight/obesity and iron deficiency anemia: a randomized controlled trial.
Front. Nutr. 10:1155947.
doi: 10.3389/fnut.2023.1155947

Effect of diet-induced weight loss on iron status and its markers among young women with overweight/obesity and iron deficiency anemia: a randomized controlled trial

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Introduction: Obesity and iron deficiency are prevalent health problems that affect billions of people all over the world. Obesity is postulated to relate to iron deficiency via reduced intestinal iron absorption due to increased serum hepcidin level, which is mediated by chronic inflammation. Weight loss in individuals with overweight or obesity and iron deficiency anemia is believed to be associated with an improvement in iron status however the evidence from clinical trials is scarce. This study was conducted to evaluate the effect of diet-induced weight loss on iron status and its markers among young women with overweight/obesity and iron deficiency anemia.

Methods: The study design was a single-blinded, randomized controlled trial with two parallel arms (weight loss intervention vs control). Study participants were recruited using the convenience sampling method through public advertisements posted and disseminated through social media. Interested and potential participants were asked to visit the Diet Clinic for eligibility screening. A total of 62 women were recruited and randomized into weight loss intervention and control group. The intervention duration was three months. The intervention group received individual consultation sessions with the dietitian and tailored energy-restricted diets. Physical activity levels, dietary intake, anthropometric measurements and clinical markers were measured at baseline and end of the trial.

Results: There was a significant decrease ($p < 0.001$) in body weight of the intervention group (-7.4 ± 2.7 kg) that was associated with significant improvements in iron status and its markers ($p < 0.01$). The intervention group experienced a significant increase in hemoglobin (0.5 ± 0.6 g/dL), serum ferritin (5.6 ± 5.8 ng/mL), and serum iron (13.0 ± 16.2 μg/dL), and a significant decrease in high-sensitivity C-reactive protein (-5.2 ± 5.6 mg/L), and serum hepcidin level (-1.9 ± 2.2 ng/mL) at the end of the trial.

Conclusion: Our findings indicate that diet-induced weight loss among participants was associated with an improvement in iron status and its related clinical markers.

Clinical Trial Registration: [https://www.thaiclinicaltrials.org/show/TCTR20221009001], identifier [TCTR20221009001].

KEYWORDS

weight loss, obesity, iron status, chronic inflammation, hepcidin, iron deficiency anemia

1. Introduction

Obesity and iron deficiency are serious public health issues affecting billions of people worldwide (1, 2). Obesity is widely prevalent among adults and associated with high morbidity and mortality rates due to adverse health effects caused by excessive fat accumulation in the body, including elevated serum lipids (3–5). Concurrently, iron deficiency is still one of the most prevalent nutritional deficiency problems at the global level (2). This deficiency will lead to iron deficiency anemia (IDA), a critical health problem, which adversely affects cognitive function, physical performance, and work productivity (6). Previously, iron deficiency has been linked to pediatric and adulthood obesity, in which obesity is considered an emerging risk factor for iron deficiency incidence (7, 8). The connection between obesity and iron deficiency could be explained by the state of low-grade chronic inflammation in obesity, which stimulates the expression of hepcidin, a key regulator of iron homeostasis (9, 10).

Young women are susceptible to weight gain and become overweight or obese due to many factors, such as unhealthy dietary patterns, sedentary lifestyles, and pregnancy (11). At the same time, young women are also at high risk of iron deficiency as their dietary iron requirements are higher than older women due to menstrual losses (12). Dieting is common among women with overweight or obesity, particularly at this stage of life (13). Energy-restricted diets have long-term beneficial health effects, but can negatively affect dietary iron intake (14–16).

Several studies have reported that individuals with overweight and obesity were associated with lower iron status and elevated systematic inflammation and serum hepcidin compared to those with normal body weight (17–26). However, very limited studies investigated the effect of weight loss on iron status, systematic inflammation, and serum hepcidin among individuals with overweight or obesity, especially in clinical trials (27). Therefore, this study was conducted to evaluate the effect of diet-induced weight loss on iron status, chronic inflammation, and serum hepcidin level among overweight or obese young women with IDA.

2. Methods

2.1. Study design and participants

This study was a single-blinded, randomized controlled trial (RCT) with two parallel arms design (weight loss intervention vs. control). The study was conducted at a private diet clinic (Gharaibeh Diet Clinic, Ajloun, Jordan). The study protocol was approved by Human Research Ethics Committee at Universiti Sultan Zainal Abidin, Terengganu, Malaysia (UniSZA/UHREC/2020/172) and Ajloun Health Directorate, Ministry of Health, Ajloun, Jordan (No.: 22/8/140). The inclusion criteria were young adult Jordanian women (18–30 years)-with Arab ethnicity, being overweight [body mass index (BMI) = 25–29.9] or obese (BMI ≥ 30), and diagnosed with mild or moderate IDA [hemoglobin = 8.0–11.9 g/dL, mean corpuscular volume (MCV) < 80 fL and serum ferritin ≤30 ng/mL]. The exclusion criteria included symptomatic patients, pregnant or lactating within the past 12 months, presence of any chronic disease or significant medical condition, being vegetarian, tobacco smoker, alcohol drinker, or drug abuser, had unstable body weight within the past 6 months (weight change ≥3% of initial body weight), irregular menstrual cycle within the past 12 months, undergone bariatric surgery, or full or partial hysterectomy, donated blood or history of hemorrhage within the past 6 months, consumption of iron supplement within the past 6 months, or any other dietary supplement within the past 3 months, and use of medications that may influence weight, iron, or inflammatory status within the past 3 months such as contraceptive medication. Study participants were recruited using the convenience sampling method through public advertisements posted and disseminated through social media. Interested and potential participants were asked to visit the Diet Clinic for eligibility screening. Informed consent was obtained from all participants who met the inclusion criteria following the Helsinki Declaration prior to randomization. Block randomization was handled by an independent collaborator with an equal allocation using a computer-generated randomization schedule. The allocation was concealed until the intervention started. The allocation sequence was concealed from the researcher and participants in sequentially numbered, opaque, sealed, and stapled envelopes. The study randomization was blinded for measurers and data collectors. All methods were performed in accordance with the relevant guidelines and regulations. In this trial, exposure was diet-induced weight loss, while primary outcomes were changes in iron status markers, high-sensitivity C-reactive protein (hsCRP), and serum hepcidin. No important changes to methods or trial outcomes after trial commencement were applied.

2.2. Weight loss intervention

The intervention duration was 3 months. The intervention group received individual consultation sessions with the dietitian on days 0, 15, 30, 45, 60, and 75 for 30 min. During the consultations, participants received tailored energy-restricted diets, i.e., energy requirement with a deficit of 500 kcal with 50, 30, and 20% of daily energy from carbohydrate, fat, and protein, respectively, education about iron-rich dietary sources, and method of recording food intake. The weight loss target was 1–2 kg for 2 weeks. The serving size of foods included in the diet was based on American food lists (28), and Jordanian food lists (29, 30). The control group was asked to continue on habitual dietary patterns throughout the participation period.

2.3. Data collection

Data were collected at baseline (day 0) and the end of the trial (day 90). Sociodemographic and physical activity data were collected using a questionnaire during face-to-face interviews. Physical activity levels were assessed using the Global Physical Activity Questionnaire (GPAQ), which has acceptable reliability and validity for measuring adult physical activity levels (31, 32). Physical activity was categorized into three levels: low, moderate, and high (33, 34). Dietary intake was measured using

Abbreviations: BMI, Body mass index; IDA, Iron deficiency anemia; GPAQ, Global physical activity questionnaire; WC, Waist circumference; HC, Hip circumference; WHR, Waist-hip ratio; RBC, Red blood cell; MCV, Mean corpuscular volume; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; TIBC, Total iron binding capacity; TS, Transferrin saturation; hsCRP, High-sensitivity C-reactive protein; CRP, C-reactive protein; RCT, randomized controlled trial.

7-day food record method. Participants were required to record all foods and beverages consumed during the day in a specific form for 7 consecutive days preceding the diet clinic visit at baseline and during the study preceding each follow-up visit. Nutrition analysis software (Food processor, version 11.9, ESHA Research, Salem, OR, United States) was used to determine average daily nutrient intake.

2.4. Anthropometric measurements

Participants' height, weight, waist circumference, hip circumference, and body fat percentage were measured by the dietitian in the morning after overnight fasting using standard procedures. Height was measured to the nearest 0.1 cm using a calibrated stadiometer (Seca 213, Germany) in the standing position without shoes. Weight was measured to the nearest 0.1 kg using a calibrated digital weight scale (Seca 876, Germany) while wearing minimal clothes without shoes. The BMI was determined by dividing the weight (kg) by squared height (m^2) and classified into overweight (25–29.9 kg/m^2) or obese (≥30 kg/m^2) (35). The waist and hip circumferences were measured to the nearest 0.1 cm using anthropometric tape (Seca 203, Germany). The waist-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. The body fat percentage of participants was measured using a bioelectrical impedance analysis device (Tanita body composition monitor, BC-601F, Tokyo, Japan) according to the manufacturer's instructions.

2.5. Blood analysis

Hematological and biochemical assays were conducted at a private certified medical laboratory (Ajloun Medical Labs, Ajloun, Jordan). Blood samples were collected from participants in the morning after overnight fasting on days 0 and 90. Complete blood count (CBC), including red cell (RBC) count, hemoglobin, hematocrit, MCV, mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), serum iron, total iron binding capacity (TIBC), serum ferritin, and hsCRP were measured according to standard medical laboratory procedures. Transferrin saturation (TS) was calculated by dividing serum iron on TIBC multiplied by 100%. Serum hsCRP was evaluated by sandwich immunodetection method using an AFIAS-6 automated immunoassay analyzer (Boditech Med Inc., Chuncheon-si, South Korea). Serum hepcidin level was determined using a human hepcidin immunoassay ELISA kit (Quantikine ELISA DHP250, R&D Systems, Minneapolis, MN, United States) according to the manufacturer's instructions.

2.6. Statistical analysis

The sample size was calculated using G*Power software, Version 3.1.9.4, assuming that the test family is *t*-tests, the statistical test is the difference between two independent means (two groups), the tails are two, the effect size is equal to 0.80, the level of significance is equal to 0.05, and the power is equal to 0.80 (36). The total calculated sample size was 52 participants (26 participants in each group). After adding 20% to account for possible attrition, the required sample size was 62 participants (31 participants in each group).

IBM SPSS Statistics for Windows (Version 26, United States) was used for data analysis. Changes in dietary intake data were calculated by subtracting the during-intervention value from the baseline value (change value = during-intervention value − baseline value). Changes in anthropometric measures, iron status markers, hsCRP, and serum hepcidin were calculated by subtracting the post-intervention value from the baseline value (change value = post-intervention value − baseline value). The normality of data was assessed by visual inspection of histograms and the Shapiro–Wilk test. Categorical variables were presented as numbers and percentages. Continuous variables were presented as means and standard deviations. Chi-squared test was conducted to determine differences in categorical variables between the intervention group and the control group. Wilcoxon signed-rank test was conducted to determine differences in physical activity levels over time between baseline and post-intervention. Independent samples *t*-test was conducted to determine the mean differences for baseline, during-intervention and change values between the intervention group and the control group. Paired-samples *t*-test was conducted to determine the differences in means between baseline and during/post-intervention. ANCOVA was used to determine the differences in post-intervention means between the intervention group and control group after adjusting for baseline values. Pearson's correlation test was run to assess the correlation between changes in anthropometric measures, iron status markers, hsCRP, and serum hepcidin. All reported p values were made based on two-tailed tests. Differences were considered statistically significant at values of $p < 0.05$.

3. Results

The study was conducted from March to September 2021. Overall, 230 women were screened, 167 did not meet the inclusion criteria, and one withdrew from participating. Sixty-two participants were randomized (1:1) into intervention and control groups and enrolled in the study. However, four participants from the intervention and four from the control group dropped out due to pregnancy. The final sample size who completed the study was 54 (27 from each group; Figure 1).

3.1. Baseline characteristics

The mean age of all participants was 26.5 ± 3.7. There were no significant differences in sociodemographic characteristics, anthropometric measurements (except waist circumference), and clinical data (except RBC count and hematocrit) between the intervention group and the control group at baseline (Table 1).

3.2. Changes in physical activity levels

About half of the participants in each group (intervention group and control group) had high physical activity levels at baseline and post-intervention. There were no significant differences in physical activity levels between the intervention group and the control group at baseline and post-intervention. Furthermore, there were no significant differences in physical activity levels over time between baseline and post-intervention for participants in the intervention group and the control group (Table 2).

3.3. Changes in dietary intake

Iron intake was significantly reduced in the intervention group (−2.2 ± 3.0 mg/day, $p = 0.001$). The mean of change in iron intake for

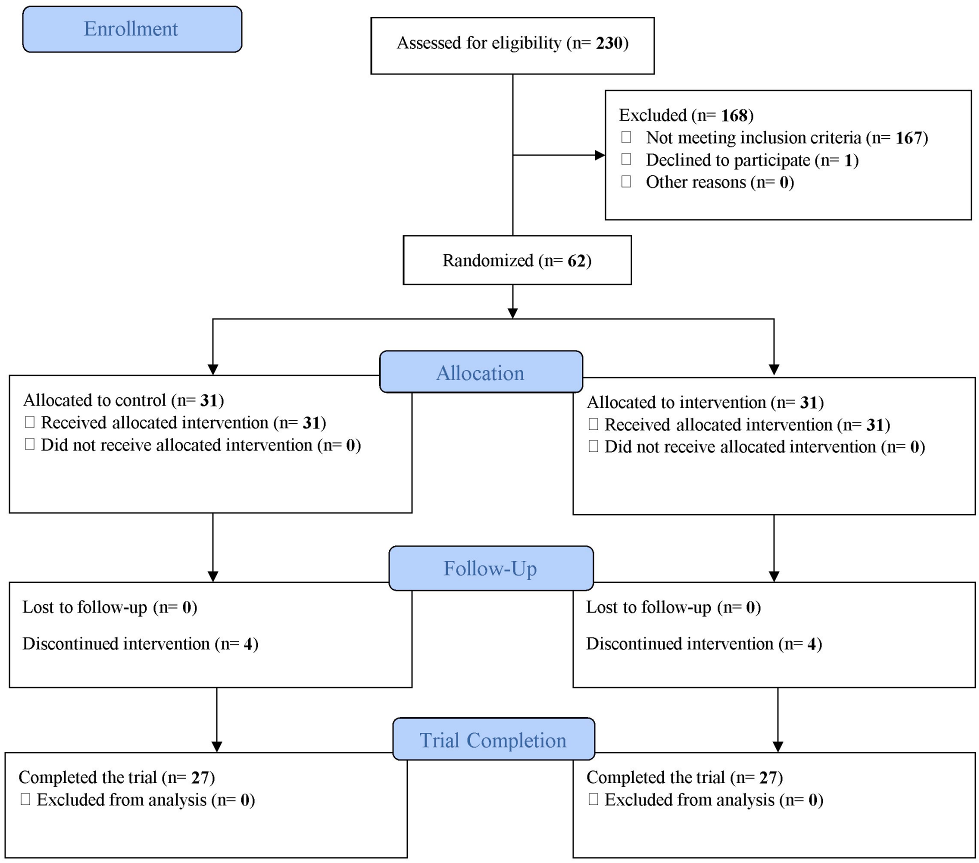

FIGURE 1
Flow chart illustrating the progress of the trial.

the intervention group (−2.2 ± 3.0 mg/day) was significantly different from that reported for the control group (0.1 ± 1.9 mg/day; $p = 0.001$). Similar results were reported for the intake of energy, protein, carbohydrate, and fat (Table 3).

3.4. Changes in body weight and anthropometric variables

Body weight was significantly reduced in both groups. However, the weight loss was higher in the intervention compared to the control group (−7.4 ± 2.7 kg vs. −0.9 ± 1.5 kg). After adjusting for baseline values, the post-intervention weight mean for the intervention group (79.2 ± 12.1 kg) was significantly lower than the control group (83.5 ± 11.4 kg; $p < 0.001$). Similar results were reported for other anthropometric variables (BMI, body fat percentage, waist circumference, hip circumference, and WHR), except that changes in hip circumference and WHR were not statistically significant for the control group (Table 4).

3.5. Changes in clinical variables

The intervention group experienced a significant increase in hemoglobin (0.5 ± 0.6 g/dL), serum ferritin (5.6 ± 5.8 ng/mL), and serum iron (13.0 ± 16.2 µg/dL), and a significant decrease in hsCRP (−5.2 ± 5.6 mg/L), and serum hepcidin level (−1.9 ± 2.2 ng/mL) at the end of the trial. Conversely, changes in these variables were not statistically significant in the control group. After adjusting for baseline values, post-intervention means for hemoglobin (11.7 ± 1.1 g/dL), serum ferritin (15.5 ± 10.4 ng/mL), and serum iron (50.2 ± 22.4 µg/dL) for the intervention group were significantly higher than the control group (11.4 ± 1.0 g/dL, 10.3 ± 7.7 ng/mL, and 46.5 ± 24.2 µg/dL, respectively; $p < 0.05$). However, post-intervention means for hsCRP (4.9 ± 6.0 mg/L), and serum hepcidin level (3.8 ± 3.0 ng/mL) for the intervention group were significantly lower than the control group (8.4 ± 7.7 mg/L and 4.9 ± 2.8 ng/mL, respectively) after adjusting for baseline values ($p < 0.05$; Table 4).

3.6. Correlations between changes in weight and clinical variables

A significant negative correlation was observed between changes in weight and changes in RBC count ($r = −0.529$), hematocrit ($r = −0.415$), MCV ($r = −0.293$), MCH ($r = −0.294$), serum ferritin ($r = −0.305$), serum iron ($r = −0.278$), and TS ($r = −0.308$). Conversely, a significant positive correlation was observed between changes in weight and changes in TIBC ($r = 0.290$), hsCRP ($r = 0.359$), and serum hepcidin ($r = 0.393$; Table 5).

TABLE 1 Baseline characteristics of study participants.

Variables*	Intervention group (*n*=31)	Control group (*n*=31)	*p* value**
Age (years)	26.9 (3.9)	26.0 (3.6)	0.347
Education level			
Secondary school	12 (38.7%)	5 (16.1%)	0.094
Diploma degree	3 (9.7%)	7 (22.6%)	
Bachelor's degree	16 (51.6%)	19 (61.3%)	
Marital status			
Single	7 (22.6%)	11 (35.5%)	0.263
Married	24 (77.4%)	20 (64.5%)	
Employment status			
Employed	5 (16.1%)	4 (12.9%)	0.665
Students	6 (19.4%)	9 (29.0%)	
Unemployed/housewives	20 (64.5%)	18 (58.1%)	
Family size	5.4 (1.9)	5.1 (2.2)	0.543
Household income			
Low (JD 250 or less)	4 (12.9%)	6 (19.4%)	0.146
Moderate (JD 251–500)	26 (83.9%)	20 (64.5%)	
High (JD 501–750)	1 (3.2%)	5 (16.1%)	
Height (cm)	160.6 (5.8)	159.7 (6.5)	0.53
Weight (kg)	86.7 (12.3)	83.7 (11.1)	0.316
BMI (kg/m^2)	33.6 (4.8)	32.9 (4.5)	0.54
Body weight status			
Overweight	6 (19.4%)	7 (22.6%)	0.755
Obese	25 (80.6%)	24 (77.4%)	
Body fat (%)	42.4 (4.7)	39.9 (5.5)	0.06
WC (cm)	99.5 (11.8)	93.6 (9.0)	**0.031**
HC (cm)	118.8 (7.8)	115.1 (7.5)	0.063
WHR	0.84 (0.07)	0.81 (0.06)	0.183
RBC count (10^6/μL)	4.7 (0.4)	5.0 (0.6)	**0.016**
Hemoglobin (g/dL)	11.2 (0.9)	11.3 (0.7)	0.415
Hematocrit (%)	36.1 (2.8)	37.7 (2.9)	**0.03**
MCV (fL)	75.1 (5.2)	74.7 (6.7)	0.794
MCH (pg)	24.1 (2.8)	23.3 (2.9)	0.29
MCHC (g/dL)	31.3 (1.4)	30.7 (1.4)	0.099
Serum ferritin (ng/mL)	9.3 (7.5)	9.7 (7.6)	0.837
Serum iron (μg/dL)	38.0 (19.8)	43.6 (18.9)	0.261
TIBC (μg/dL)	351.9 (58.0)	369.0 (53.3)	0.232
TS (%)	11.5 (6.8)	12.3 (6.4)	0.638
hsCRP (mg/L)	10.5 (9.9)	9.3 (10.4)	0.644
Serum hepcidin (ng/mL)	5.1 (3.2)	4.5 (3.4)	0.453

*BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR: waist-hip ratio; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TIBC, total iron binding capacity; TS, transferrin saturation; hsCRP, High-sensitivity C-reactive protein.
**Categorical variables were analyzed using Chi-squared test and expressed as numbers and percentages. Continuous variables were analyzed using independent samples *t*-test and expressed as means and standard deviations. *p* values < 0.05 are significantly different and presented in bold.

4. Discussion

In this study, we found that diet-induced weight loss among young women with overweight or obesity was associated with an improvement in iron indicators including a decrease in chronic inflammation and serum hepcidin level. There are few studies that previously investigated the effect of weight loss on iron status (37–40). One study was conducted among 15 obese children from Italy who

TABLE 2 Physical activity levels of study participants at baseline and post-intervention.

Physical activity levels	Intervention group (*n*=27)	Control group (*n*=27)	*p* value*
Baseline (at day 90)			
Low	6 (22.2%)	7 (25.9%)	0.819
Moderate	8 (29.6%)	6 (22.2%)	
High	13 (48.1%)	14 (51.9%)	
Post-intervention			
Low	7 (25.9%)	9 (33.3%)	0.821
Moderate	5 (18.5%)	4 (14.8%)	
High	15 (55.6%)	14 (51.9%)	
p value‡	0.909	0.588	

*Chi-squared test was conducted to determine differences in physical activity levels between the intervention group and the control group. Values of $p < 0.05$ are significantly different.
‡Wilcoxon signed-rank test was conducted to determine differences in physical activity levels over time between baseline and post-intervention. Values of $p < 0.05$ are significantly different.

TABLE 3 Change in energy, macronutrients, fiber, and micronutrients intake of study participants.

Variables	Intervention group (*n*=27)	Control group (*n*=27)	*p* value	Recommended intake# (Females, 19–30years)
Energy (kcal/day)				–
Baseline (at day 90)	1,742 (355)	1,706 (394)	0.725‡	
During-intervention	1,323 (240)	1,708 (418)	**<0.001**‡	
p value	**<0.001**$	0.912$		
Change	−419 (203)	2 (108)	**<0.001**‡	
Protein (g/day)				46 g/day
Baseline (at day 90)	61.7 (12.5)	63.1 (13.4)	0.696‡	
During-intervention	51.6 (16.1)	63.4 (16.8)	**0.011**‡	
p value	**<0.001**$	0.824$		
Change	−10.1 (12.1)	0.3 (6.4)	**<0.001**‡	
Carbohydrate (g/day)				130 g/day
Baseline (at day 90)	225.9 (54.7)	208.3 (53.8)	0.238‡	
During-intervention	186.0 (49.8)	208.7 (57.4)	0.126‡	
p value	**<0.001**$	0.907$		
Change	−39.9 (41.6)	0.4 (19.1)	**<0.001**‡	
Fat (g/day)				Not determined
Baseline (at day 90)	67.4 (14.5)	70.3 (20.8)	0.548‡	
During-intervention	43.2 (15.0)	70.4 (22.7)	**<0.001**‡	
p value	**<0.001**$	0.975$		
Change	−24.1 (17.6)	0.1 (7.8)	**<0.001**‡	
Fiber (g/day)				25 g/day
Baseline (at day 90)	16.9 (4.8)	14.6 (3.6)	0.062‡	
During-intervention	15.7 (9.2)	14.9 (4.4)	0.691‡	
p value	0.377$	0.631$		
Change	−1.2 (7.0)	0.2 (2.4)	0.322‡	
Iron (mg/day)				18 mg/day
Baseline (at day 90)	11.5 (3.9)	11.2 (3.6)	0.754‡	
During-intervention	9.3 (4.8)	11.3 (4.8)	0.129‡	
p value	**0.001**$	0.751$		
Change	−2.2 (3.0)	0.1 (1.9)	**0.001**‡	

(Continued)

TABLE 3 (Continued)

Variables	Intervention group (*n*=27)	Control group (*n*=27)	*p* value	Recommended intake[#] (Females, 19–30years)
Vitamin C (mg/day)				
Baseline (at day 90)	63.5 (38.4)	52.7 (23.0)	0.216[‡]	
During-intervention	64.6 (52.2)	50.4 (27.6)	0.218[‡]	75 mg/day
p value	0.874[§]	0.411[§]		
Change	1.0 (33.5)	−2.4 (14.8)	0.631[‡]	
Vitamin A (μg RAE/day)				
Baseline (at day 90)	360.0 (348.8)	432.5 (497.3)	0.538[‡]	
During-intervention	306.9 (451.2)	366.3 (281.1)	0.564[‡]	700 μg RAE/day
p value	0.358[§]	0.442[§]		
Change	−53.2 (295.0)	−66.2 (441.1)	0.899[‡]	
Vitamin D (μg/day)				
Baseline (at day 90)	0.27 (0.22)	0.27 (0.21)	0.960[‡]	
During-intervention	0.22 (0.21)	0.26 (0.22)	0.523[‡]	15 μg/day
p value	0.286[§]	0.690[§]		
Change	−0.04 (0.21)	−0.01 (0.12)	0.462[‡]	
Vitamin E (mg/day)				
Baseline (at day 90)	3.3 (2.6)	4.1 (2.7)	0.287[‡]	
During-intervention	2.1 (1.8)	3.9 (2.5)	**0.006**[‡]	15 mg/day
p value	0.050[§]	0.456[§]		
Change	−1.2 (3.0)	−0.2 (1.7)	0.160[‡]	
Vitamin K (μg/day)				
Baseline (at day 90)	72.0 (125.9)	97.2 (119.4)	0.453[‡]	
During-intervention	94.9 (349.3)	88.6 (149.3)	0.932[‡]	90 μg/day
p value	0.660[§]	0.670[§]		
Change	22.9 (267.1)	−8.6 (103.7)	0.571[‡]	
Vitamin B1 (Thiamine; mg/day)				
Baseline (at day 90)	1.05 (0.46)	1.00 (0.38)	0.696[‡]	
During-intervention	0.87 (0.47)	1.01 (0.43)	0.241[‡]	1.1 mg/day
p value	**0.004**[§]	0.699[§]		
Change	−0.18 (0.29)	0.01 (0.14)	**0.004**[‡]	
Vitamin B2 (Riboflavin; mg/day)				1.1 mg/day
Baseline (at day 90)	0.79 (0.35)	0.86 (0.40)	0.465[‡]	
During-intervention	0.61 (0.40)	0.81 (0.27)	**0.033**[‡]	
p value	**0.004**[§]	0.317[§]		
Change	−0.18 (0.29)	−0.05 (0.25)	0.082[‡]	
Vitamin B3 (Niacin; mg/day)				14 mg/day
Baseline (at day 90)	13.0 (5.1)	13.2 (4.2)	0.918[‡]	
During-intervention	10.3 (5.7)	12.9 (4.4)	0.066[‡]	
p value	**0.003**[§]	0.484[§]		
Change	−2.7 (4.3)	−0.3 (1.9)	**0.009**[‡]	
Vitamin B6 (Pyridoxine; mg/day)				1.3 mg/day
Baseline (at day 90)	0.64 (0.27)	0.61 (0.21)	0.673[‡]	
During-intervention	0.59 (0.40)	0.58 (0.24)	0.886[‡]	
p value	0.478[§]	0.268[§]		
Change	−0.04 (0.30)	−0.03 (0.12)	0.807[‡]	

(Continued)

TABLE 3 (Continued)

Variables	Intervention group (*n*=27)	Control group (*n*=27)	*p* value	Recommended intake[#] (Females, 19−30years)
Vitamin B12 (Cobalamin ; µg/day)				2.4 µg/day
Baseline (at day 90)	1.14 (1.02)	2.05 (4.79)	0.338[‡]	
During-intervention	0.78 (0.89)	1.15 (0.89)	0.140[‡]	
p value	0.135[$]	0.321[$]		
Change	−0.36 (1.20)	−0.90 (4.63)	0.555[‡]	
Biotin (µg/day)				30 µg/day
Baseline (at day 90)	5.08 (3.27)	4.61 (3.25)	0.596[‡]	
During-intervention	5.03 (4.57)	4.45 (3.24)	0.593[‡]	
p value	0.939[$]	0.762[$]		
Change	−0.05 (3.26)	−0.15 (2.63)	0.896[‡]	
Folate (µg/day)				400 µg/day
Baseline (at day 90)	267.3 (156.1)	238.6 (98.2)	0.422[‡]	
During-intervention	226.8 (201.4)	235.7 (101.8)	0.839[‡]	
p value	0.077[$]	0.725[$]		
Change	−40.5 (114.5)	−2.9 (42.3)	0.119[‡]	
Pantothenic acid (mg/day)				5 mg/day
Baseline (at day 90)	2.71 (1.42)	2.59 (1.06)	0.742[‡]	
During-intervention	2.21 (1.06)	2.54 (1.02)	0.253[‡]	
p value	**0.008**[$]	0.520[$]		
Change	−0.50 (0.90)	−0.06 (0.46)	**0.029**[‡]	
Calcium (mg/day)				1,000 mg/day
Baseline (at day 90)	542.1 (178.4)	545.2 (187.2)	0.951[‡]	
During-intervention	450.8 (188.3)	540.9 (241.3)	0.132[‡]	
p value	**0.027**[$]	0.835[$]		
Change	−91.3 (202.9)	−4.3 (105.7)	0.054[‡]	
Magnesium (mg/day)				310 mg/day
Baseline (at day 90)	142.6 (52.9)	140.7 (44.1)	0.887[‡]	
During-intervention	125.9 (88.6)	142.1 (56.7)	0.426[‡]	
p value	0.206[$]	0.786[$]		
Change	−16.7 (66.8)	1.4 (27.3)	0.201[‡]	
Manganese (mg/day)				1.8 mg/day
Baseline (at day 90)	2.05 (0.87)	1.82 (0.77)	0.313[‡]	
During-intervention	1.85 (1.34)	1.90 (1.06)	0.880[‡]	
p value	0.246[$]	0.344[$]		
Change	−0.19 (0.85)	0.08 (0.45)	0.141[‡]	
Phosphorus (mg/day)				700 mg/day
Baseline (at day 90)	533.6 (221.6)	530.0 (189.3)	0.948[‡]	
During-intervention	427.5 (219.8)	525.0 (214.4)	0.105[‡]	
p value	**0.002**[$]	0.767[$]		
Change	−106.2 (156.2)	−5.0 (86.7)	**0.005**[‡]	
Potassium (mg/day)				2,600 mg/day
Baseline (at day 90)	1185.1 (385.6)	1133.5 (314.2)	0.592[‡]	
During-intervention	1096.5 (660.8)	1117.4 (339.8)	0.885[‡]	
p value	0.324[$]	0.574[$]		
Change	−88.5 (457.8)	−16.1 (147.3)	0.440[‡]	

(Continued)

TABLE 3 (Continued)

Variables	Intervention group (n=27)	Control group (n=27)	p value	Recommended intake[#] (Females, 19–30years)
Sodium (mg/day)				1,500 mg/day
Baseline (at day 90)	2648.0 (781.7)	2681.9 (660.6)	0.864[‡]	
During-intervention	2105.4 (543.1)	2712.9 (870.9)	**0.004**[‡]	
p value	**<0.001**[$]	0.765[$]		
Change	−542.7 (624.0)	31.0 (533.1)	**0.001**[‡]	
Zinc (mg/day)				8 mg/day
Baseline (at day 90)	4.62 (1.67)	4.80 (1.88)	0.712[‡]	
During-intervention	3.65 (2.37)	4.73 (1.88)	0.069[‡]	
p value	**0.010**[$]	0.716[$]		
Change	−0.97 (1.81)	−0.07 (0.99)	**0.029**[‡]	
Fluoride (mg/day)				3 mg/day
Baseline (at day 90)	0.16 (0.07)	0.17 (0.13)	0.704[‡]	
During-intervention	0.12 (0.09)	0.17 (0.13)	0.091[‡]	
p value	0.052[$]	0.248[$]		
Change	−0.03 (0.08)	0.01 (0.03)	**0.026**[‡]	
Copper (µg/day)				900 µg/day
Baseline (at day 90)	737.8 (325.8)	819.6 (583.9)	0.528[‡]	
During-intervention	578.5 (344.6)	703.3 (308.7)	0.167[‡]	
p value	**0.004**[$]	0.272[$]		
Change	−159.3 (261.8)	−116.3 (538.8)	0.711[‡]	
Chromium (µg/day)				25 µg/day
Baseline (at day 90)	1.17 (0.63)	0.89 (0.68)	0.124[‡]	
During-intervention	1.03 (1.00)	0.96 (0.82)	0.772[‡]	
p value	0.531[$]	0.421[$]		
Change	−0.14 (1.13)	0.07 (0.43)	0.384[‡]	
Iodine (µg/day)				150 µg/day
Baseline (at day 90)	50.2 (27.5)	56.1 (45.6)	0.570[‡]	
During-intervention	40.2 (47.2)	57.2 (54.3)	0.225[‡]	
p value	0.260[$]	0.791[$]		
Change	−10.0 (44.9)	1.2 (23.1)	0.259[‡]	
Molybdenum (µg/day)				45 µg/day
Baseline (at day 90)	14.0 (21.6)	4.0 (7.6)	**0.030**[‡]	
During-intervention	15.5 (45.2)	4.2 (10.2)	0.215[‡]	
p value	0.806[$]	0.716[$]		
Change	1.5 (32.0)	0.2 (3.0)	0.833[‡]	
Selenium (µg/day)				55 µg/day
Baseline (at day 90)	60.2 (31.6)	58.8 (25.5)	0.851[‡]	
During-intervention	49.5 (36.0)	58.7 (30.5)	0.314[‡]	
p value	**0.025**[$]	0.987[$]		
Change	−10.7 (23.5)	−0.04 (12.3)	**0.043**[‡]	

[#]Food and Nutrition Board, Institute of Medicine, National Academies: Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes: https://ods.od.nih.gov/HealthInformation/nutrientrecommendations.aspx.
[‡]Independent samples t-test was conducted to determine differences in baseline, during-intervention and change means between the intervention group and the control group. Values of $p < 0.05$ are significantly different and presented in bold.
[$]Paired-samples t-test was conducted to determine differences in means between baseline and during-intervention for participants in the intervention group and the control group. Values of $p < 0.05$ are significantly different and presented in bold.

TABLE 4 Change in anthropometric and clinical variables of study participants.

Variables*	Intervention group (*n*=27)	Control group (*n*=27)	*p* value
Weight (kg)			
Baseline (at day 90)	86.6 (12.7)	84.4 (11.5)	0.520[‡]
Post-intervention	79.2 (12.1)	83.5 (11.4)	**<0.001**[#]
p value	**<0.001**[§]	**0.004**[§]	
Change	−7.4 (2.7)	−0.9 (1.5)	**<0.001**[‡]
BMI (kg/m²)			
Baseline (at day 90)	33.6 (4.9)	33.0 (4.8)	0.666[‡]
Post-intervention	30.7 (4.6)	32.6 (4.7)	**<0.001**[#]
p value	**<0.001**[§]	**0.004**[§]	
Change	−2.9 (1.1)	−0.3 (0.6)	**<0.001**[‡]
Body fat (%)			
Baseline (at day 90)	42.6 (4.8)	39.7 (5.8)	0.050[‡]
Post-intervention	38.2 (5.3)	38.9 (5.9)	**<0.001**[#]
p value	**<0.001**[§]	**0.008**[§]	
Change	−4.3 (2.0)	−0.8 (1.4)	**<0.001**[‡]
WC (cm)			
Baseline (at day 90)	99.2 (12.1)	94.1 (9.4)	0.087[‡]
Post-intervention	86.6 (11.1)	91.2 (10.8)	**<0.001**[#]
p value	**<0.001**[§]	**0.015**[§]	
Change	−12.7 (5.4)	−2.9 (5.7)	**<0.001**[‡]
HC (cm)			
Baseline (at day 90)	119.0 (8.0)	115.6 (7.6)	0.124[‡]
Post-intervention	111.9 (9.6)	114.1 (10.0)	**<0.001**[#]
p value	**<0.001**[§]	0.075[§]	
Change	−7.1 (4.5)	−1.5 (4.1)	**<0.001**[‡]
WHR			
Baseline (at day 90)	0.83 (0.07)	0.81 (0.06)	0.279[‡]
Post-intervention	0.77 (0.06)	0.80 (0.05)	**0.001**[#]
p value	**<0.001**[§]	0.088[§]	
Change	−0.06 (0.05)	−0.02 (0.04)	**0.001**[‡]
RBC count (10^6/μL)			
Baseline (at day 90)	4.7 (0.4)	5.1 (0.6)	**0.015**[‡]
Post-intervention	5.1 (0.5)	5.0 (0.6)	**<0.001**[#]
p value	**<0.001**[§]	0.091[§]	
Change	0.4 (0.4)	−0.1 (0.3)	**<0.001**[‡]
Hemoglobin (g/dL)			
Baseline (at day 90)	11.2 (0.9)	11.3 (0.8)	0.545[‡]
Post-intervention	11.7 (1.1)	11.4 (1.0)	**0.022**[#]
p value	**<0.001**[§]	0.246[§]	
Change	0.5 (0.6)	0.1 (0.6)	**0.022**[‡]
Hematocrit (%)			
Baseline (at day 90)	36.0 (2.6)	37.6 (3.0)	**0.037**[‡]
Post-intervention	37.2 (3.0)	37.0 (3.5)	**0.007**[#]
p value	**0.006**[§]	0.133[§]	
Change	1.2 (2.1)	−0.6 (2.0)	**0.002**[‡]
MCV (fL)			
Baseline (at day 90)	74.8 (5.4)	74.1 (6.9)	0.709[‡]

(Continued)

TABLE 4 (Continued)

Variables*	Intervention group (n=27)	Control group (n=27)	p value
Post-intervention	77.7 (7.5)	74.4 (7.4)	**0.005**[#]
p value	**<0.001**[§]	0.689[§]	
Change	2.9 (3.7)	0.2 (2.9)	**0.004**[‡]
MCH (pg)			
Baseline (at day 90)	24.1 (2.9)	23.1 (3.0)	0.253[‡]
Post-intervention	25.3 (3.1)	23.4 (2.4)	**0.007**[#]
p value	**0.001**[§]	0.425[§]	
Change	1.2 (1.8)	0.2 (1.5)	**0.033**[‡]
MCHC (g/dL)			
Baseline (at day 90)	31.3 (1.4)	30.7 (1.4)	0.115[‡]
Post-intervention	32.2 (1.2)	31.1 (1.2)	**0.021**[#]
p value	**0.003**[§]	0.277[§]	
Change	0.9 (1.5)	0.4 (1.6)	0.189[‡]
Serum ferritin (ng/mL)			
Baseline (at day 90)	9.9 (7.9)	9.6 (7.4)	0.913[‡]
Post-intervention	15.5 (10.4)	10.3 (7.7)	**<0.001**[#]
p value	**<0.001**[§]	0.321[§]	
Change	5.6 (5.8)	0.6 (3.3)	**<0.001**[‡]
Serum iron (μg/dL)			
Baseline (at day 90)	37.2 (18.6)	44.2 (20.1)	0.191[‡]
Post-intervention	50.2 (22.4)	46.5 (24.2)	**0.025**[#]
p value	**<0.001**[§]	0.437[§]	
Change	13.0 (16.2)	2.3 (15.1)	**0.015**[‡]
TIBC (μg/dL)			
Baseline (at day 90)	348.1 (57.4)	363.3 (52.1)	0.313[‡]
Post-intervention	330.7 (49.4)	360.7 (45.1)	**0.002**[#]
p value	**0.003**[§]	0.496[§]	
Change	−17.4 (27.4)	−2.6 (19.5)	**0.026**[‡]
TS (%)			
Baseline (at day 90)	11.4 (6.6)	12.6 (6.7)	0.488[‡]
Post-intervention	16.0 (8.8)	13.3 (7.8)	**0.005**[#]
p value	**<0.001**[§]	0.447[§]	
Change	4.7 (5.6)	0.6 (4.4)	**0.005**[‡]
hsCRP (mg/L)			
Baseline (at day 90)	10.1 (9.7)	8.8 (10.7)	0.650[‡]
Post-intervention	4.9 (6.0)	8.4 (7.7)	**<0.001**[#]
p value	**<0.001**[§]	0.706[§]	
Change	−5.2 (5.6)	−0.4 (5.9)	**0.004**[‡]
Serum hepcidin (ng/mL)			
Baseline (at day 90)	5.8 (2.9)	5.1 (3.2)	0.435[‡]
Post-intervention	3.8 (3.0)	4.9 (2.8)	**0.006**[#]
p value	**<0.001**[§]	0.685[§]	
Change	−1.9 (2.2)	−0.2 (2.2)	**0.005**[‡]

*BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-hip ratio; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TIBC, total iron binding capacity; TS, transferrin saturation; hsCRP, high-sensitivity C-reactive protein.

[#]ANCOVA test was conducted to determine differences in post-intervention means between the intervention group and the control group after adjusting for baseline values as a covariate. Values of $p < 0.05$ are significantly different and presented in bold.

[‡]Independent samples t-test was conducted to determine differences in baseline and change means between the intervention group and the control group. Values of $p < 0.05$ are significantly different and presented in bold.

[§]Paired-samples t-test was conducted to determine differences in means between baseline and post-intervention for participants in the intervention group and the control group. Values of $p < 0.05$ are significantly different and presented in bold.

TABLE 5 Pearson's correlation between changes in anthropometric measures, iron status markers, hsCRP, and serum hepcidin for all study participants (n=54).

Variables*	RBC count (10^6/µL)	Hemoglobin (g/dL)	Hematocrit (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Serum ferritin (ng/mL)	Serum iron (µg/dL)	TIBC (µg/dL)	TS (%)	hsCRP (mg/L)	Serum hepcidin (ng/mL)
Weight (kg)	**−0.529**	−0.252	**−0.415**	**−0.293**	**−0.294**	−0.089	**−0.305**	**−0.278**	**0.290**	**−0.308**	**0.359**	**0.393**
BMI (kg/m²)	**−0.516**	−0.265	**−0.419**	**−0.293**	**−0.306**	−0.110	**−0.298**	**−0.285**	**0.270**	**−0.310**	**0.379**	**0.402**
Body fat (%)	**−0.534**	**−0.271**	**−0.457**	**−0.279**	**−0.350**	−0.220	**−0.281**	−0.230	**0.314**	−0.251	0.228	**0.466**
WC (cm)	**−0.385**	0.023	**−0.272**	−0.223	−0.105	0.026	−0.173	−0.056	0.146	−0.111	0.244	**0.312**
HC (cm)	**−0.347**	−0.186	**−0.272**	−0.230	−0.072	−0.087	−0.133	−0.148	0.103	−0.229	0.039	**0.361**
WHR	−0.223	0.148	−0.153	−0.134	−0.066	0.078	−0.126	0.022	0.149	0.003	0.259	0.154
hsCRP (mg/L)	0.007	−0.204	−0.116	−0.033	−0.132	−0.123	−0.197	−0.229	0.051	−0.204	–	0.068
Serum hepcidin (ng/mL)	−0.191	−0.198	−0.210	**−0.303**	−0.176	−0.260	−0.045	−0.234	0.236	−0.210	0.068	–

*RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TIBC, total iron binding capacity; TS, transferrin saturation; hsCRP, high-sensitivity C-reactive protein. Correlation coefficients are determined using Pearson's correlation test. Correlation is statistically significant at value of p < 0.05 and significant correlations are presented in bold.

participated in a 6-month weight loss program. By the end of that study, the children had a significant weight loss, a significant increase in iron absorption, and a significant decrease in serum hepcidin (37). In another study, children with overweight and obesity who participated in a school-based physical exercise study for 8 months showed a significant decrease in BMI z-score, C-reactive protein (CRP), and serum hepcidin, and a significant increase in serum iron (38). A study among young women with overweight and obesity showed that participants who achieved at least 10% weight loss had significantly higher mean serum iron and mean TS compared to those who lost less than 5% of baseline weight (39). Additionally, a recent study concluded that weight loss improved serum iron markers via a positive effect on low-grade chronic inflammation based on significant changes in body weight, CRP level, and iron markers among premenopausal Turkish women with overweight and obesity who participated in a weight loss trial (40). The findings of all the above-mentioned studies were in harmony with the current study results, which reported significant improvements in iron markers and a significant decrease in hsCRP and serum hepcidin.

Interestingly, our results revealed that diet-induced weight loss in the intervention group improved iron status despite a lower mean intake of dietary iron. A study reported that the iron supplement was less effective in improving iron status in children with high BMI-for-age *z*-scores (41). These findings indicate that iron status in individuals with overweight and obesity may be affected by chronic inflammation and hepcidin levels above and beyond dietary intake of iron although this requires further investigation.

Although a significant positive correlation was observed between changes in weight and changes in both hsCRP and serum hepcidin. The levels of hsCRP and serum hepcidin were not correlated. Current evidence proposed that the elevation in serum hepcidin associated with obesity is affecting iron absorption through inflammatory pathways (7). The regulation of hepcidin by inflammation occurs in response to certain pro-inflammatory cytokines such as interleukin-6. Interleukin-6 triggers hepcidin synthesis via signal transducer and activator of transcription 3-dependent pathways (42). In this study, only hsCRP is used as a measure of pro-inflammatory activity. Interleukin-6 could have a higher correlation with serum hepcidin.

To our knowledge, this is the first study conducted among participants with overweight/obesity and IDA using a RCT design. RCT is a rigorous study design used to examine cause-effect relationships between an intervention and outcome. In addition, we used the gold standard 7-day food record to measure dietary intake, which helped to reduce measurement bias. Nonetheless, this study was conducted at a single site, which may limit the population source; however, appropriate randomization techniques were applied to avoid bias. While metabolic measures such as serum glucose level and lipid profile were not included in this study, the use of only hsCRP to indicate chronic inflammation limited the outcomes. The intervention duration also involved festive seasons, which may affect the intervention and outcomes. Long-term studies of more than 3 months, using multi-centers, with participants from multi-ethnic backgrounds, and including interleukin-6 level as another indicator of pro-inflammatory activity are highly recommended for future studies. Nevertheless, the results have proven the importance of diet-induced weight loss to correct iron deficiency in individuals with overweight or obesity. This evidence could be used as the basis for the development of low-cost early treatment for IDA, as opposed to supplementation, which eventually will help reduce the overall treatment cost for health sectors.

5. Conclusion

Our findings indicate that diet-induced weight loss among young women with overweight/obesity and IDA was associated with an improvement in iron status and its related clinical markers. This effect was suggested to link with reduced chronic inflammation and serum hepcidin levels due to reduced intestinal iron absorption mechanism. This finding proves the positive effects of diet-induced weight loss and can be used as one of the bases for treatment guidelines in women at risk of IDA, particularly those overweight or obese.

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 Human Research Ethics Committee at Universiti Sultan Zainal Abidin, Terengganu, Malaysia (UniSZA/UHREC/2020/172) and Ajloun Health Directorate, Ministry of Health, Ajloun, Jordan (No.: 22/8/140). The patients/participants provided their written informed consent to participate in this study.

Author contributions

NA, AA, and HA-J: conceptualization, methodology, validation, investigation, resources, supervision, project administration, and visualization. NA: software, formal analysis, data curation, writing—original draft preparation, and funding acquisition. AA and HA-J: writing—review and editing. All authors contributed to the article and approved the submitted version.

Funding

This study was self-funded by NA (PhD Candidate).

Acknowledgments

The authors would like to thank Hedayh Gharaibeh and Sana'a Smadi from Gharaibeh Diet Clinic, Ajloun, Jordan, Fakher Gharaibeh from Gharaibeh Medical Clinic, Ajloun, Jordan, Khaled Alshlool and his professional team from Ajloun Medical Labs, Ajloun, Jordan, and Yasmeen Jaber from Masoud Est. for Medical and Scientific Supplies, Amman, Jordan for their contribution in study conducting, data collection, and blood analysis.

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

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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 05 June 2023
DOI 10.3389/fnut.2023.1159809

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RECEIVED 06 February 2023
ACCEPTED 15 May 2023
PUBLISHED 05 June 2023

CITATION
Egele VS and Stark R (2023) Specific health beliefs mediate sex differences in food choice. *Front. Nutr.* 10:1159809.
doi: 10.3389/fnut.2023.1159809

Specific health beliefs mediate sex differences in food choice

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Objective: Although sex differences in dietary habits are well documented, the etiology of those differences is still a focus of research. The present study examines the role of specific health beliefs regarding healthy amounts of food for food choice and its relation to sex, more specifically, the assumption that sex differences in food choices are mediated by differentiating health beliefs.

Method: 212 German participants (44.3% female) aged 18–70 answered an online self-report questionnaire on their dietary habits and health beliefs, based on the recommendations of the German Nutrition Society.

Results: Most of the anticipated sex differences in food choice and some differences in health beliefs were found. The mediation hypothesis was partly supported, as the relationship between sex and fruit, vegetable, and fish consumption was mediated by the respective health beliefs. However, no mediation effects were found for meat, egg, cereal, and milk product consumption.

Conclusion: The support for the mediation hypothesis aligns with previous findings and indicates that health beliefs might be an important pathway to fostering healthier food choices, especially for men. Nonetheless, sex differences in food choice were only partially mediated by sex differences in specific health beliefs, indicating that future studies might benefit from parallel mediation analyses to reveal the impact of other relevant factors influencing sex differences in food choice.

KEYWORDS

food choice, health beliefs, sex differences, mediation, diet

1. Introduction

Poor diet is one of the most important issues nowadays, both in terms of a burden for the healthcare system as well as an influence on individual's health and overall quality of life (1–3). As the rates of obesity and overweight have nearly doubled since the 1980s, and obesity is mainly attributed to poor diet and eating habits (4, 5), fostering preventive health behavior is of great importance. Although poor diet is a nationwide phenomenon, men seem to be even more affected by it than women, as the prevalence of diseases associated with poor nutrition [e.g., obesity, cardiovascular disease, and diabetes (2) is higher for men (6–8)]. A search for causes has consistently shown that sex differences in dietary patterns are an important influencing factor (9–11). Since food choices are significantly influenced by health beliefs and it is known that men's and women's health beliefs differ, it is important to take a closer look at the role of health beliefs regarding dietary behavior depending on sex. A deeper understanding of the etiology of sex-related differences in food choice might allow to tailor interventions more specifically to the target group and, therefore, work more effectively.

A large number of studies demonstrate that men's diets differ from women's and can sometimes be seen as worse than women's (12, 13). Women make food choices that are closer to the national dietary guidelines (14), which is evident in a wide range of food categories. For example, women consume more fruit and vegetables, as well as more high-fiber foods than men, such as cereals and whole-grain bread (15–18). In contrast to this, men eat more eggs, milk products, fish, and meat than women (15, 18, 19), and a larger amount of food in men's diets is derived from animal products (20). Recent studies also show that women report a lower liking of meat than men (21) and tend to avoid meat in their diet (22). Men report a higher consummation of eggs than women (15). Wham and Worsley (23) showed that sex was a significant predictor of milk consumption, men drank more milk than women, and fewer men than women were non-consumers. Similar findings concerning milk product consumption were also found in longitudinal analyses (24).

Although sex differences in dietary patterns have been demonstrated in many studies, less is known about the etiology of the differences in food consumption. Even though the importance of understanding the influences on food choice for men and women has been recognized for years the topic is still the subject of scientific studies today (21, 25–28).

Food choices are determined by psychological, social, and cultural factors (21, 29–32). However, health beliefs seem to be of particular importance when it comes to explaining sex differences in food choices (9). For example, predisposing factors, such as beliefs, knowledge, and attitudes, and reinforcing factors, such as personal resources, were found to be associated with actual fruit, vegetable, and meat consumption (21, 33, 34). Further, especially the belief in the importance of a high fruit and vegetable diet had a great impact on fruit and vegetable intake. Also, more variance in fruit and vegetable intake was explained by psychological factors than by demographic characteristics.

Individuals' beliefs about specific foods and eating behavior can be characterized as action-regulation variables (35). Health beliefs can be defined as one's personal experience about all health-related topics (36). In contrast to knowledge, a belief is not based on objective principles or learned facts but on one's personal experience (37, 38). Health beliefs and their effects on food choice have been examined previously (39–44), indicating that health beliefs are strongly and positively associated with food choices (32, 45).

Health beliefs differ between men and women (9, 22). Concerning general diet-related health beliefs, women rate the factor "health" as more important than men when making food choices (15, 22). The findings of general diet-related health beliefs are also reflected in health beliefs regarding specific food categories. For example, it has been shown that women consider nutrient-dense foods as well as high-fiber foods like cereals, fruit, and vegetables (15, 29) to be healthier than men. Consistent with these findings, women attribute significantly more importance to health beliefs such as "avoiding high-fat foods," "adequate intake of fiber," "adequate consumption of fruit" and "avoiding additional salt" (11). Analogously, men believe high meat consumption to be desirable (46, 47) and consider a diet with meat and fish as more important for their health than women do (48). Men also value eggs more than women (15). Regarding milk products, differences in health beliefs are not entirely clear, as Wham and Worsley (23) stated. Women seem to have more positive attitudes toward them, but they are also more concerned about the fat content (49). It also seems that men and women like milk products equally (15).

As outlined above, sex-related differences in health beliefs and actual food consumption have often been replicated. Furthermore, numerous studies provide evidence for a close relationship between health beliefs about food and actual food consumption (9, 22, 32).

First evidence indicates a mediating function of health beliefs. For example, several studies have shown that women eat more foods that they consider to be beneficial to their health (22) and which are in line with their life goals (50). In addition, Wardle and colleagues (11) tested the relationship between sex, food choice (i.e., fat, high-fiber foods, fruit, and salt), and health beliefs. The particular health beliefs referred to the importance of the food choice for one's health on a scale from 1 (very low importance) to 10 (very high importance). In this study, they demonstrated that health beliefs are associated with both sex and actual dietary behaviors, and have a mediating effect (11). Recent studies show that about 40% of sex differences in food choices can be explained by health beliefs (9).

Despite these remarkable first results, the effects of specific health beliefs on sex differences in food choices have not been studied extensively and were limited to rather superficial assessments (11). There is a research gap concerning the role of specific health beliefs about healthy amounts of food for food choice and its relation to sex. Kraus (35) showed in a meta-analysis that the correlations of self-reported health behavior with beliefs are higher when the levels of specificity in beliefs and behavior are comparable. Thus, to foster a deeper understanding of the food choices of men and women, it seems obvious to examine the role of very specific health beliefs, namely beliefs on the amount of food that is considered to be healthy.

Therefore, the goals of the present study are as follows: First, previously shown sex differences in food choices ought to be replicated. Secondly, sex differences in specific health beliefs (i.e., food choices personally considered to be healthy) will be examined. Thirdly, the mediating role of these specific health beliefs on sex differences in food choices will be investigated.

> *H1*: Women eat more fruit, vegetables, and cereals than men. Men eat more meat, fish, eggs, and milk products than women.
>
> *H2*: Women believe larger amounts of fruit, vegetables, and cereals to be healthy rather than men do. Men believe larger amounts of meat, fish, and eggs to be healthy more than women do. For milk products, sex differences will be examined exploratively.
>
> *H3*: The association between sex and actual food consumption is mediated by specific health beliefs.

2. Methods

The conduct of this study complied with the ethical standards of the responsible committee (Anonymized).

2.1. Sample

Previously reported effect sizes of sex differences in diet and physical activity were mostly small (29), thus, small effects were anticipated (51). The intended sample size calculated by G*Power 3.1 was 212 participants (52). The acquired sample included 216 German participants. Four participants were excluded from the analyses, as they did not complete the entire questionnaire and dropped out. Therefore, the final sample contained 212 participants (44.3% female) between the ages of 18 and 70 ($M = 31.03$, SD = 13.65). The mean age of the 94 female participants was 25.87 years (SD = 9.82, range 18–60), and the mean age of the 118 male participants was 35.14 years (SD = 14.87, range 18–70). 75% of the sample had graduated from high school and nearly 32% of those participants had a university degree.

2.2. Instruments

For demographics, sex, age, and education were assessed by rating scales.

Dietary habits were measured with seven items based on the recommendations of the German Nutrition Society (53). The German Nutrition Society divides food into seven groups: vegetables, fruit, cereals, milk products, meat, fish, and eggs. It is recommended to eat at least three portions of vegetables per day, as well as at least two serving sizes of fruit per day, two serving sizes of cereals, and two serving sizes of dairy products. In addition, it is recommended to consume two serving sizes of meat, two serving sizes of fish, and three eggs per week. To assess dietary habits, the subjects´ average amount of servings consumed per day was assessed for vegetables, fruit, cereals, milk products, meat, fish, and eggs (e.g., How many servings of fruit did you eat on average per day in the last 7 days?). The items translated from German are included in the Supplementary material. Here, to ensure better comparability, the approach of other authors was followed (29), who also suggested working with serving sizes (50). Therefore, before answering the questions, subjects were presented with an example item for a fruit and vegetable serving, which were based on the guidelines of the German Nutrition Society (53). A short-form consumption questionnaire was chosen, as it was shown previously that the short-form achieves similar precision to a long-form questionnaire (i.e., a detailed query of fruit and vegetable types), with the advantage of being quicker to answer (54).

Health beliefs of dietary behavior were assessed similarly to the actual dietary behavior. The number of servings per day that the subjects considered healthy were assessed for vegetables, fruit, cereals, milk products, meat, fish, and eggs (i.e., How many servings of fruit do you consider to be healthy?). Again, the items translated from German are included in the Supplementary material. Dietary habits and health beliefs were assessed using an open-response format to avoid the confounding effects of a forced-choice format (55).

2.3. Procedure

All hypotheses were specified before the data were collected. The online questionnaire was implemented using SoSci Survey (56). First of all, participants gave informed consent before taking part and agreed to the data protection regulation. Then, they provided information on their health beliefs. Thereafter, health behavior was assessed. Finally, subjects were asked to provide information about their attitudes and socio-demographic data.

2.4. Analytic strategies

Data analysis was conducted using IBM SPSS Statistics 28 and version 3.2 of the PROCESS macro by Hayes (57). The significance level was set at $\alpha = 0.05$. Outliers were excluded based on absolute deviation around the median, as suggested by Leys et al. (58) because this method is considered particularly robust.

As food intake is known to change as individuals age (59), age was included as a covariate in all analyses. Analyses of covariance (ANCOVA) were used to analyze if food consumption and health beliefs differ between men and women, controlling for age. To test whether the relationship between sex and food consumption was mediated by specific health beliefs, the PROCESS macro module was used (57). In this analysis, testing the indirect path is recommended to determine mediating effects (57, 60). The assumptions for the statistical procedures were ensured before the data analyses. Data is available on request due to privacy and ethical restrictions.

3. Results

3.1. Testing for sex differences in food consumption and respective health beliefs

As displayed in Table 1, women ate significantly more fruit, vegetables, cereals, and eggs, than men, who ate significantly more meat than women. Regarding fish and milk product consumption, no significant sex differences were found. The covariate, age, was not significantly related to fruit, vegetable, cereal, meat, and milk product intake, but there was a significant relation of age to fish intake. In support of hypothesis 1, women reported eating more servings of fruit, vegetables, and cereals per day, and men reported eating more meat. However, contrary to the hypothesis, women reported eating more eggs per day and the expected sex differences for fish and milk products consumption were not found.

Moreover, women considered significantly larger amounts of fruit, vegetables, and fish, to be healthy, than men did, whereas no significant sex differences in health beliefs were found for meat, milk products, eggs, and cereals. The covariate, age, was significantly related to beliefs on vegetables, and cereals, but not to beliefs on fruit, meat, fish, eggs, and milk products. Results supported hypothesis 2 for health beliefs on fruit, and vegetables, but not for the remaining food categories, where differences were either non-significant (meat and cereals) or contrary to the hypothesis (fish). Beliefs about milk products did not differ for men and women.

3.2. Testing for mediating effects of health beliefs on the relationship between sex and food consumption

The PROCESS macro module by Hayes (57) was used to test if health beliefs mediate the relationship between sex and food consumption. In these analyses, sex was included as the independent variable, food consumption as the dependent variable, and health

TABLE 1 Descriptives and test statistics for Hypothesis 1 (food choice) and Hypothesis 2 (health beliefs).

Measure	Men			Women			Sex differences				Covariate: age			
	n	*M*	*SD*	*n*	*M*	*SD*	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Food choice														
Fruit	111	1.31	1.13	86	2.10	1.29	18.46	1, 194	<0.001	0.09	< 0.01	1, 194	0.958	< 0.01
Vegetables	109	1.44	1.26	78	2.79	1.42	34.96	1, 184	<0.001	0.16	3.29	1, 184	0.071	0.02
Meat	114	1.25	1.29	88	0.85	1.09	5.16	1, 199	0.024	0.03	0.02	1, 199	0.889	< 0.01
Fish	83	0.09	0.12	63	0.02	0.07	2.93	1, 143	0.089	0.02	15.25	1, 143	< 0.001	0.10
Eggs	109	0.46	0.53	83	0.70	0.77	6.34	1, 189	0.013	0.03	0.27	1, 189	0.605	< 0.01
Cereals	108	1.74	1.36	81	2.47	1.56	8.90	1, 186	0.003	0.05	0.31	1, 186	0.581	< 0.01
Milk products	109	1.19	1.02	82	1.13	0.86	0.16	1, 188	0.687	< 0.01	< 0.01	1, 188	0.965	< 0.01
Health beliefs														
Fruit	116	1.64	0.98	87	2.30	0.99	25.14	1, 200	<0.001	0.11	2.17	1, 200	0.143	0.01
Vegetables	115	1.82	1.25	88	2.95	1.22	27.40	1, 200	<0.001	0.12	10.96	1, 200	0.001	0.05
Meat	117	0.59	0.49	92	0.50	0.57	1.63	1, 206	0.203	0.01	0.49	1, 206	0.484	< 0.01
Fish	117	0.48	0.39	91	0.69	0.54	9.89	1, 205	0.002	0.05	0.03	1, 205	0.859	< 0.01
Eggs	115	0.65	0.57	89	0.73	0.61	0.28	1, 201	0.599	< 0.01	1.78	1, 201	0.183	0.01
Cereals	111	1.27	0.80	82	1.60	0.85	2.96	1, 190	0.087	0.02	6.37	1, 190	0.012	0.03
Milk products	118	1.18	1.08	94	1.23	1.30	0.62	1, 209	0.432	< 0.01	2.09	1, 209	0.150	0.01

Food consumption and health beliefs are scaled in portions per day. *n*, sample size; *M*, mean; *SD*, standard deviation; *F*, *F*-statistic; *p*, value of *p*; *df*, degrees of freedom; η_p^2, partial eta-squared.

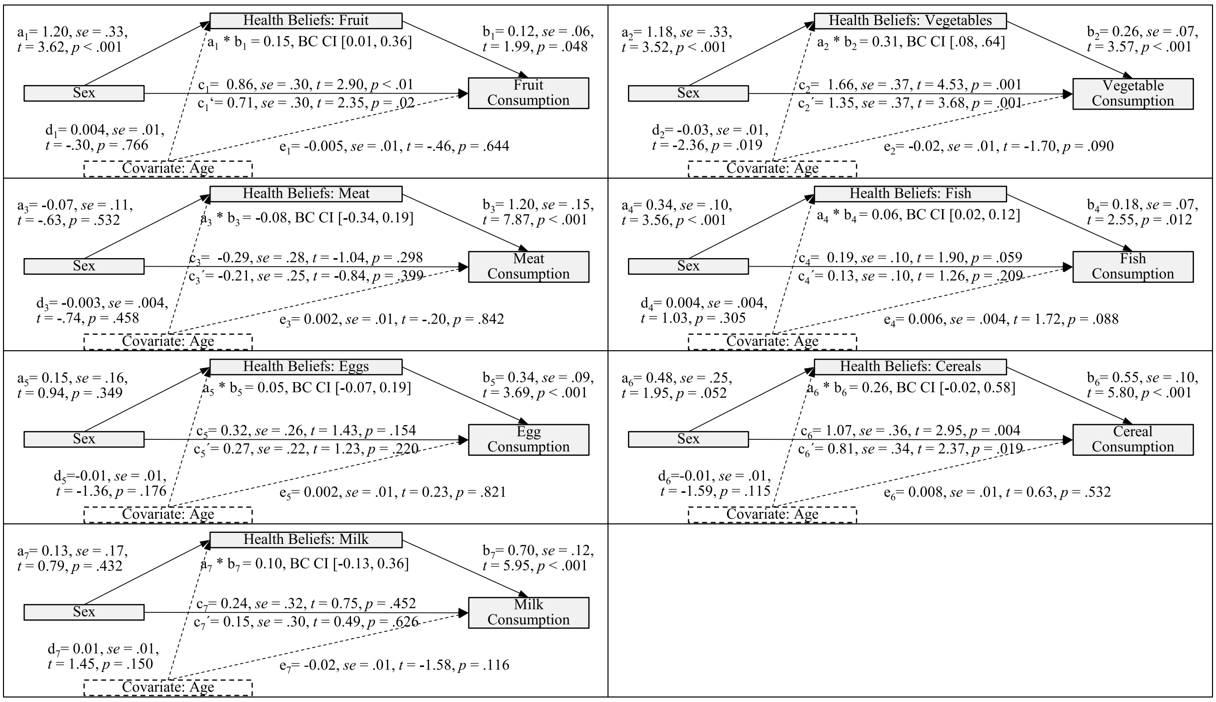

FIGURE 1
Statistical models for a mediating effect of health beliefs on the relation of sex and food choice (Hypothesis 3). a: effect of gender on health beliefs (women are coded 1, men 0); b: effect of health beliefs on consumption; c: total effect of sex on consumption; c′: direct effect of sex on consumption; d: effect of age on health beliefs; e: effect of age on consumption; a*b: indirect effect of sex on consumption mediated by health beliefs while controlling for age; t: test statistic; *se*: standard error; BC CI: 95% bias-corrected bootstrap confidence interval.

belief as a mediator. As a covariate, age was included in the analyses. For each food category, a separate mediation analysis was conducted. As depicted in Figure 1, health beliefs fully mediated the effects of sex on fish consumption. Sex differences in fruit consumption as well as in vegetable consumption were partially mediated by specific health beliefs. Sex differences in meat, egg, cereal, and milk product consumption were not mediated by specific health beliefs. Thus, hypothesis 3 was partly supported.

TABLE 2 Overview of the fingings for Hypothesis 1 (food choice), Hypothesis 2 (health beliefs), and Hypothesis 3 (mediation).

	Food Choice		Health Beliefs		Mediation	
Measure	Hypothesis	Finding	Hypothesis	Finding	Hypothesis	Finding
Fruit	Women eat more fruit than men.	✓	Women believe larger amounts of fruit to be healthy.	✓	The association between sex and fruit consumption is mediated by specific health beliefs.	✓
Vegetables	Women eat more vegetables.	✓	Women believe larger amounts of vegetables to be healthy.	✓	The association between sex and vegetable consumption is mediated by specific health beliefs.	✓
Meat	Men eat more meat.	✓	Men believe larger amounts of meat to be healthy.	✓	The association between sex and meat consumption is mediated by specific health beliefs.	▬
Fish	Men eat more fish.	✓	Men believe larger amounts of fish to be healthy.	✗	The association between sex and fish consumption is mediated by specific health beliefs.	✓
Eggs	Men eat more eggs.	✓	Men believe larger amounts of eggs to be healthy.	▬	The association between sex and egg consumption is mediated by specific health beliefs.	▬
Cereals	Women eat more cereals.	✗	Women believe larger amounts of cereals to be healthy.	▬	The association between sex and cereal consumption is mediated by specific health beliefs.	▬
Milk products	Men eat more milk products.	▬	Exploratory analysis.	▬	The association between sex and milk product consumption is mediated by specific health beliefs.	▬

✓, expected differences; ▬, no significant differences; ✗, significant differences contrary to hypothesis.

A concise overview of the hypotheses and results is presented in Table 2.

4. Discussion

The current study investigated the effects of specific health beliefs on the relation between sex and health behavior. Firstly, a replication of previously shown sex differences in food choices was attempted. Secondly, sex differences in specific health beliefs (i.e., food choices personally considered to be healthy) were examined. Thirdly, the mediating role of these specific health beliefs on sex differences in food choices was investigated.

4.1. Sex differences in health behavior and health beliefs

In line with previous findings, it was replicated that women eat more fruit, vegetables, and cereals than men, while men eat more meat. Health beliefs for fruit and vegetable consumption were also replicated. This corresponds with previous studies reporting that women consume more fruit and vegetables (15, 17, 29), just like the findings that women consider fruit and vegetables to be healthier than men and attribute significantly more importance to an adequate consumption of fruit (11, 15, 29).

Whereas the finding that women report consuming larger amounts of cereals is compatible with previous findings (16, 18), differences in health beliefs on cereals were not found in the present study. A similar pattern appeared for meat. As expected, men reported eating more meat than women. Although previous findings highlight the importance of meat for men (46, 47), no sex differences in the health beliefs on meat were found yet. Perhaps, women accord higher importance to cereals and men attribute higher importance to meat, but the amount of cereals resp. meat considered healthy does not vary for men and women.

Contrary to previous findings, women reported eating more eggs than men and no significant sex differences were found in the health beliefs concerning eggs. Hu and colleagues (61) discuss the possibility of inaccurate self-reports concerning egg consumption. Although previous studies have shown that egg consumption can be reported with relatively high accuracy (62, 63), it is unclear whether that was the case in the present study and whether the accuracy is comparable for men and women. As women tend to have higher knowledge of nutrition and diet (64), it might be possible that they are better at assessing which foods contained eggs, which might explain the higher reported consummation and the missing differences in the health beliefs.

In the present study, no significant sex differences were found in the reported fish consumption, which contradicts the assumption that men eat more fish than women which has been shown specifically for wild fish (65) as well as raw oysters (66). The sex differences in health beliefs on fish seem to contradict previous literature, claiming that men believe a diet with fish to be more important than women (48). But, as fish consumption correlates positively with the consumption of other foods that are considered healthy [e.g., fruit and vegetables (67)], and women, in particular, eat more "healthy foods" (17, 68), perhaps this phenomenon resulted in the missing differences in the reported fish consumption and explains the differences in health beliefs. Furthermore, some previous studies found similar patterns with women considering seafood and grilled fish slightly healthier than men, descriptively, but did not differ significantly in their beliefs (69).

Regarding milk product consumption, the anticipated differences in behavior were not found, and there were also no significant sex differences in the respective health beliefs. Perhaps, the ambivalence as stated by Wham and Worsley (23) with women being more appreciative of the nutritional value than men, but concerned about the fat content, eclipses potential sex differences. In addition to this, there has been an increasing controversy regarding milk products in recent years (70). For example, there have been claims that dairy products increase the risk of chronic diseases like obesity, type 2 diabetes, cardiovascular diseases, osteoporosis, and cancer. Therefore, it seems as if milk products have become less relevant to people's lifestyles, and there is increasing skepticism about the health consequences of consuming milk products (23). Yet, amongst those who consume milk products, the health benefits of these products are still valued highly both by men and women (63).

In previous studies, the effect sizes for the sex differences in health behavior and health beliefs were rather small (11, 29). In this study, sex differences in food consumption and health beliefs were more articulated with medium to high effect sizes (51, 68). An evident explanation comes from the statistical analyses used. As potential age-related differences in food intake could have impacted not only food intake (59), but also health beliefs and the relation of both, age was included in all analyses as a covariate. The rationale for this decision is not only supported theoretically but seems to be particularly relevant in this study because of systematic age differences between the two quasi-experimental groups despite the random selection of participants. Not including age as a covariate, in this case, might have led to confounding gender effects with age effects. From an empirical standpoint, however, controlling potential age effects did not seem to be quite as relevant; the results of the statistical analyses and the effect sizes changed only marginally, when not controlling age effects in food choice. Therefore, contextual explanations are also drawn upon. Perhaps, the more pronounced sex differences in food choice can be explained by cultural factors, as the importance of cultural heritage for food choice and food preferences has previously been established (71). Future studies could consider cultural factors regarding dietary behavior in addition to the influence of health beliefs.

Considering these reflections, the results of the present study are rather alarming in terms of external validity, since considerable sex differences in health beliefs and food choices were found in a rather educated German sample. The sample consisted mostly of well-educated participants. In the present sample, nearly 75% of participants had graduated from high school. Compared to nationwide data regarding educational attainment, the sample, therefore, does not seem representative of Germany, where an average of 32% of adults have a high school diploma (72). In the present study, the higher percentage of participants with higher educational attainment may have led to a variance restriction in health behaviors, presumably making the effects more pronounced in a more heterogeneous sample. It seems possible that sex differences in food choices and health beliefs might be even more articulated in a sample with a wider range of education and socioeconomic status (11). Correlations of health behaviors, such as healthy eating and intelligence as well as socioeconomic status, have been widely documented (73, 74). Multiple studies yielded evidence for a positive relation between the adoption and adherence to healthy eating practices and better health outcomes (75, 76), indicating that the articulated sex differences in food choice and health beliefs might translate into nutritional differences and impact health in the long term (11). Thus, the need for research to understand sex differences and their provenance in dietary intake and health beliefs seems even more important.

4.2. The mediating effect of specific health beliefs

As expected, health beliefs mediated the relation between sex and actual food consumption for fruit, vegetables, and fish. Analogous to the findings of Wardle and colleagues (11), sex differences in food choices concerning fruit and vegetables were partially mediated by sex differences in specific health beliefs. Thus, differences in health beliefs could explain sex differences in food choice, but even after the introduction of the mediator, the predictor still has some remaining effects. Wardle and colleagues (11) hypothesized that women might be more concerned about health considerations and also more likely to translate those attitudes into actions, which might explain the remaining sex differences in food choices.

Sex differences in fish consumption were fully mediated by health beliefs. Perhaps, many other influencing factors that play an important role in fruit and vegetable consumption, like the "5 a day" campaigns (77, 78), are less important for fish consumption. Therefore, factors like health beliefs may explain most sex differences in fish consumption. It is also possible that this finding is more like a testing effect: if participants do not exactly know what they believe to be a healthy amount of fish to eat per day, they might simply be basing their beliefs on their behavior. This assumption would lead to higher correlations between behavior and beliefs. Nonetheless, in this study, the correlation between the health beliefs for fish and fish consumption was not higher than the respective correlations for the other six food categories.

Statistics failed to demonstrate evidence of sex differences in food consumption being mediated by specific health beliefs for meat, eggs, cereals, and milk products consumption. Several explanatory approaches can be used to interpret these results. It is conceivable that there might actually be no mediating effect in this respect, since the test power should have been given by the sample planning preceding the data collection (described in the methods section).

However, it is also possible that the questioning of health beliefs was too coarse, i.e., one should not have asked for the categories given by the German Nutrition Society [e.g., "cereals" (53)], but with higher specificity (e.g., white flour products, whole grain products, etc.). Indeed, previous research demonstrated gender differences at this level of specificity (79). However, this is contradicted by the fact that gender differences in consumption were mostly found when considering food choice. Therefore, the health beliefs were perhaps covered too specifically to take a mediating role. Previous studies have often assessed broader health beliefs and focused on fewer food categories (11). Concerning the food categories, which did not provide clear mediation effects in the present study, unfortunately, few previous findings have been published so far so replication is required at this point. A conceptual replication could consider whether more specific health beliefs or broader health beliefs than in the present study take on a mediating role with respect to the relationship between gender differences and food choice.

4.3. Implications for research and practice

Our findings suggest that specific health beliefs explain some of the sex differences in dietary behavior. Given the rather suboptimal health behavior, especially among men, it seems appropriate to tailor different health interventions, to adapt the health education for men and women, and to target primarily the modification of specific health beliefs of men in the future. Similar conclusions were drawn by recent studies (21). Although an intervention targeting knowledge on healthy eating might not be sufficient to elicit behavioral consequences, since health beliefs may be influenced by knowledge but they are more based on personal experience than on objective principles or learned information (37, 38), numerous previous studies found significant gaps in knowledge about the basic recommendations for a healthy diet. On top of that, there were considerable sex differences in knowledge, and men had even less knowledge than women (64). Thus, interventions fostering knowledge on healthy eating, for example regarding the benefits of a plant-based diet rich in fruits and vegetables, could result in men changing their specific health beliefs to be closer to the official recommendations for healthy behaviors.

However, as mentioned before, according to the mediation results, other factors influencing food choice may also play an important role in sex differences in healthy eating, like food preferences or attitudes toward health. For example, sex differences in the beliefs of the importance of healthy eating were shown to contribute to the sex differences in food choices, as well as differences in dieting beliefs (11). For future research, examining the different influencing factors by parallel mediation analyses seems to be relevant, as it seems plausible that both general health beliefs, whether a food is more "healthy" or "unhealthy," in combination with specific health beliefs on the optimal amount of food, as well as general dieting beliefs, may serve as mediators for the relation of sex and health behavior. Furthermore, extending the research on the role of health beliefs to other food categories than fruit and vegetables, as demonstrated in this study, seems to be of great importance to address existing research gaps and interpretive challenges in this regard.

5. Limitations

It must be noted that a limitation of the present work is the survey method. Dietary behaviors were collected retrospectively, using an online self-report questionnaire. This assessment method may have resulted in recall biases, subjects not being able to participate in the study due to the online survey format (80), or socially desirable response behavior (81). Despite these limitations, the assessment method was chosen because it is cost-effective (54) and has a high test economy (82). Nevertheless, the limitations of retrospective self-reports as a means to assess dietary behaviors can be addressed in future studies through situational surveys, third-party interviews, or more objective collection methods.

Another limitation concerns the quasi-experimental research design without measurement repetition. Since there was only one measurement time point, causal interpretations about the relationship between beliefs and behavior are limited (82). However, the study design chosen in the present work offers the advantage that the motivation of the participants can be better maintained, the chosen recording of health behavior is not an intervention compared to diary studies, and the survey in the natural environment is time-saving and is associated with high ecological validity (82).

6. Conclusion

This study aimed at exploring the relationship between sex, dietary behaviors, and specific health beliefs. Concerning dietary behavior and specific health beliefs, most previously established sex differences were replicated, for example, the finding that women eat more fruit and vegetables than men, and believe more servings of fruit and vegetables to be healthy. Moreover, sex differences in specific health beliefs were shown to explain sex differences in dietary behavior for fruit, vegetable, and fish consumption. Although other factors influencing food choice and their relation to specific health beliefs should be considered in future studies, the present findings hint at the relevance of tailored health interventions to alter specific health beliefs in men and women to improve their dietary behavior.

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 Ethics Committee of the Faculty of Empirical Human and Economic Sciences of Saarland University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

VE: conceptualization, methodology, investigation, data curation, formal analysis, visualization, writing-original draft preparation, writing-reviewing, and editing. RS: supervision, conceptualization, methodology, resources, formal analysis, writing-reviewing, and editing. 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.

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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.2023.1159809/full#supplementary-material

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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 15 June 2023
DOI 10.3389/fnut.2023.1197485

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RECEIVED 31 March 2023
ACCEPTED 26 May 2023
PUBLISHED 15 June 2023

CITATION
Sulhariza HZ, Zalilah MS and Geeta A (2023) Maternal hemoglobin change from early pregnancy to second trimester is associated with risk of gestational diabetes mellitus: a retrospective cohort study.
Front. Nutr. 10:1197485.
doi: 10.3389/fnut.2023.1197485

Maternal hemoglobin change from early pregnancy to second trimester is associated with risk of gestational diabetes mellitus: a retrospective cohort study

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Introduction: The accrual of iron that is reflected in high maternal hemoglobin (Hb) status is increasingly recognized as a risk factor for gestational diabetes mellitus (GDM). Changes in maternal Hb level could also implicate glycemic status in pregnancy. This study aimed to determine the associations between maternal Hb levels and their changes with GDM.

Methods: In this retrospective cohort study, a total of 1,315 antenatal records of mothers with singleton pregnancies from eight health clinics of a district in the northern region of Peninsular Malaysia who delivered between 1st January 2016–31st December 2017 were analyzed. Data extracted from the records were socio-demographic, anthropometric, obstetrical, and clinical data. Hb levels were extracted at booking (<14 weeks) and second trimester (14–28 weeks). Change in Hb was determined by subtracting the Hb level in the second trimester from the booking Hb level and was categorized as decreased, unchanged, and increased Hb. The associations between maternal Hb levels and their changes with GDM risk were analyzed using multiple regression, adjusting for covariates in four different models. Model 1: maternal age and height. Model 2: covariates of Model 1 added with parity, history of GDM, and family history of diabetes. Model 3: covariates of Model 2 added with iron supplementation at booking. Model 4: covariates of Model 3 added with Hb level at booking.

Results and Discussions: Unchanged Hb level from booking to second trimester was significantly associated with GDM risk in Model 1 (AOR: 2.55; 95% CI: 1.20, 5.44; $p<0.05$), Model 2 (AOR: 2.45, 95% CI: 1.13, 5.34; $p<0.05$) Model 3 (AOR: 2.42; 95% CI: 1.11, 5.27; $p<0.05$), and Model 4 (AOR: 2.51; 95% CI: 1.15, 5.49; p<0.05). No significant associations were observed between maternal Hb levels and GDM in the study.

Conclusion: Unchanged Hb levels from the booking (<14 weeks of gestation) to the second trimester (14–28 weeks) increased GDM risk. Further investigation is warranted to evaluate the associations between changes in maternal Hb and GDM risk and to identify potential factors influencing this relationship.

KEYWORDS

gestational diabetes mellitus, hemoglobin level, hemoglobin change, iron supplement, retrospective cohort

10.3389/fnut.2023.1197485

Introduction

Hyperglycemia that is first detected at any time during pregnancy can be classified as either diabetes in pregnancy (DIP) or gestational diabetes mellitus (GDM) (1). DIP may be an undiagnosed type 2 diabetes mellitus (T2DM) or "overt diabetes" identified in the first trimester while GDM develops in the second and third trimesters (2–5). Globally, an estimated 21.1 million live births were exposed to some forms of hyperglycemia in pregnancy, of which 80.3% were due to GDM (6). GDM prevalence is generally considered to be somewhere from 1 to 28% of all pregnancies. The variation in prevalence rates could also be related to the diversity of the populations studied, the screening methods, and the diagnostic criteria used. Nevertheless, with the increasing prevalence of T2DM, the incidence of GDM is also on the rise wherever the rate of obesity is prevalent (7–9). In the current global epidemic of diabetes, the age of onset has decreased significantly, which concurrently affects a significant proportion of reproductive-age women (7–9).

In 2016, the national surveillance on Maternal and Child Health reported that the prevalence of hyperglycemia during pregnancy in Malaysia was 13.5% (10). However, this report did not distinguish the types of maternal hyperglycemia. A systematic review reported a pooled prevalence of GDM in Malaysia at 21.5% (11). The high prevalence was due to the high heterogeneity of studies that could be influenced by subject recruitment, diagnosis criteria, screening standards, and the definition of GDM (11). On the contrary, two systematic reviews of the GDM pooled prevalence in Asian countries reported a lower prevalence (10.1–11.5%) in Malaysia, in which only two local studies were included in the analysis (12, 13).

Iron accumulation is increasingly recognized to be associated with an increased risk of T1DM and has been proposed to be involved in the pathophysiological mechanism of T2DM (14) as well as GDM (15, 16). Although iron is essential for many important metabolic processes, the excessive iron level may be pathological. Through the Fenton reaction, iron can generate reactive oxygen leading to oxidative stress, affecting the β-cells to dysfunction and may reduce insulin secretion and increases insulin resistance (17). Hemoglobin (Hb) is the largest body iron pool in the body that is commonly used as a crude iron biomarker (18). Maternal anemia and high Hb concentration during pregnancy have been reported to increase the risks of adverse pregnancy outcomes and maternal health (19–22). Pregnant women with Hb <11.0 g/dL are considered anemic and Hb levels within the normal range (11.0–14.0 g/dL) during pregnancy are considered beneficial for the well-being of the mother and fetus (23). Anemia in pregnancy is associated with poor maternal outcomes such as preterm birth, low birth weight, infection, and neonatal complications (21, 24). On the other hand, high maternal Hb increases blood viscosity, causing placental perfusion that leads to poor maternal-fetal exchange which would result in adverse pregnancy outcomes such as low birth weight, preterm births, preeclampsia, GDM and stillbirths (25–27).

There is increasing evidence of the relationship between elevated Hb and GDM (25, 28, 29). However, the available literature reported mixed findings compared to the association of Hb status with T1DM and T2DM. During pregnancy, women need to have Hb level ≥ 11.0g/dL to ensure an uncomplicated pregnancy, healthy development of the fetus, and maturity of the newborn child. In Malaysia, efforts to ensure a lower incidence of iron deficiency anemia (IDA) in pregnancy include the practice of iron supplementation as prophylaxis or even as a treatment and dietary advice on the intake of iron-rich foods (30, 31). High maternal Hb level has always been perceived as a sign of good nutritional status rather than as a contributing factor to adverse pregnancy outcomes, such as GDM. It has also been reported that the changes in maternal Hb levels from early to mid- or late pregnancy could implicate pregnancy outcomes (22, 32), but none are specific to GDM. As there are gaps in the available literature on the relationships between maternal Hb level and its changes with GDM, this study aimed to determine the associations of Hb concentrations at booking and second trimester and changes in Hb concentrations from booking (<14 weeks) to the second trimester (14–28 weeks) with GDM risk.

Methods

Data sources

Data for this retrospective cohort study was obtained from antenatal cards in eight health clinics (HCs) in Kuala Muda, Kedah. The antenatal card is a well-established record by the Ministry of Health Malaysia (MOH). Women receiving antenatal care services in HCs are issued two copies of antenatal cards, one kept by the women and the second by HCs. For this study, data were derived from the second copy of antenatal cards of women who delivered from January 2016 to December 2017. Maternal information extracted from the antenatal cards were socio-demographic characteristics (e.g., maternal age, educational level, ethnicity, and follow-up date), obstetrical information (e.g., gravidity, parity, history of GDM, and family history of diabetes), anthropometric measurements (e.g., weight at booking and height), and clinical information (e.g., maternal glucose, Hb, and iron supplementation).

Sample size and study population

Using a formula for cohort study (33), the minimum sample needed for this study was 430 women, based on the prevalence of GDM in Malaysian women (11.8%) (34). The inclusion criteria were Malaysian, singleton pregnancy with a complete antenatal record from booking until the second oral glucose tolerance test (OGTT) in the second trimester. The exclusion criteria included maternal age < 19 years old, incomplete OGTT records, diabetes, blood disorders, cardiovascular disease, infectious disease, thyroid disorder, and placenta previa.

There were 7,324 registered births for the eight HCs from 1st January 2016 to 31st December 2017. Of the total number, 1698 antenatal cards were damaged or could not be found, leaving 5,626 cards available for screening. About 1,356 women had antenatal care elsewhere and attended antenatal visits in Kuala Muda after 32 weeks. A total of 2,563 antenatal cards had incomplete records of biochemical and clinical data between booking until the second trimester with 302 women had miscarriage or intrauterine death (IUD), 402 were admitted to the hospital before the second OGTT due to various medical conditions, 759 women made the antenatal booking at the HCs but continued to follow up in other antenatal care clinics but came back for delivery, and 1,028 with no records of OGTT. The remaining 1707 were checked for inclusion and exclusion criteria. The final sample included in this study comprised 1,315 antenatal records with complete data on two times OGTT, biochemical, and clinical data (Figure 1).

Maternal data and other measurements

The socio-demographic information included the date of birth, ethnicity, and education level. Age of women was calculated by subtracting the date of birth from the date of the first antenatal visit (booking). Obstetrical information extracted were gravidity, parity, history of GDM, and family history of diabetes. As pre-pregnancy weight was not available in the study, weight at booking (4th–13th week of pregnancy) was used to estimate the pre-pregnancy body mass index (BMI). BMI was calculated and categorized according to the World Health Organization classification; underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2) (35).

Women in this study underwent a 1-step 75g OGTT before 14 weeks of gestation (OGTT 1) and was repeated during 24–34 weeks of gestation (OGTT 2). The screening involved a fasting glucose plasma (FPG) test and a 2-h postprandial (2-HPP). GDM was diagnosed if the results were ≥ 5.6 mmoL/L for FPG and ≥ 7.8 mmoL/L for 2-HPP (MOH, 2013). Hb levels were extracted at booking (4th–13th week) and at the highest gestational week of each trimester that was available (first trimester: 4th–13th week; second trimester: 14th–28th week). The study used a reference of Hb concentration based on the low Hb cut-offs of <11.0 g/dL, also classified as anemia in pregnancy (30, 36) and used a suggestion of Hb ≥13.0 g/dL from a meta-analysis study as high Hb reference (25). Change in Hb from booking until the second trimester was calculated to measure the difference of Hb value at booking compared to Hb value at the second trimester. The change in Hb was calculated by

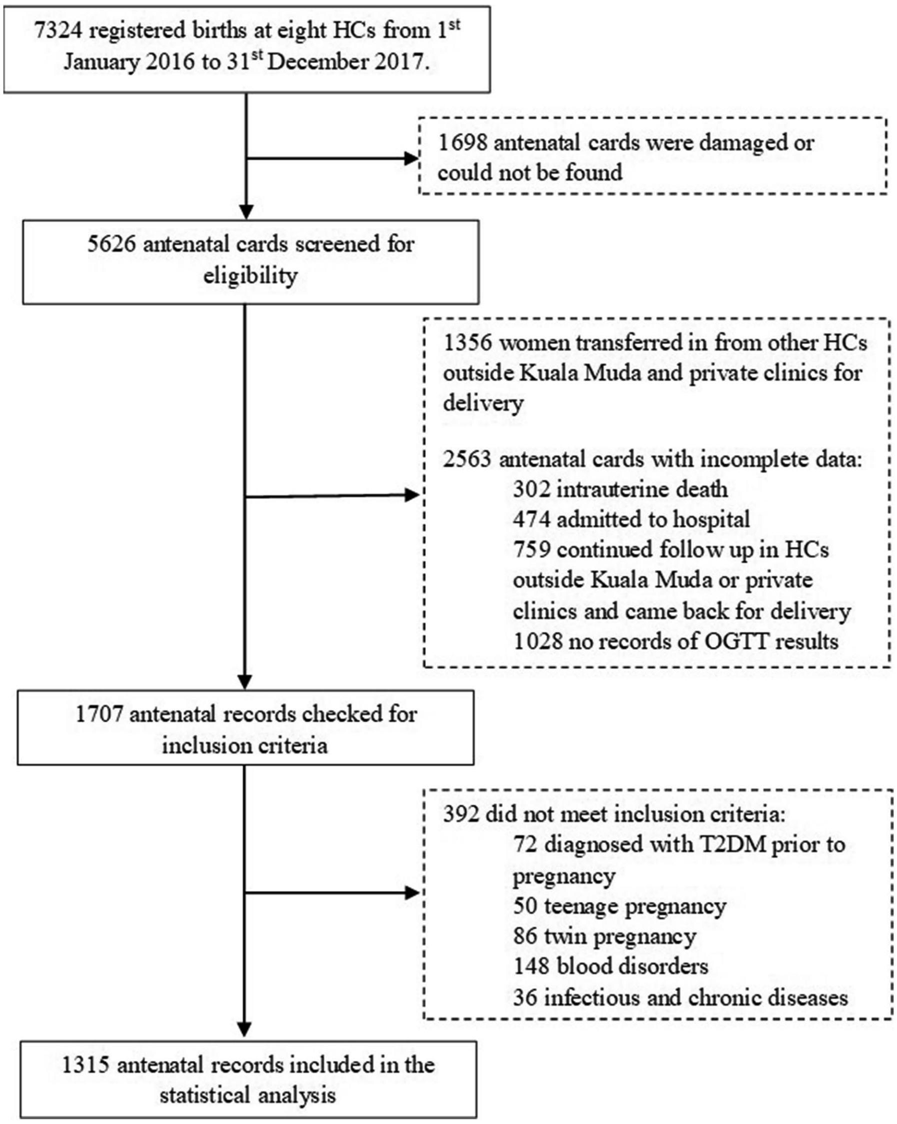

FIGURE 1
Selection process of the antenatal records.

subtracting the Hb value at the second trimester from the Hb value at booking (second trimester Hb–booking Hb). The Hb change was then categorized as decreased, unchanged, and increased Hb value in the second trimester.

Iron supplementation

Information on iron supplements consumed included the type of iron supplement, dosage, and duration of intake from booking until the second trimester, whether prescribed by the health personnel or self-purchased by the women. The reported types of iron supplements in the study were ferrous fumarate, ferrous sulfate, ferrous gluconate, iron (III)-hydroxide polymaltose complex (IPC), and iron dextran. The dosage and duration of iron supplement intake were calculated based on the following formula:

Duration of iron supplement intake (week):

$$\textit{Gestational week of the second trimester} - \textit{gestational week of booking}$$

The daily dosage of iron supplement intake:

$$\frac{\textit{Total dosage of iron supplement intake}\left(\textit{booking until the second trimester}\right)}{\left(\textit{Duration of iron supplement intake}\right)\times\left(7\ \textit{days}\right)}$$

The daily dosage of iron supplement intake was classified based on the iron supplement daily intake recommendation for pregnancy (37). The recommendation for daily oral iron supplementation to prevent maternal anemia is 30 mg to 60 mg of elemental iron. For a pregnant woman with anemia (Hb <11.0 g/dL), the elemental iron should be increased to 120 mg daily until the Hb level increases to ≥11.0 g/dL (37).

Statistical analysis

All continuous data were tested for normality and presented as mean and standard deviation (SD), while the median was reported for variables that did not comply with normal distribution. Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to describe the data. Comparisons of continuous variables between groups were examined using the *t*-test and analysis of variance (ANOVA) wherever applicable. The chi-square (χ^2) test was used for categorical variables to check for associations between variables. All covariates were tested and those with value of p <0.25 were considered in the analysis of maternal Hb status and GDM risk relationship. Four models were built in the multivariate logistic regression analysis. Model 1 adjusted for maternal age and height. Parity, history of GDM, and family history of diabetes were added to covariates of Model 1 as Model 2. For Model 3, iron supplementation at booking was added to the covariates of Model 2. Lastly, the Hb level at booking was added to covariates of Model 3 as Model 4. Additionally, Hb <11.0 g/dL and decreased Hb were defined as the reference group. All statistical tests were two-tailed, and the significance level was set at $p < 0.05$.

Results

Sample characteristics

Table 1 compares the characteristics of non-GDM and GDM women. The prevalence of GDM was 17.8% (1,081/234). GDM women (31.50 ± 5.00 years) were significantly older than non-GDM (30.20 ± 5.01 years). GDM women had a higher percentage of multiparous (24.4% vs. 18.5%), family history of diabetes mellitus (51.3% vs. 45.4%), and more history of GDM (17.1% vs. 5.4%) than non-GDM women. There was a significant difference in height between non-GDM (1.56 ± 0.06 m) and GDM (1.55 ± 0.06 m) in which, the proportion of height < 1.50 m was higher in the GDM group (15.8% vs. 10.9%). No significant difference in booking BMI status was observed between GDM (26.51 ± 4.77 kg/m^2) and non-GDM (26.61 ± 5.67 kg/m^2) women. Non-GDM women (48.67 ± 28.08 mg) took a higher dose of elemental iron from iron supplements dailycompared to GDM women (46.25 ± 25.77 mg) but the difference was not significant. In this study, iron supplementation was not associated with GDM ($\chi^2 = 1.52$; $p > 0.05$).

Hemoglobin status

No significant difference was observed in Hb concentration at booking and the second trimester between non-GDM and GDM women (Table 2). GDM women were more likely to have Hb concentration ≥ 13.0 g/dL (booking = 38.5% vs. 34.7%; second trimester = 11.2% vs. 10.0%) compared to non-GDM. The change of Hb from booking to the second trimester was significantly associated with maternal glycemia status ($\chi^2 = 6.29$; $p < 0.05$) but no significant mean difference was observed between GDM and non-GDM groups ($t = -0.27$; $p > 0.05$). More non-GDM women had decreased Hb than GDM women (82.1% vs. 80.8%), while the proportion of unchanged Hb levels was higher among GDM compared to non-GDM (4.7% vs. 1.9%). Table 3 presents Hb concentration level stratified by change of Hb from booking to the second trimester (decreased, unchanged and increased). The increased group had significantly lower Hb concentration at booking than the decreased and unchanged group ($F = 122.20$; $p < 0.01$). In the second trimester, the Hb concentration of the decreased group was significantly lower than the unchanged and the increased groups ($F = 103.67$; $p < 0.01$). It was also observed that Hb status at booking and second trimester were significantly associated with Hb changes ($p < 0.01$). Additionally, the GDM incidence was significantly dependent on the Hb changes, whereby the unchanged Hb had the highest proportion of GDM incidence (34.4%) than the other groups ($\chi^2 = 6.29$; $p < 0.05$).

Hemoglobin status and GDM risk

Four models adjusted for various maternal covariates to investigate the associations of Hb status with the risk of GDM are presented in Table 4. Hb concentration at booking and in the second trimester was not significantly associated with GDM risk.

TABLE 1 Characteristics of women (N=1,315).

Variables	Maternal glycemia[a]			
	Non-GDM (n=1,081)	GDM (n=234)	t-value/χ^2	Value of p
Age in years (Mean ± SD)	30.20 ± 5.01	31.50 ± 5.00	−3.61	0.00**
<25	159 (14.7)	19 (8.2)	12.59	0.01*
25–29	334 (30.9)	64 (27.4)		
30–34	348 (32.2)	80 (34.2)		
≥35	240 (22.2)	71 (30.2)		
Education level in years (Mean ± SD)	13.16 ± 2.80	13.12 ± 2.81	0.20	0.84
Secondary and lower	568 (52.6)	126 (53.9)	0.30	0.96
STPM/diploma/certificate	291 (26.9)	59 (25.2)		
Higher institution	222 (20.5)	49 (20.9)		
Occupation status				
Working	666 (61.6)	143 (61.1)	0.02	0.89
Not working	415 (38.4)	91 (38.9)		
Parity (Mean ± SD)	1.37 ± 1.27	1.55 ± 1.43	−1.82	0.07
0	343 (31.7)	68 (29.0)	4.53	0.21
1	285 (26.4)	61 (26.1)		
2	253 (23.4)	48 (20.5)		
≥3	200 (18.5)	57 (24.4)		
Medical history of GDM	58 (5.4)	40 (17.1)	38.37	<0.00**
Family history of diabetes	491 (45.4)	120 (51.3)	2.66	0.10
Height in meters (Mean ± SD)	1.56 ± 0.06	1.55 ± 0.06	2.45	0.01*
<1.50	118 (10.9)	37 (15.8)	5.27	0.15
1.50–1.55	368 (34.0)	73 (31.2)		
1.56–1.60	349 (32.3)	78 (33.3)		
>1.60	246 (22.8)	46 (19.7)		
Booking[c] BMI (kg/m^2) (Mean ± SD)	26.61 ± 5.67	26.51 ± 4.77	0.27	0.79
Underweight (<18.5)	72 (6.7)	9 (3.8)	5.49	0.14
Normal (18.5–24.9)	378 (35.0)	88 (37.6)		
Overweight (25.0–29.9)	353 (32.7)	87 (37.2)		
Obese (≥30.0)	278 (25.6)	50 (21.4)		
Iron supplementation at booking			4.68	0.10
Yes	660 (61.1)	156 (66.6)		
No	421 (38.9)	78 (33.4)		
Elemental iron intake daily from booking[b] to second trimester (mg)	48.67 ± 28.08	46.25 ± 25.77	1.21	0.23
Duration of intake (week)	19.42 ± 3.49	19.69 ± 3.45	−1.07	0.29
Daily dosage (mg)[c]				
≤60.00	788 (72.9)	179 (76.8)	1.52	0.22
>60.00	293 (27.1)	54 (23.2)		

[a]GDM was classified according to the Ministry of Health Malaysia (30) criteria as either or both FPG ≥ 5.6 mmol/L or 2-h postprandial ≥ 7.8 mmol/L.
[b]First antenatal visit at < 14th week of gestational age.
[c]Classification of daily elemental iron supplement dosage was based on WHO (36) recommendation.
*p < 0.05; **p < 0.01.

TABLE 2 Hemoglobin status of women (N=1,315).

	Maternal glycemia[a]			
	Non-GDM (n=1,081)	GDM (n=234)	t-value/χ^2	Value of p
Hemoglobin level at booking [b] (g/dL) (Mean ± SD)	12.63 ± 1.13	12.70 ± 1.16	−9.84	0.40
<11.0	68 (6.3)	11 (4.7)	1.74	0.42
11.0–12.9	638 (59.0)	133 (56.8)		
≥13.0	375 (34.7)	90 (38.5)		
Hemoglobin level of second trimester (g/dL) (Mean ± SD)	11.62 ± 1.06	11.71 ± 0.95	−1.22	0.22
<11.0	230 (21.3)	38 (16.2)	3.06	0.22
11.0–12.9	743 (68.7)	170 (72.6)		
≥13.0	108 (10.0)	26 (11.2)		
Change of hemoglobin: second trimester–booking (Mean ± SD)	−1.01 ± 1.20	−0.99 ± 1.13	−0.27	0.79
Decreased[c] (−1.39 ± 0.88)	888 (82.1)	189 (80.8)	6.29	0.04*
Unchanged[d] (0)	21 (1.9)	11 (4.7)		
Increased[e] (0.84 ± 0.79)	172 (15.9)	34 (14.5)		

[a]GDM is classified according to the Ministry of Health Malaysia (30) criteria as either or both FPG ≥ 5.6 mmoL/L or 2-h postprandial ≥ 7.8 mmoL/L.
[b]First antenatal visit at < 14th week of gestational age. [c]Hemoglobin values of second trimester < booking.
[d]Hemoglobin values of second trimester = booking.
[e]Hemoglobin values of second trimester > booking.
*p < 0.05; **p < 0.01.

TABLE 3 Hemoglobin level and GDM incidence stratified by hemoglobin changes[a] (N=1,315).

Hemoglobin level (g/dL)	Decreased[b] Hb (n=1,077)	Unchanged[c] Hb (n=32)	Increased[d] Hb (n=206)	F-value /χ^2	Value of p
Booking[e] (Mean ± SD)	12.84 ± 1.03 [x]	12.51 ± 1.10 [y]	11.60 ± 1.09 [x,y]	122.20	<0.01**
(Range)	(9.50–16.60)	(10.60–15.40)	(8.30–14.30)		
<11.0	33 (3.1)	3 (9.4)	43 (16.5)	164.56	<0.01**
11.0–12.9	557 (51.7)	19 (59.4)	146 (70.9)		
≥13.0	487 (45.2)	10 (31.2)	17 (8.3)		
Gestational week of measurement	9.23 ± 2.17	8.69 ± 2.42	9.33 ± 2.26		
Second trimester (Mean ± SD)	11.46 ± 0.96 [x,y]	12.51 ± 1.10 [x]	12.45 ± 1.00 [y]	103.67	<0.01**
(Range)	(7.50–14.30)	(10.60–15.40)	(8.60–15.40)		
<11.0	253 (23.5)	3 (9.4)	12 (5.8)	125.99	<0.01**
11.0–12.9	758 (70.4)	19 (59.4)	136 (66.0)		
≥13.0	66 (6.1)	10 (31.2)	58 (28.2)		
Gestational week of measurement	26.37 ± 1.73	26.47 ± 1.19	26.30 ± 1.69		
GDM, n (%)	189 (17.5)	11 (34.4)	34 (16.5)	6.29	0.043*

Values are presented as mean ± SD for continuous variables and n (%) for dichotomous variables.
[a]Hb changes were calculated by subtracting Hb at booking from the second trimester.
[b]Hb values of the second trimester < booking.
[c]Hb values of the second trimester = booking.
[d]Hb values of the second trimester > booking.
[e]First antenatal visit at < 14th week of gestational age.
[x,y]Similar alphabets indicate a significant difference between groups.
* < 0.05, **p < 0.01.

However, women with unchanged Hb were significantly associated with the GDM risk compared to women with decreased Hb. The risk of developing GDM for women with unchanged Hb in the second trimester compared to booking was similar among the four models (2.4 to 2.6 times, p = 0.02).

Discussion

The prevalence of GDM in this study was higher than the reported prevalence in Europe, North America, and the Caribbean, whereby the median estimate of GDM prevalence was 5.8 and 7.0%, respectively

TABLE 4 Adjusted odd ratios for the association between maternal hemoglobin and gestational diabetes mellitus.

	Model 1		Model 2		Model 3		Model 4	
	Adjusted OR	Value of *p*	Adjusted OR	Value of *p*	Adjusted OR	Value of *p*	Adjusted OR	Value of *p*
Hb level at B (g/dL)								
<11.0	1.00		1.00		1.00		-	-
11.0–12.9	1.37 [0.70, 2.67]	0.36	1.25 [0.63, 2.46]	0.52	1.30 [0.66, 2.58]	0.45	-	-
≥13.0	1.46 [0.74, 2.89]	0.27	1.39 [0.70, 2.77]	0.35	1.49 [0.74, 2.99]	0.26	-	-
Hb level at T2 (g/dL)								
<11.0	1.00		1.00		1.00		1.00	
11.0–12.9	1.39 [0.95, 2.04]	0.09	1.45 [0.98, 2.15]	0.06	1.48 [1.00, 2.19]	0.05	1.42 [0.95, 2.14]	0.09
≥13.0	1.51 [0.87, 2.63]	0.15	1.62[0.92, 2.86]	0.09	1.64 [0.93, 2.89]	0.09	1.57 [0.87, 2.84]	0.14
Change of Hb: T2 - B								
Decreased [d]	1.00		1.00		1.00		1.00	
Unchanged [e]	2.55 [1.20, 5.44]	0.02*	2.45 [1.13, 5.34]	0.02*	2.42 [1.11, 5.27]	0.03*	2.51 [1.15. 5.49]	0.02*
Increased [f]	0.94 [0.63, 1.41]	0.78	0.93 [0.62, 1.40]	0.73	0.91 [0.60, 1.37]	0.65	1.00 [0.65, 1.55]	0.99

T2: second trimester. B: booking.
[d]Hb values of T2 = B.
[e]Hb values of T2 < B.
[f]Hb values of T2 > B.
Model 1–Adjusted for age and height.
Model 2–Adjusted for age, height, parity, history of GDM, and family history of diabetes.
Model 3–Adjusted for age, height, parity, history of GDM, family history of diabetes, and iron supplement intake at booking.
Model 4–Adjusted for age, height, parity, history of GDM, family history of diabetes, iron supplementation at booking, and Hb status at booking.
*$p<0.05$.

(7). As the Asian population has a higher risk of GDM, a higher prevalence in the present study than in the Western population is expected. However, the GDM prevalence in the present study was also higher than in other Asian countries such as Japan (2.8%), India (8.8%), South Korea (10.5%), China (12.6%), and Iran (14.9%). The prevalence was similar to Thailand (17.1%) and Singapore (17.6%), but lower than Hong Kong (32.5%), Taiwan (38.6%) (13), and pooled prevalence in Malaysia at 21.5% (11).

High maternal Hb is associated with an increased risk of poor maternal health, namely preeclampsia and GDM (25, 28). Studies have reported different values of high Hb status in the first trimester to be associated with risk of GDM with Turkish women at ≥12.2 g/dL (38), Finnish women at >12.0 g/dL (39), and Republic of Kosovo women at ≥13.0 g /dL (40). Similarly, studies in the Middle Eastern and Asian countries (Iran, Pakistan, Palestine and Thailand) also reported a significant association between high Hb status during the first trimester with GDM but with a more consistent Hb cut-off value of ≥12.5 g/dL (41–46). In China, several studies reported a significant association between Hb concentration of >13.0 g/dL during the first trimester and increased risk of GDM (47, 48). On the contrary, the present study did not find a significant association between GDM and Hb concentration in the first trimester. The difference in mean Hb level and the proportion of elevated Hb level (≥13.0 g/dL) in the GDM group and the non-GDM group of the present study was not noticeable, which showed that both groups entered pregnancy with the same Hb status.

Additionally, there was no significant association found between Hb level in the second trimester and GDM risk in the present study. Women in this study were intensively given iron supplements and maternal nutrition advice as anemia preventive measures during antenatal care to avoid iron deficiency anemia (IDA), which is known to be related to adverse pregnancy outcomes (24, 49). However, there were no data on dietary intake in this study that can be used to examine the total iron intake on top of iron supplements. A study in a university hospital in Kuala Lumpur reported that Hb cut-off at 11.5 g/dL in the second trimester was significantly associated with GDM. The GDM group also had higher hematocrit levels than the non-GDM group, which was an indicator of high iron status (34). Chen et al. (50) also found a significant association between high iron status in the second trimester with GDM. Women with the highest quintile serum ferritin level (>131 pmol/L) had a twofold increase in GDM risk compared to women in the lower quintile. Likewise, a study in Iran reported a significant association between high serum iron in the second trimester with GDM occurrence. The association remained significant even after adjusting for confounders (51). These three studies, however, only screened GDM in 24–28 weeks of pregnancy and not during the first trimester (<14 weeks of gestation). Therefore, overt diabetes could have been included in the analysis which affected the significant findings. High iron status is hypothesized to affect glucose metabolism which increases diabetes risk, and perhaps women with overt diabetes may manifest the same high iron effects since pre-pregnancy (14, 52, 53). On the contrary, this study only included cases with true GDM that were confirmed during booking (<14 weeks of gestation).

Unchanged Hb status in the second trimester compared to booking was found to be significantly associated with GDM. A plausible explanation for the significant association between unchanged Hb and GDM is that unchanged Hb during pregnancy may reflect iron overload. The mean Hb for the unchanged subgroup at booking was 12.51 ± 1.10 g/dL which is similar to the cut-off point for high Hb concentration in the first trimester that increases GDM risk in several previous studies in middle-east and Asian countries (41–46). The anemia rate in the unchanged Hb subgroup was maintained at 9.4% in the second trimester compared to booking. The expansion of plasma volume in the unchanged Hb subgroup was less likely to have profound changes in Hb possibly because of iron supplementation that reduced the anemia incidence as pregnancy progresses (54, 55). Thus, the high Hb concentration > 12.5 g/dL at booking was maintained in the second trimester.

Most studies hypothesized that the significant association between elevated Hb and GDM risk was confounded by nutritional status, specifically iron, through diet or supplementation that contributed to iron overload (38–40, 43, 56). However, a woman could exhibit iron deficiency without anemia despite having a normal Hb (≥12.0 g/dL). Iron deficiency anemia (IDA) is a late manifestation of iron deficiency; thus, Hb value alone may not be the most sensitive indicator of body iron storage (24, 57–59). Even though Hb is one of the reliable tests for assessing iron status, it is more suitable to assess iron depletion and anemia (57, 59–61). As there is increasing evidence of a relationship between high iron status and increased risk of GDM, it is necessary to use other sensitive iron biomarkers, particularly serum ferritin, to know the iron status not only among anemia women.

Routine iron intake during early pregnancy <14 weeks until the second trimester in non-deprived iron women, could increase the risk of GDM (62). However, iron supplement intake in this study did not contribute to GDM risk. Women with unchanged Hb in this study could have also consumed high iron from food other than iron supplements which lead to iron accumulation. Another reason could be the elevated serum ferritin that is also known to be associated with the risk of GDM. Serum ferritin may be an indicator of iron stores as well as inflammation of cells (63, 64). Nevertheless, there was no information on dietary iron and serum ferritin status in this study to confirm the associations, other than iron supplementation.

Strengths of the study

The strength of the study is that it was a multicentre study that included women from rural and urban areas. The sample size of the study was also large. Furthermore, the study included analyzes of Hb change impact on GDM risks which was an area with limited published Malaysian studies available. To avoid selection bias in the study, several strategies were undertaken. First, the inclusion criteria were restricted to healthy pregnant women. Second, disease conditions of the women that could affect the results of GDM were also specified. Third, compliance with antenatal care appointments was used as a sample selection to ensure the consistency of antenatal care data. Fourth, the study only included women who underwent two times OGTTs, which were done during the first and second trimester. This confirmed the glycemic status of the women during early pregnancy; thus, women with diabetes in pregnancy can be identified and excluded from the study. Finally, being a retrospective design, there was no recall bias involved as all the data were based on what had been recorded in the antenatal cards.

Limitations of the study

This study is not without limitations. Incomplete records in the antenatal cards caused the loss of many subjects from contributing to the study. There is also a possibility of observational bias arising from documenting errors. The study only extracted data from the antenatal cards of HCs copy. The documentation by the health personnel was handwritten in the mother's copy and HCs copy. Therefore, there is a high chance of wrongly copied data in either antenatal card. The present study only evaluates maternal Hb which does not reflect the actual iron status. The other iron indices to confirm the plasma expansion effects, such as serum iron, ferritin, transferrin, and total iron-binding capacity (TIBC) in this study, are limited as the blood investigations are only applicable to women with anemia during pregnancy. Moreover, the present study did not have data on the dietary iron intake that will give information on the total iron intake during pregnancy. The iron supplementation in the present study was based on the records of iron supplements prescribed with limited compliance records in the antenatal cards. Thus, reports on the iron supplement intake were based on the assumption that the women consumed the supplement as indicated. Therefore, the study is not presenting the actual iron supplementation of the women that could have implicated the no association findings between GDM and iron supplementation.

Conclusion

The significant association between unchanged Hb status and GDM risk observed in the present study indicates the need to revise the policies on iron supplementation for pregnant women, especially for high Hb status during pre-pregnancy or non-deprived iron women. However, this suggestion does not repudiate the iron supplement prophylaxis dose of 30 mg daily for pregnant women recommended by the WHO, as Malaysian women of reproductive age are still prone to iron deficiency. Future studies that employ prospective design are warranted to evaluate the mechanisms involved in the unchanged Hb-GDM relationship to further understand the connection. Such findings could give a better insight into developing appropriate health and nutrition strategies to reduce the increasing rate of GDM in Malaysia.

Data availability statement

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Research and Ethics Committee National Institute of Health, Malaysia. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

HZS and MSZ conceived and designed the study and responsible for data management and analysis. HZS conducted the research including data collection and interpreted the data and wrote the first draft of the manuscript. MSZ supervised and critically revised the manuscript for important and intellectual content. AG supervised and revised the manuscript for important and intellectual content. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors are grateful to Pejabat Kesihatan Daerah Kuala Muda's contribution to the study. The authors would specifically like to thank Yong Heng Yaw, Nur Amni, Zalikha, Zei Pei, and Nurrussaadah for their assistance in the data collection process. The authors would like to thank the Director General of Health, Malaysia for permission to publish this study.

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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frontiers | Frontiers in Nutrition

TYPE Hypothesis and Theory
PUBLISHED 27 June 2023
DOI 10.3389/fnut.2023.1219704

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OPEN ACCESS

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RECEIVED 09 May 2023
ACCEPTED 02 June 2023
PUBLISHED 27 June 2023

CITATION
Białek-Dratwa A, Kokot T, Czech E, Całyniuk B, Kiciak A, Staśkiewicz W, Stanjek-Cichoracka A, Słoma-Krześlak M, Sobek O, Kujawińska M, Grot M, Szczepańska E and Muc-Wierzgoń M (2023) Dietary trends among Polish women in 2011–2022—cross-sectional study of food consumption frequency among women aged 20–50 in Silesia region, Poland. *Front. Nutr.* 10:1219704.
doi: 10.3389/fnut.2023.1219704

Dietary trends among Polish women in 2011–2022—cross-sectional study of food consumption frequency among women aged 20–50 in Silesia region, Poland

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Background: Women's nutrition should be different from that of men. Women have lower energy requirements than men. And the need for certain vitamins and minerals is higher in women, this applies to iron, calcium, magnesium, vitamin D and vitamin B9 (folic acid). This is related to hormonal changes including menstruation, pregnancy, breastfeeding and the onset of menopause. Through hormonal changes and the changing physiological state, women are at greater risk of anaemia, bone weakness and osteoporosis.

The aim of the study was to assess changes in the dietary pattern among women from the Silesian Agglomeration in Poland between 2011 and 2022.

Material and method: The survey was conducted in 2011 (March–May 2011) and in 2022 (October–November 2022) among women living in the Silesian Agglomeration (Silesia region) in Poland aged 20–50. After consideration of the inclusion and exclusion criteria, 745 women were included in the final analysis, including 437 women screened in 2011 and 308 women screened in 2022.

The research tool used in this publication was a survey questionnaire consisting of 2 parts. The first part of the questionnaire consisted of demographic data. The second part of the study focused on the dietary habits of the women surveyed and the frequency of consumption of individual foods (FFQ).

Results: More women in 2022 ate breakfast than in 2011 (77.6% vs. 63.8% $p<0.001$), were more likely to eat breakfast I at home (73.1% vs. 62.5%; $p<0.001$), were more likely to eat breakfast II (39.0% vs. 35.2%; $p=0.001$), were more likely to eat breakfast II at home (28.6% vs. 19.2%; $p=0.002$), and were more likely to eat lunch at work (16.6% vs. 3.4%; $p<0.001$). Women in 2022 were more likely to consume fast-food ($p=0.001$), salty snacks (chips, crisps) ($p<0.001$) and sweets

(p<0.001). Women in 2022 were more likely to consume whole-grain bread (p<0.001), wholemeal pasta (p<0.001), brown rice (p<0.001), oatmeal (p<0.001), buckwheat groats (p=0.06), and bran (p<0.001) than women in 2011. They were less likely to consume white bread (p<0.0001), light pasta (p=0.004), white rice (p=0.008) and cornflakes (p<0.001) in 2022.

Women in 2022 were significantly more likely to consume vegetables (p<0.001) than women in 2011.

Conclusion: Eating habits in Silesia region women changed between 2011 and 2022. In 2022, women were more likely to choose cereal products considered health-promoting and rich in dietary fiber (including whole-grain bread, whole-grain pasta, oatmeal, bran) were more likely to consume vegetables, dry pulses and vegetarian dinners, and consumed less meat, cured meats, fish and dairy products. Consumption of fast-food, salty snacks (such as chips) and sweets increased.

KEYWORDS

nutrition, women, diet, eating habits, lifestyle

1. Introduction

Among its initiatives aimed at reducing behavioral risk factors, the World Health Organization's (WHO) Global Action Plan for the Prevention and Control of Noncommunicable Diseases includes strategies for addressing unhealthy dietary patterns; other components include physical inactivity, tobacco use, and harmful alcohol use (1). The World Health Organization advises balancing energy intake, cutting back on saturated and trans fats while boosting consumption of unsaturated fats, increasing fruit and vegetable consumption, and cutting back on sugar and sodium intake. Many of these dietary objectives are found naturally in regional diets, like the Mediterranean diet, or are included in evidence-based diets created to lower disease risk, like the Mediterranean-DASH intervention for neurodegenerative delay (MIND) and dietary approaches to stop hypertension (DASH) diets (2–4).

A balanced diet is one that delivers enough macronutrients to satisfy the body's energy and physiologic needs without causing excess intake, as well as enough micronutrients and fluids to satisfy its physiological needs. Carbohydrates, proteins, and lipids, collectively known as macronutrients, provide the energy required for cellular functions essential for daily operation. Minimal amounts of micronutrients (vitamins and minerals) are necessary for healthy growth, development, metabolism, and physiologic function (5). Proteins in food offer both energy and amino acids. Animal and plant sources both contribute to dietary proteins, although the former is thought to be a richer source because of the diversity of amino acids, high digestibility, and higher bioavailability. Saturated fatty acids, which are present in animal-based sources of protein, have been associated with cancer, dyslipidemia, and cardiovascular disease. Although the exact processes are unclear, red meat, and processed meat in particular, has been associated to an increased risk of colorectal cancer (6–8).

Trans fats and, to a lesser extent, saturated fats are linked to adverse health impacts, including an increased risk of death, whereas unsaturated fats are linked to decreased cardiovascular and mortality risks. Due to their necessity for healthy growth and reproduction but inability to be created by the body, essential fatty acids, which include the omega-3 and omega-6 families of polyunsaturated fatty acids, must be consumed. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been extensively researched for their potential health benefits, with evidence suggesting positive effects such as cardioprotection, preventing cognitive decline, reducing inflammation, sustaining muscle mass, and improving systemic insulin resistance. EPA and DHA are found in seafood, particularly oily fish, and supplements are widely available for those who cannot reach the prescribed intakes through diet alone. Nuts, certain seeds, and plant oils contain alpha-linolenic acid, the primary omega-3 fatty acid found in plants (9–12).

Cereals, fruits, legumes, and vegetables are the richest sources of carbohydrates, which are the body's main energy source. Whole grains are preferred over processed grains in terms of their health advantages since processed grains have less fiber and micronutrient content because their germ and cereal have been removed during milling. A higher intake of whole grains has been associated with a lower risk of coronary heart disease, stroke, cardiovascular disease, and cancer, as well as a lower risk of death from any cause, cardiovascular disease, cancer, respiratory disease, diabetes, and infectious disease, according to meta-analyses of prospective cohort studies. Both calories and dietary fiber, which encourages satiety and has positive benefits on digestion, cholesterol levels, and glycemic management, are present in fresh fruits and vegetables. The benefits of consuming fibre in the daily diet are based on the type of fibre consumed: soluble (e.g., pectin, gums, plant mucilage, polysaccharides), or insoluble (e.g., cellulose, lignans). The main sources of insoluble fibre are cereal products, especially whole-grain cereals such as whole-grain bread, whole-grain pasta, bran, groats and whole-grain rice. Soluble fibre can be found in fruit and vegetables. Insoluble dietary fibre stimulates saliva secretion, increases the volume of food content resulting in a greater feeling of satiety, stimulates blood circulation and intestinal peristalsis, protects against constipation, reduces the risk of intestinal diverticulosis, rectal polyps and varices, and colon cancer. Soluble dietary fibre loosens faecal masses, thus preventing constipation, reduces cholesterol absorption, lowers the rate of carbohydrate absorption, thus slowing the rise in blood glucose after a meal. Studies have observed that there is a link between a low intake of dietary fibre and increased risk and mortality from cardiovascular disease (including ischaemic heart disease and cerebrovascular disease). Fresh fruits and vegetables are also significant sources of phytochemicals, which are bioactive substances believed to be responsible for many of the health advantages connected with fruit and vegetable consumption (13–19). Examples of phytochemicals include polyphenols, phytosterols, and carotenoids. These many phytochemicals' confusing molecular effects include their antioxidative abilities, control over nuclear transcription factors, lipid metabolism, and production of inflammatory mediators. For instance, studies on flavonoids have revealed that these phytochemicals have some advantages in the treatment of obesity and diabetes by increasing insulin secretion and reducing insulin resistance. The risk of noncommunicable diseases (NCDs) such hypertension, cardiovascular disease, chronic obstructive pulmonary disease, lung cancer, and metabolic syndrome has been demonstrated to be inversely related to fruit and vegetable consumption (20–23). Nowadays, with the pace of life quickening and availability to processed foods being simpler than ever, it's crucial to pay attention to what we consume and how it affects our bodies.

The main purpose of the study was to assess changes in the diet of women from the Silesian Agglomeration in Poland in the years 2011–2022. The main purpose of the study was based on the following specific purposes: a comparison was made between the frequency of consumption of particular food products, taking into account their health-promoting aspects (vegetables, fruit, dry leguminous seeds, cereal products with high content of dietary fibre, yoghurts, cottage cheese, fish) and those which may negatively affect health (fast food, sweets, salty snacks, fried food, cereal products from refined flour with low content of dietary fibre, products containing sugar, e.g., sweet cheeses among Polish women in 2011 and 2022 sweet cheeses) in 2011 and 2022 among Polish women. The study asked the following research questions:

- Have there been changes in dietary patterns among women between 2011 and 2022?
- Has there been an increase in the frequency of consumption of foods considered health-promoting among women?
- Has the frequency of consumption of products negatively affecting health decreased?

2. Materials and methods

2.1. Test sample

The survey was conducted in 2011 (March–May 2011) and in 2022 (October–November 2022) among women living in the Silesian Agglomeration (Silesia region) in Poland aged 20–50. The 2011 survey was conducted among random selected women living in the Silesia region. The survey in 2022, on the other hand, was conducted anonymously using the Computer-Assisted Web Interview (CAWI) method; the online survey was distributed in local forums and discussion groups among women residing in the Silesia region. The 2022 survey was conducted using the CAWI method; the sampling was completely random (according to the assumed inclusion and exclusion criteria of the survey). However, some risk of error should be taken into account that the female participants of the survey showed more interest in nutrition.

2.2. Inclusion and exclusion criteria

The inclusion criteria for the study were: female gender, residence in the Silesian Agglomeration, consent to participate, and correct and complete completion of the questionnaire.

On the other hand, the criteria for exclusion from the study were: gender other than female, age below 20 years and above 50 years, use of an unconventional diet (e.g., vegan, vegetarian, ketogenic, low-carb diet), disease entity determining elimination of the entire food group, place of residence other than Silesia region, lack of consent to participate in the study, incorrectly completed questionnaire.

After consideration of the inclusion and exclusion criteria, 745 women were included in the final analysis, including 437 women screened in 2011 and 308 women screened in 2022.

2.3. Research tool

The research tool used in this publication was a survey questionnaire consisting of 2 parts. The first part of the questionnaire consisted of demographic data. The study obtained the following demographic data: gender, age, education (primary, vocational, secondary, tertiary) and body weight and height—from this, body mass index (BMI) was calculated and interpreted based on World Health Organisation (WHO) recommendations for adults: <18.5 kg/m^2—underweight, 18.5–24.9 kg/m^2—average weight, 25.0–29.9 kg/m^2—overweight, 30.0–34.9 kg/m^2—grade I obesity, 35.0–39.9 kg/m^2—grade II obesity, >40 kg/m^2 grade III obesity (24). The levels of education adopted in the study were set according to Polish legal regulations: primary education, vocational education, secondary education (high school) and higher education (university).

The second part of the study focused on the dietary habits of the women surveyed and the frequency of consumption of individual foods (FFQ). The study assessed: the number of meals consumed per day, frequency of consumption of individual meals, place of consumption of meals, and the fact of eating meals with other family members. In the study of the frequency of consumption (FFQ) of individual food products, a 6-grade scale was taken into account: I do not consume at all, several times a month, several times a week, once a day, 2–3 times a day, 4 and more times a day to standardise the results. The consumption of fast-food products (including chips, casseroles, hamburgers, and pizza); salty snacks (chips, crisps, etc.); cereal products (divided by the number of meals consumed and the number of meals consumed); and other food products (divided by the number of meals consumed were taken into account); cereal products (subdivided into those that are health-promoting: wholemeal bread, wholemeal pasta, brown rice, oatmeal, buckwheat groats, muesli, bran and products with lower nutritional value: light bread—not made from wholemeal flour, pasta made from refined flour, white rice, cornflakes), vegetables, fruit, potatoes and dry pulses such as soya/lentils/peas/beans; dairy products and dairy products (yoghurt, buttermilk, kefir, white cheese, cottage cheese, sugar-sweetened fruit cheese, yellow cheese), meat and fish (meat, fish, cold cuts), vegetarian dinners. The study also included the consumption of sweets, drinks such as sugar-sweetened and unsweetened coffee and tea, sugar-sweetened and unsweetened juices, water, sugar-sweetened and unsweetened juices, water, sugar-sweetened and unsweetened carbonated drinks, and energy drinks. An assessment was also made of the thermal treatments most commonly used for meal preparation (boiling, steaming, frying, fat-free frying, baking, braising, grilling), as well as the type of fat used for frying and bread spreads (butter, lard, olive oil, vegetable oil, butter and margarine mix, hardened margarine).

The FFQ questionnaire was developed based on the principles of nutrition in force in 2011 for women in Poland. It was based on the principles of nutrition of the Polish Institute of Food and Nutrition in Warsaw (IŻŻ). In Poland in 2011, the institution responsible for setting nutrition standards was the IŻŻ (25, 26). The nutrition rules for women in 2022 have changed. They were developed by the National Centre for Nutrition Education (NCEZ), which is currently responsible for setting nutrition standards in Poland (27, 28). Professor Jarosz's expert team established the nutrition standards in force in 2011(IŻŻ) and the standards in force in 2022 (NCEZ) despite the change in the name of the scientific unit.

2.4. Statistical analysis

The statistical analysis used descriptive and analytical methods available in Statistica v. 13.3 (StatSoft Inc., Tulsa, OK, United States). The statistical significance of differences between frequencies of qualitative variables was assessed based on the results of Pearson's chi-square test and the test with Yates correction. Analysis of correlations was based on Kendall's Tau coefficient and V-Cramer. The arithmetic mean (M) and standard deviation (SD), as well as the median (Me) and interquartile range (IQR) values were used to describe BMI, body weight, height and age of the study group. Statistical significance of differences between distributions of quantitative variables was assessed using the Mann–Whitney U test. Interpretation of the results was carried out based on the criterion of statistical significance $p < 0.05$.

2.5. Ethical consents

All study participants were informed of the purpose of the study, its anonymity and asked to accept the data sharing policy. Information about conscious and voluntary participation in the study was included at the beginning of the questionnaire. Due to the nature of the study, consent was sought from the Bioethics Committee of the Silesian Medical University in Katowice. In accordance with Resolution No. KNW/0022/KB1/151/I/11 of 06.12.2011. The Bioethics Committee took a positive opinion on the project of a medical experiment concerning the study of dietary habits in different groups of the population in terms of the occurrence of overweight and obesity.

3. Results

Table 1 shows the characteristics of the study group of women with respect to the study year 2011 and 2022. There were differences

TABLE 1 Characteristics of the study group of women by year of study 2011 and 2022.

Variable	2011		2022		Total 2011 and 2022		Test p correlation coefficient
	n	(%)	*n*	(%)	*N*	(%)	
Woman	437 (58.7%)		308 (41.3%)		745 (100.0%)		
Mean age (years) (median; interquartile range)	38.67 ± 4.74 (39.00; 7.00)		33,90 ± 6.70 (35.00; 8.50)		36.69 ± 6.10 (37.00; 7.00)		$U = 10.00$ $p < 0.001$
Mean body weight (kg) (median; interquartile range)	64.93 ± 11.83 (63.00; 13.00)		70.35 ± 16.97 (67.00; 19.50)6		67.17 ± 14.42 (64.00; 15.00)		$U = -3.93$ $p < 0.001$
Average height (cm) (median; interquartile range)	164.28 ± 5.97 (164.00; 8.00)		166.32 ± 5.99 (165.00; 8.00)		165.12 ± 6.06 (164.00; 10.00)		$U = -4.05$ $p < 0,001$
Mean BMI (kg/m^2) (median; interquartile range)	24.01 ± 3.88 (23.42; 4.68)		25.39 ± 5.82 (24.09; 6.25)		24.58 ± 4.83 (23.59; 5.17)		$U = -2.26$ $p = 0.024$
Residence: city	434	(99.3%)	251	(81.5%)	685	(91.9%)	Chi^2 = 77.48 $p < 0.001$ $\tau_b = -0.32$
Village	3	(0.7%)	57	(18.5%)	60	(8.1%)	
BMI interpretation: underweight	9	(2.1%)	9	(2.9%)	18	(2.4%)	Chi^2 = 17.6 $p < 0.001$ $\tau_c = 0.11$
Normweight	286	(65.5%)	169	(54.9%)	455	(61.1%)	
Overweight	109	(24.9%)	78	(25.3%)	187	(25.1%)	
Obesity	33	(7.6%)	52	(16.9%)	85	(11.4%)	
Education: basic	36	(8.2%)	0	(0.0%)	36	(4.8%)	Chi^2 = 222.45 $p < 0.001$ $\tau_c = 0.57$
professional	107	(24.5%)	8	(2.6%)	115	(15.4%)	
Medium	178	(40.7%)	52	(16.9%)	230	(30.9%)	
Higher	116	(26.6%)	248	(80.5%)	364	(48.9%)	

Chi^2, Pearson's chi^2 test; U, Mann–Whitney U test; p, significance level, correlation coefficient: τ_c, Kendall's τ_c; τ_b, Kendall's τ_b; V_C, Cramer's V.

among the studied women in terms of age ($p < 0.001$), mean body weight ($p < 0.001$), mean height ($p < 0.001$), mean BMI ($p = 0.02$), place of residence ($p < 0.001$), BMI interpretation ($p < 0.001$) and education ($p < 0.001$). Considering the results, it should be noted that the mean BMI increased by 1.38 kg/m^2.

Table 2 shows the results for the number of meals consumed by the female respondents and the place of consumption. Comparing meal intake by location and time, in 2011 women were more likely to eat three and four meals per day, while in 2022 some women extended the number of meals to five (18.5% vs. 24.7%; $p = 0.29$). More women in 2022 ate breakfast than in 2011 (77.6% vs. 63.8% $p < 0.001$), were more likely to eat breakfast I at home (73.1% vs. 62.5%; $p < 0.001$), were more likely to eat breakfast II (39.0% vs. 35.2%; $p = 0.001$), were more likely to eat breakfast II at home (28.6% vs. 19.2%; $p = 0.002$), and were more likely to eat lunch at work (16.6% vs. 3.4%; $p < 0.001$). A not great proportion of women in both 2011 and 2022 did not eat lunch at all.

Table 3 assesses the frequency of consumption of anti-health foods such as fast-food (casseroles, burgers, pizza, chips), salty snacks

TABLE 2 Meal consumption characteristics by location and time by 2011 and 2022.

Variable	2011		2022		Total 2011 and 2022		Test *p* correlation coefficient
	n	(%)	*n*	(%)	*N*	(%)	
How many meals do you eat in a day?							
1–2 meals	24	(5.5%)	13	(4.2%)	37	(5.0%)	Chi^2 = 5.01 p = 0.287 τ_c = 0.08
3 meals	135	(30.9%)	82	(26.6%)	217	(29.1%)	
4 meals	181	(41.4%)	125	(40.6%)	306	(41.1%)	
5 meals	81	(18.5%)	76	(24.7%)	157	(21.1%)	
Over 5	16	(3.7%)	12	(3.9%)	28	(3.7%)	
Do you eat breakfast every day?							
Not	77	(17.6%)	16	(5.2%)	93	(12.5%)	Chi^2 = 27.43 p < 0.001 V_C = 0.19
Not always	81	(18.6%)	53	(17.2%)	134	(18.0%)	
Yes	279	(63.8%)	239	(77.6%)	518	(69.5%)	
Where do you eat your first breakfast most often?							
I do not eat	31	(7.1%)	9	(2.9%)	40	(5.4%)	Y = 17.37 p < 0.001 V_C = 0.15
Home	273	(62.5%)	225	(73.1%)	498	(66.8%)	
On the way to work	2	(0.5%)	6	(1.9%)	8	(1.1%)	
At work	131	(29.9%)	68	(22.1%)	199	(26.7)	
Do you eat a second breakfast every day?							
Not	177	(40.5%)	87	(28.2%)	264	(35.4%)	Chi^2 = 13.08 p = 0.001 V_C = 0.13
Not always	106	(24.3%)	101	(32.8%)	207	(27.8%)	
Yes	154	(35.2%)	120	(39.0%)	274	(36.8%)	
Where do you eat your second breakfast most often?							
I do not eat	124	(28.4%)	60	(19.5%)	184	(24.7%)	Y = 16.65 p = 0.002 V_C = 0.15
Home	84	(19.2%)	88	(28.6%)	172	(23.1%)	
On the way to work	4	(0.9%)	1	(0.3%)	5	(0.7%)	
Elsewhere	8	(1.8%)	12	(3.9%)	20	(2.7%)	
At work	217	(49.7%)	147	(47.7%)	364	(48.8%)	
Where do you eat lunch most often?							
I do not eat lunch	5	(1.1%)	2	(0.6%)	7	(0.9%)	Y = 39.07 p < 0.001 V_C = 0.23
Home	417	(95.4%)	255	(82.8%)	672	(90.2%)	
At work	15	(3.4%)	51	(16.6%)	66	(8.7%)	
How often do you eat dinner together with other family members							
Daily	160	(36.6%)	104	(33.8%)	264	(35.4%)	Chi^2 = 5.79 p = 0.122 τ_c = −0.05
Several times a week	166	(38.0%)	114	(37.0%)	280	(37.6%)	
Once a week. Usually at the weekend	102	(23.3%)	74	(24.0%)	176	(23.6%)	
Less than once a week	9	(2.1%)	16	(5.2%)	25	(3.4%)	

Chi^2, Pearson's chi^2 test; Y, chi^2 test with Yates correction; p, significance level, correlation coefficient: τ_c, Kendall's τ_c; V_C, Cramer's V.

TABLE 3 Characteristics of the consumption of anti-health products in the study group of women by year of study.

Variable	2011		2022		Total 2011 and 2022		Test p correlation coefficient
	n	(%)	*n*	(%)	*N*	(%)	
How often do you eat casseroles, hamburgers, pizza etc.?							
At all	114	(26.1%)	47	(15.3%)	161	(21.6%)	$Y = 16.37$ $p = 0.001$ $\tau_c = 0.12$
Several times a month	315	(72.1%)	247	(80.2%)	562	(75.4%)	
Several times a week	7	(1.6%)	13	(4.2%)	20	(2.7%)	
Once a day	1	(0.2%)	1	(0.3%)	2	(0.3%)	
How often do you eat salty snacks (crisps, sticks)?							
At all	138	(31.6%)	54	(17.5%)	192	(25.8%)	$Y = 51.84$ $p < 0.001$ $\tau_c = 0.23$
Several times a month	260	(59.5%)	176	(57.1%)	436	(58.5%)	
Several times a week	27	(6.2%)	68	(22.1%)	95	(12.8%)	
Once a day	10	(2.3%)	6	(2.0%)	16	(2.1%)	
2–3 times a day	2	(0.4%)	4	(1.3%)	6	(0.8%)	
How often do you eat sweets?							
At all	37	(8.5%)	26	(8.4%)	63	(8.5%)	$Y = 25.65$ $p < 0.001$ $\tau_c = 0.17$
Several times a month	171	(39.1%)	78	(25.3%)	249	(33.4%)	
Several times a week	134	(30.7%)	94	(30.5%)	228	(30.6%)	
Once a day	69	(15.8%)	71	(23.1%)	140	(18.8%)	
2–3 times a day	23	(5.2%)	37	(12.0%)	60	(8.0%)	
4 or more times a day	3	(0.7%)	2	(0.7%)	5	(0.7%)	

Y, chi^2 test with Yates correction; *p*, significance level; τ_c, Kendall's τ_c correlation coefficient.

and sweets. Women in 2022 were more likely to consume fast-food ($p = 0.001$), salty snacks (chips, crisps) ($p < 0.001$) and sweets ($p < 0.001$).

Tables 4, 5 assess the consumption of cereal products. Women in 2022 were more likely to consume whole-grain bread ($p < 0.001$), wholemeal pasta ($p < 0.001$), brown rice ($p < 0.001$), oatmeal ($p < 0.001$), buckwheat groats ($p = 0.06$), and bran ($p < 0.001$) than women in 2011. They were less likely to consume white bread ($p < 0.0001$), light pasta ($p = 0.004$), white rice ($p = 0.008$) and cornflakes ($p < 0.001$) in 2022.

The study also assessed the consumption of health-promoting foods such as vegetables, fruit, dry pulses and potatoes. Women in 2022 were significantly more likely to consume vegetables ($p < 0.001$) than women in 2011. More than half of women consumed vegetables 2–3 times a day (2022 48.4% vs. 2011 14.4%; $p < 0.001$). They were more likely to consume fruit 2–3 times a day in 2022 than 2011 ($p = 0.118$), but this difference is not statistically significant. They were also more likely to consume dry pulses such as soya, lentils, chickpeas, broad beans or beans ($p < 0.001$). In contrast, women were less likely to consume potatoes in 2022 than in 2011. ($p < 0.001$; Table 6).

The consumption of dairy products was assessed. Women in 2022 were less likely to consume natural yoghurt ($p < 0.001$), buttermilk ($p < 0.001$), natural cottage cheese ($p < 0.001$), yoghurt and flavoured cheese, e.g., fruit ($p < 0.001$), and yellow cheese ($p = 0.005$) than women in 2011 (Table 7).

In 2022, women in the study population consumed less meat than in 2011 ($p < 0.001$), consumption of cold cuts ($p < 0.001$) as well as fish decreased ($p = 0.001$). On the other hand, the consumption of vegetarian so-called meatless dinners increased ($p < 0.001$; Table 8).

4. Discussion

Diet is a factor that significantly determines nutritional status. Many factors influence the health of any woman. The first is a lifestyle, which determines a person's health to the greatest extent. Lifestyle components can include diet, physical activity, alcohol consumption or smoking. These components are modifiable factors and can be changed at any time, and every woman has the right to decide about her life. In addition, health is affected by the physical environment (soil, air and water pollution), the social environment (family situation, economic situation, housing or psychological problems), work (toxic substances, dust, noise), genetic conditions or the state of health services (29).

It has been modified over the last few years. One of the factors influencing changes in the population's nutritional status is the lifestyle change caused by the COVID-19 pandemic. Restriction of leaving the residence, travel, remote work, social isolation, restriction of stationary shopping, and closure of gastronomy, gyms and other sports facilities required lifestyle adaptation to the restrictions in place (30). Studies analysing changes in the nutritional status of women of the Polish population during the COVID-19 pandemic indicate an increase in body weight and BMI. In a study by Blaszczyk-Bęben et al. (31). The body weight of 45.86% of the women studied during social isolation increased significantly. In contrast, Sidor and Rzymski (32) found that dietary changes during quarantine could potentially cause weight changes as a result of less physical activity, changes in food intake and stress associated with the new situation; 29.9% of respondents reported an increase in weight during quarantine and the

TABLE 4 Frequency of consumption of health-promoting cereal products among female respondents by year of study.

Variable	2011 *r.*		2022 *r.*		Total 2011 and 2022		Test *p* correlation coefficient
	n	(%)	*n*	(%)	*N*	(%)	
Wholemeal bread							
4 or more times a day	2	(0.5%)	0	(0.0%)	2	(0.3%)	$Y = 32.27$ $p < 0.001$ $\tau_c = 0.09$
2–3 times a day	32	(7.3%)	20	(6.5%)	52	(7.0%)	
Once a day	84	(19.2%)	50	(16.2%)	134	(18.0%)	
Several times a week	90	(20.6%)	116	(37.7%)	206	(27.6%)	
Several times a month	143	(32.7%)	89	(28.9%)	232	(31.1%)	
at all	86	(19.7%)	33	(10.7%)	119	(16.0%)	
Wholemeal pasta							
Several times a week	15	(3.4%)	36	(11.7%)	51	(6.8%)	$Chi^2 = 168.10$ $p < 0.001$ $\tau_c = 0.44$
Several times a month	55	(12.6%)	155	(50.3%)	210	(28.2%)	
At all	367	(84.0%)	117	(38.0%)	484	(65.0%)	
Brown rice							
Several times a week	6	(1.4%)	15	(4.9%)	21	(2.8%)	$Y = 81.21$ $p < 0.001$ $\tau_c = 0.26$
Once a day	7	(1.6%)	0	(0.0%)	7	(0.9%)	
Several times a month	63	(14.4%)	123	(39.9%)	186	(25.0%)	
At all	361	(82.6%)	170	(55.2%)	531	(71.3%)	
Oatmeal							
2–3 times a day	5	(1.1%)	5	(1.6%)	10	(1.3%)	$Y = 97.34$ $p < 0.001$ $\tau_c = 0.37$
Once a day	19	(4.4%)	35	(11.4%)	54	(7.3%)	
Several times a week	32	(7.3%)	61	(19.8%)	93	(12.5%)	
Several times a month	117	(26.8%)	128	(41.6%)	245	(32.9%)	
At all	264	(60.4%)	79	(25.6%)	343	(46.0%)	
Buckwheat groats							
Once a day	3	(0.7%)	3	(1.0%)	6	(0.8%)	$Y = 7.53$ $p = 0.056$ $\tau_c = 0.08$
Several times a week	14	(3.2%)	22	(7.1%)	36	(4.8%)	
Several times a month	240	(54.9%)	174	(56.5%)	414	(55.6%)	
At all	180	(41.2%)	109	(35.4%)	289	(38.8%)	
Muesli							
2–3 times a day	5	(1.1%)	1	(0.3%)	6	(0.8%)	$Y = 6.35$ $p = 0.174$ $\tau_c = -0.04$
Once a day	23	(5.3%)	7	(2.3%)	30	(4.0%)	
Several times a week	52	(11.9%)	39	(12.7%)	91	(12.2%)	
Several times a month	128	(29.3%)	91	(29.5%)	219	(29.4%)	
At all	229	(52.4%)	170	(55.2%)	399	(53.6%)	
Bran							
2–3 times a day	1	(0.2%)	3	(1.0%)	4	(0.5%)	$Y = 27.79$ $p < 0.001$ $\tau_c = 0.07$
Once a day	26	(6.0%)	4	(1.3%)	30	(4.0%)	
Several times a week	24	(5.5%)	25	(8.1%)	49	(6.6%)	
Several times a month	63	(14.4%)	77	(25.0%)	140	(18.8%)	
At all	323	(73.9%)	199	(64.6%)	522	(70.1%)	

Chi^2, Pearson's chi^2 test; Y, chi^2 test with Yates correction; p, significance level, correlation coefficient: τ_c, Kendall's τ_c.

maximum reported gain was 10 kg. Significantly higher gains were observed in overweight and obese subjects (32). Analogous data were obtained by Dobrowolski and Włodarek (33). The average weight gain during the first quarantine during the pandemic averaged 2 kg and was associated with decreased physical activity and increased consumption of total food and energy-dense products (33). The COVID-19 pandemic is not the only factor contributing to increased body weight and BMI over the past

TABLE 5 Frequency of intake of nutrient-reduced cereal products among female respondents by year of study.

Variable	2011 *r.*		2022 *r.*		Total 2011 and 2022		Test *p* correlation coefficient
	n	(%)	*n*	(%)	*N*	(%)	
White bread							
4 or more times a day	8	(1.8%)	1	(0.3%)	9	(1.2%)	$Y = 74.71$ $p < 0.001$ $\tau_c = -0.31$
2–3 times a day	148	(33.9%)	33	(10.7%)	181	(24.3%)	
Once a day	94	(21.5%)	58	(18.8%)	152	(20.4%)	
Several times a week	82	(18.8%)	90	(29.3%)	172	(23.1%)	
Several times a month	64	(14.6%)	85	(27.6%)	149	(20.0%)	
At all	41	(9.4%)	41	(13.3%)	82	(11.0%)	
Pasta							
Once a day	6	(1.4%)	0	(0.0%)	6	(0.8%)	$Y = 13.50$ $p = 0.004$ $\tau_c = -0.10$
Several times a week	107	(24.5%)	57	(18.5%)	164	(22.0%)	
Several times a month	288	(65.9%)	211	(68.5%)	499	(67.0%)	
At all	36	(8.2%)	40	(13.0%)	76	(10.2%)	
White rice							
Once a day	5	(1.1%)	1	(0.3%)	6	(0.8)	$Y = 11.90$ $p = 0.008$ $\tau_c = -0.07$
Several times a week	43	(9.8%)	33	(10.7%)	76	(10.2%)	
Several times a month	348	(79.6%)	221	(71.8%)	569	(76.4%)	
At all	41	(9.4%)	53	(17.2%)	94	(12.6%)	
Cornflakes							
2–3 times a day	7	(1.6%)	1	(0.3%)	8	(1.1%)	$Y = 39.46$ $p < 0.001$ $\tau_c = -0.22$
Once a day	13	(3.0%)	2	(0.7%)	15	(2.0%)	
Several times a week	48	(11.0%)	13	(4.2%)	61	(8.2%)	
Several times a month	146	(33.4%)	71	(23.1%)	217	(29.1%)	
At all	223	(51.0%)	221	(71.7%)	444	(59.6%)	

Y, chi^2 test with Yates correction; *p*, significance level, correlation coefficient: τ_c, Kendall's τ_c.

decade. The prevalence of obesity in adults in the United States aged 20 years and older, defined as a BMI ≥30 kg/m^2, was 30.5% in 2000 and 39.8% 15 years later (34). The prevalence of severe obesity (BMI > 40) increased at an even more alarming rate in adults, moving from 3.9% in 2000 to 6.6% in 2010 (35). Changes in the global food system and sedentary lifestyles are widely recognised as the main reasons for the increase in obesity prevalence worldwide. In line with these trends, the main driver of the obesity epidemic appears to be Western lifestyle modernisation (36). Between 1997 and 2017, the prevalence of overweight increased in Polish women from 30% to 32.2%, while at the same time, the prevalence of obesity decreased from 19 to 16.1% (37). Stoś et al. (38) conducted the study in 2019/20 and included 900 women. The mean age was 51.7 ± 19.8 years. According to the WHO classification, 33.9% of women aged 18–29 were overweight or obese; the percentage of women with abnormal body weight increased with age. The highest percentage of women with abnormal body weight was aged 60–69 years (71.5% of women). Almost half of the women in the study (49.2%) had abnormal body weight, defined as overweight or obese (38).

Considering our results, it should be noted that the average body mass index BMI increased by 1.37 kg/m2. The % of women with obesity also increased from 7.6% in 2011 to 16.9% in 2022, and the number of overweight women was 24.9% in 2011 and 25.3% in 2022. The data presented confirms that overweight and obesity in the Polish female population was already a serious problem before the COVID-19 pandemic, the pandemic itself and the associated restrictions potentially exacerbating the issues raised in the study.

The changes we identified in dietary patterns among working-age women over 2011–2022 was significant. When embarking on the 2011 survey, we did not define assumptions in the questionnaire such as lockdown, total remote working, hybrid remote working, and widespread quarantines during which entire families were not allowed to leave their homes and flats for weeks at a time. The survey conducted in 2022 already took into account the new state of functioning in society associated with the COVID pandemic, which had prevailed for 2 years. At the same time, the survey was already conducted after solid pandemic restrictions, where the use of grocery shops, restaurants and fast-food bars was restored from before the pandemic period.

Research conducted during the COVID-19 pandemic showed that not everyone adapted to the new conditions to the same extent. This was also observed in the dietary habits of Polish adults over 40 years of age, those living with children, those living in regions with a higher gross domestic product and those who did not eat at home before the pandemic (39). Adherence to dietary recommendations was also influenced by psychological factors and the ability to cope with difficult situations and adapt quickly to changing circumstances (40). Many studies have addressed lifestyle characteristics in the last 3 years,

TABLE 6 Frequency of vegetable, fruit, and legume consumption among female respondents by year of study.

Variable	2011 *r.*		2022 *r.*		Total 2011 and 2022		Test *p* correlation coefficient
	n	(%)	*n*	(%)	*N*	(%)	
Vegetables							
4 or more times a day	11	(2.5%)	20	(6.5%)	31	(4.1%)	$Y = 128.99$ $p < 0.001$ $\tau_c = 0.34$
2–3 times a day	63	(14.4%)	149	(48.4%)	212	(28.5%)	
Once a day	162	(37.1%)	55	(17.8%)	217	(29.1%)	
Several times a week	157	(35.9%)	61	(19.8%)	218	(29.3%)	
Several times a month	36	(8.2%)	23	(7.5%)	59	(7.9%)	
At all	8	(1.8%)	0	(0.0%)	8	(1.1%)	
Potatoes							
2–3 times a day	12	(2.7%)	0	(0.0%)	12	(1.6%)	$Y = 175.24$ $p < 0.001$ $\tau_c = -0.44$
Once a day	127	(29.1%)	14	(4.5%)	141	(18.9%)	
Several times a week	203	(46.4%)	109	(35.4%)	312	(41.9%)	
Several times a month	71	(16.3%)	173	(56.2%)	244	(32.8%)	
At all	24	(5.5%)	12	(3.9%)	36	(4.8%)	
Legumins							
2–3 times a day	7	(1.6%)	7	(2.3%)	14	(1.9%)	$Y = 21.57$ $p < 0.001$ $\tau_c = 0.17$
Once a day	7	(1.6%)	10	(3.2%)	17	(2.3%)	
Several times a week	30	(6.9%)	43	(14.0%)	73	(9.7%)	
Several times a month	229	(52.4%)	172	(55.8%)	401	(53.8%)	
At all	164	(37.5%)	76	(24.7%)	240	(32.2%)	
Fruit							
4 or more times a day	8	(1.8%)	5	(1.6%)	13	(1.7%)	$Y = 8.78$ $p = 0.118$ $\tau_c = 0.07$
2–3 times a day	80	(18.3%)	77	(25.0%)	157	(21.1%)	
Once a day	167	(38.2%)	116	(37.7%)	283	(38.0%)	
Several times a week	129	(29.5%)	71	(23.1%)	200	(26.9%)	
Several times a month	40	(9.2%)	34	(11.0%)	74	(9.9%)	
At all	13	(3.0%)	5	(1.6%)	18	(2.4%)	

Y, Chi^2 test with Yates correction; *p*, significance level, correlation coefficient: τ_c, Kendall's τ_c. The consumption of dairy products was assessed. Women in 2022 were less likely to consume natural yoghurt ($p < 0.001$), buttermilk ($p < 0.001$), natural cottage cheese ($p < 0.001$), yoghurt and flavoured cheese, e.g., fruit ($p < 0.001$), and yellow cheese ($p = 0.005$) than women in 2011. (Table 7).

including dietary adherence considering the COVID pandemic-19. The methodology of most studies was based on qualitative methods assessing dietary habits, taking into account the frequency of consumption of product groups and the direction of change in their consumption during the pandemic (41, 42). Studies highlight that the consequences of social isolation caused by COVID-19 can include a change in eating behaviour. Among others, the following were observed: increased breakfast intake, reduced consumption of fried foods and meals consumed in restaurants and fast food, and increased consumption of fresh produce (43–46). The frequency of consumption of fruit, legumes and vegetables also increased (47).

The study by Górecka et al. confirmed our obtained results regarding the frequency of consumption of specific product groups. Two opposing dietary patterns were observed: a pro-healthy one associated with increased consumption of whole-grain products, vegetables, fruit and water, and an unhealthy one with the consumption of processed meat, fast food, confectionery and alcohol and sweets was increased (39). In a study by Bolesławska et al. (48), a significantly higher percentage of women also declared eating five meals compared to the previous period ($p < 0.0001$), an increase in the frequency of consumption of potatoes excluding chips and chips ($p = 0.0026$), sweets ($p = 0.0127$), eggs ($p = 0.0011$) and canned meat ($p = 0.0166$), and a decrease in the consumption of fast food ($p = 0.0038$) and instant and ready-made soups ($p = 0.0327$). Vegetables among the women surveyed were consumed several times a day by 36.5% of respondents before the lockdown and 34.5% during the lockdown ($p = 0.6747$). The fruit was less popular (20.5% before lockdown vs. 23.5% during lockdown, $p = 0.9220$).

The changes in the women's diets in the self-study included the distribution of the number of meals. In 2011, women were more likely to eat three or four meals daily; in 2022, some women expanded to five per day. More women in 2022 ate breakfast than in 2011 (77.6% vs. 63.8%) ($p < 0.001$), were more likely to eat breakfast at home (73.1% vs. 62.5%) ($p < 0.001$), were more likely to eat breakfast II (39.0% vs. 35.2%) ($p = 0.001$), more often had their second breakfast at home (28.6% vs. 19.2%) ($p = 0.002$), more often had their lunch at work (16.6% vs. 3.4%) ($p < 0.001$). The increase in the number of meals consumed is confirmed by a study by Bolesławska et al. (48). Also, in Oleszko's 2019 study, most Silesia region women eat 4–5 meals (59.20%) (49).

TABLE 7 Frequency of consumption of dairy products such as natural yoghurts, cheeses, cottage cheese, and flavoured yoghurts and cheeses among female respondents by year of survey.

Variable	2011		2022		Total 2011 and 2022		Test p correlation coefficient
	n	(%)	n	(%)	N	(%)	
Natural yoghurt							
2–3 times a day	31	(7.1%)	6	(2.0%)	37	(5.0%)	$Chi^2 = 28.77$ $p < 0.001$ $\tau_c = -0.20$
Once a day	111	(25.4%)	45	(14.6%)	156	(20.9%)	
Several times a week	152	(34.8%)	114	(37.0%)	266	(35.7%)	
Several times a month	103	(23.6%)	103	(33.4%)	206	(27.7%)	
At all	40	(9.1%)	40	(13.0%)	80	(10.7%)	
Buttermilk							
2–3 times a day	14	(3.2%)	0	(0.0%)	14	(1.9%)	$Y = 89.23$ $p < 0.001$ $\tau_c = -0.34$
Once a day	38	(8.7%)	5	(1.6%)	43	(5.8%)	
Several times a week	116	(26.5%)	31	(10.1%)	147	(19.7%)	
Several times a month	184	(42.1%)	148	(48.0%)	332	(44.6%)	
At all	85	(19.5%)	124	(40.3%)	209	(28.0%)	
Curd cheeses/ cottage cheese							$Y = 22.52$ $p < 0.001$ $\tau_c = -0.17$
2–3 times a day	16	(3.7%)	3	(1.0%)	19	(2.6%)	
Once a day	37	(8.5%)	19	(6.2%)	56	(7.5%)	
Several times a week	195	(44.6%)	105	(34.1%)	300	(40.3%)	
Several times a month	163	(37.3%)	147	(47.7%)	310	(41.6%)	
At all	26	(5.9%)	34	(11.0%)	60	(8.0%)	
Fruit cheeses/yoghurts							
2–3 times a day	13	(3.0%)	1	(0.3%)	14	(1.9%)	$Y = 173.19$ $p < 0.001$ $\tau_c = -0.50$
Once a day	34	(7.8%)	4	(1.3%)	38	(5.1%)	
Several times a week	154	(35.2%)	31	(10.1%)	185	(24.8%)	
Several times a month	148	(33.9%)	75	(24.3%)	223	(29.9%)	
At all	88	(20.1%)	197	(64.0%)	285	(38.3%)	
Yellow cheeses							
4 or more times a day	5	(1.1%)	1	(0.3%)	6	(0.8%)	$Y = 16.73$ $p = 0.005$ $\tau_c = -0.12$
2–3 times a day	18	(4.1%)	11	(3.6%)	29	(3.9%)	
Once a day	65	(14.9%)	45	(14.6%)	110	(14.8%)	
Several times a week	231	(52.9%)	127	(41.2%)	358	(48.0%)	
Several times a month	98	(22.4%)	101	(32.8%)	199	(26.7%)	
At all	20	(4.6%)	23	(7.5%)	43	(5.8%)	

Chi^2, Pearson's Chi^2 test; Y, Chi^2 test with Yates correction; p, significance level, correlation coefficient: τ_c, Kendall's τ_c.

A small percentage of women in 2011 and 2022 did not eat lunch. It was 1.14% in 2011 and 0.65% in 2022. In Poland, there is a traditional model of meal consumption that includes: breakfast eaten in the morning at home or after coming to work, followed by a second breakfast usually eaten at school/workplace/work around 10 a.m. to 12 p.m. The next meal is a traditional lunch eaten after returning from work, while in the evening, dinner is eaten, which is often served in the form of sandwiches. In Poland, a lunch-type meal at the workplace is still rare. Poles, irrespective of gender, are more likely to eat lunch at home after coming from work around 3 p.m., between 6 a.m. and 2 p.m., around 4 p.m. when they work between 7 a.m. and 3 p.m., and after 5 p.m. when they work until 4 p.m. According to Art, this may be due to Polish labour law, which only allows for one break during 8 h of work. 134 of the Labour Code, "an employee has the right to a break of at least 15 min counted as working time" (50), the lack of tradition of eating lunch at work, as well as the lack of places to eat meals at the workplace and financial issues (meals in the form of sandwiches prepared at home are cheaper than buying a ready-made lunch).

In their study, women in 2022 were more likely to consume fast food ($p = 0.001$), salty snacks (chips, crisps) ($p < 0.001$) and sweets ($p < 0.001$) than women in 2011. Similar results were obtained in a study by Sidor and Rzymski; one-third of the subjects admitted to consuming sweets daily during the lockdown period (32). In the 2019 study by Oleszko et al, the frequency of sweet consumption was lower than in their study 24.48% of women consumed sweets daily. In their study, more than 35.0% consumed sweets daily (49). Comparing fast-food consumption,

TABLE 8 Frequency of intake of products that are a source of protein among female respondents by year of study.

Variable	2011		2022		Total 2011 and 2022		Test *p* correlation coefficient
	n	(%)	*n*	(%)	*N*	(%)	
Meat							
2–3 times a day	8	(1.8%)	10	(3.3%)	18	(2.4%)	$Y = 23.93$ $p < 0.001$ $\tau_c = -0.10$
Once a day	69	(15.8%)	34	(11.0%)	103	(13.8%)	
Several times a week	278	(63.6%)	179	(58.1%)	457	(61.4%)	
Several times a month	75	(17.2%)	60	(19.5%)	135	(18.1%)	
At all	7	(1.6%)	25	(8.1%)	32	(4.3%)	
Fish							
2–3 times a day	3	(0.7%)	2	(0.6%)	5	(0.7%)	$Y = 18.00$ $p = 0.001$ $\tau_c = -0.11$
Once a day	6	(1.4%)	6	(2.0%)	12	(1.6%)	
Several times a week	94	(21.5%)	45	(14.6%)	139	(18.7%)	
Several times a month	320	(73.2%)	225	(73.1%)	545	(73.1%)	
At all	14	(3.2%)	30	(9.7%)	44	(5.9%)	
Cold cuts							
4 or more times a day	8	(1.8%)	1	(0.3%)	9	(1.2%)	$Y = 186.13$ $p < 0.001$ $\tau_c = -0.50$
2–3 times a day	46	(10.5%)	1	(0.3%)	47	(6.3%)	
Once a day	165	(37.8%)	25	(8.1%)	190	(25.5%)	
Several times a week	163	(37.3%)	152	(49.4%)	315	(42.3%)	
Several times a month	48	(11.0%)	117	(38.0%)	165	(22.2%)	
At all	7	(1.6%)	12	(3.9%)	19	(2.5%)	
Vegetarian lunches/dinners							
2 times a day	3	(0.7%)	13	(4.2%)	16	(2.2%)	$Y = 162.14$ $p < 0.001$ $\tau_c = 0.33$
Once a day	3	(0.7%)	48	(15.6%)	51	(6.8%)	
Several times a week	106	(24.2%)	131	(42.5%)	237	(31.8%)	
Several times a month	267	(61.1%)	68	(22.1%)	335	(45.0%)	
At all	58	(13.3%)	48	(15.6%)	106	(14.2%)	

Y, chi^2 test with Yates correction; *p*, significance level, correlation coefficient: τ_c, Kendall's τ_c.

the results from Oleszko et al. (49) are comparable to 9.2% consuming fast-food several times a week vs. their own study's 9.41%.

Many vegetable compounds positively affect the cardiovascular system, prevent diabetes and cancer and reduce anxiety and depressive symptoms. This is due to phytonutrients found in plant foods or naturally occurring in plant foods (51). With advances in science, various chemical compounds in vegetables have been identified to have therapeutic effects. Among these, the most potent are antioxidants and bioflavonoids, the primary pigments in vegetables (52). Phytonutrients are believed to reduce the danger of many chronic diseases by defending against free radicals, detoxifying carcinogens and modifying metabolic activation, or influencing processes that modify the course of cancer cell development. In the daily diet, colourful vegetables are strongly associated with improved eye health, gastrointestinal health and reduced risk of cardiovascular disease, chronic disease and cancer (53).

According to Eurostat data, in Poland in 2014 0 portions of fruit and vegetables were consumed by 33.2.% of Polish women, 59.5% consumed 1–4 portions of fruit and vegetables per day, and 11.8% had 5 or more portions. In 2019 5 portions of fruit and vegetables were consumed by less than 10.6% of Polish women. 57.3% consumed 1–4 portions and 0 portions, as many as 32.2% of Polish women (54). Considering current Polish dietary recommendations, an average adult Polish woman should consume at least 400 g of vegetables and fruit per day—with a higher intake of vegetables than of fruit. Data from the Central Statistical Office in Poland indicate that the average monthly intake in 2020 was 11.98 kg excluding potatoes which gives a daily vegetable intake of 399 g. Compared to 2016, the average intake decreased by 21 g/day (55).

In our study, women in 2022 were significantly more likely to consume vegetables ($p < 0.001$) than women in 2011. More than half of the women consumed vegetables several times daily (2022 54.9% vs. 2011 16.9%). They were more likely to consume fruit several times a day in 2022 than in 2011. They were also more likely to consume dry pulses such as soya, lentils, chickpeas, broad beans or beans ($p < 0.001$). In contrast, women were less likely to consume potatoes in 2022 than in 2011 ($p < 0.001$). In the 2019 study by Oleszko et al., the largest number of women surveyed consumed 1–2 portions of fruit and vegetables daily (59.38%), and 32.12% declared 3–4 portions per day (49).

In the 2022 self-study, women were more likely to consume whole-grain bread ($p < 0.001$), wholemeal pasta ($p < 0.001$), brown rice ($p < 0.001$), oatmeal ($p < 0.001$), buckwheat groats ($p = 0.056$), and bran

($p < 0.001$) than women in 2011. In contrast, they were less likely to consume white bread ($p < 0.001$), pasta ($p > 0.004$), white rice ($p = 0.008$) and cornflakes ($p < 0.001$) in 2022. The more frequent choice of whole-grain bread than white bread (46.70% vs. 41.85%) confirms the study by Oleszko et al. (39).

In the 2019 study by Oleszko et al, the majority of women consumed milk and dairy products occasionally (46.00%) (39), confirming the trend we also observed in our study that women in 2022 were less likely to consume natural yoghurt ($p < 0.001$), buttermilk ($p < 0.001$), natural cottage cheese ($p < 0.001$), yoghurt and flavoured cheese, e.g., fruit ($p < 0.001$), and yellow cheese ($p = 0.005$ than women in 2011). The study by Oleszko et al. (39) also considered the consumption of fish, meat, and cold cuts—most respondents consumed fish several times a month (79.51%). Moreover, meat and cold cuts, 48.26% consumed several times a week. In the 2022 self-reported survey, women consumed meat less frequently than in 2011 ($p < 0.001$), consumption of cold cuts ($p < 0.001$), as well as fish, decreased ($p = 0.001$).

All these changes can be attributed to several factors: increased consumer and health awareness (increased consumption of vegetables, whole-grain cereals, choice of vegan dinners, reduced consumption of cold cuts and meat), diagnosis of food allergies and intolerances, especially when it comes to the consumption of dairy products and the widespread availability of alternative dairy products such as plant-based drinks, plant-based yoghurts based on soya, coconut, cashew nuts or almonds, dietary fashions (vegan dinners, alternative foods, e.g., plant-based yoghurts) and the price of products (especially fish).

4.1. Strengths and limitations

There are limitations to survey that need to be taken into account when evaluating and interpreting the results. The 2022 survey was based on an anonymous online questionnaire. The questionnaire was conducted using the CAWI method. This type of data collection is widely accepted and convenient for collecting large amounts of information in groups that are often difficult to reach. However, there is an inability to verify the data. The researchers in both 2011 and 2022 did not measure respondents' weight and height, but these were declared by the respondents. Therefore, the weight and height of the respondents, and the BMI calculated from them, should be regarded more as a rough estimate than an exact value. The study was conducted in Silesia (Poland), where in other regions of Poland women's diets may be different from those in our study, there is a limitation of the local dietary pattern, characteristic of this region of Poland. The studies conducted in both 2011 and 2021 cover the same population of women from the Silesian agglomeration, so it is reasonable to compare this population. This study uses a simplified approach to summarise the overall prevalence of food group intake by relating it to the recommendations of the Institute of Food and Nutrition and the National Centre for Nutrition Education, and does not distinguish the intake of individual food types from each food category. However, this was done deliberately to avoid any negative impact on the length and content of this questionnaire. Finally, this survey reviews eating behaviour over a 10 years period, and the 2022 survey was conducted after the lockdown period associated with the COVID-19 pandemic, which may also distort the survey results. The study has the advantage of group size and the re-use of the same questionnaire tool, so diet can be accurately compared over the years among the women surveyed.

5. Conclusion

Based on the study, we can draw the following conclusions: there have been changes in the diet of women living in Silesia (Poland) over the last decade. Disturbing trends were observed in the consumption of milk and dairy products, fast-food, salty snacks (chips, crisps) and sweets, which may contribute to the occurrence of diseases resulting from poor nutrition such as cardiovascular diseases, cancer, diabetes. At the same time, health-promoting dietary trends were observed in the study group of women, such as increased consumption of whole-grain cereals, vegetables, fruits and legumes. The results of the study will help determine the future direction of nutrition education, taking into account current dietary mistakes, in order to minimise the negative impact of nutrition on women's future health and to formulate ministerial prevention programmes.

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 Bioethics Committee of the Silesian Medical University in Katowice in accordance with Resolution No. KNW/0022/KB1/151/I/11 of 06.12.2011. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AB-D and TK: conceptualization, methodology, and validation. AB-D and EC: formal analysis and investigation. AK and BC: resources. OS and AS-C: data curation. AB-D, MS-K, and WS: writing—original draft preparation. AB-D, EC, and WS: writing—review and editing. MK and MG: visualization. MM-W and ES: supervision. AB-D: project administration. 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

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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 22 September 2023
DOI 10.3389/fnut.2023.1273976

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RECEIVED 07 August 2023
ACCEPTED 11 September 2023
PUBLISHED 22 September 2023

CITATION
Mazza E, Troiano E, Mazza S, Ferro Y, Abbinante A, Agneta MT, Montalcini T and Pujia A (2023) The impact of endometriosis on dietary choices and activities of everyday life: a cross-sectional study.
Front. Nutr. 10:1273976.
doi: 10.3389/fnut.2023.1273976

The impact of endometriosis on dietary choices and activities of everyday life: a cross-sectional study

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Introduction: Endometriosis is characterized by ectopic endometrial tissue and severe pain; frequently, women afflicted by this condition resort to non-medical interventions, such as dietary modifications. The aim of this study is to assess the impact of endometriosis on dietary patterns and quality of life.

Methods: An online survey was conducted among Italian women with endometriosis to gather self-reported demographic, clinical, dietary habit, and daily life data post-diagnosis.

Results: A total of 4,078 participants were included. Following an endometriosis diagnosis, 66% reported changes in eating habits, and 92% experienced a decline in daily life. Respondents chose dietary interventions: gluten-free (15%), anti-inflammatory (8%), Mediterranean (7.1%), or ketogenic (4%) diets, to improve health and reduce symptoms. The study revealed a shift in eating habits, with increased consumption of vegetables, fruits (10%), cereals, legumes (6.6%), and fish (4.5%), while reducing dairy products (18.4%), soy-containing foods (6.7%), and high saturated fats (8%). Eating habit changes correlated with endometriosis stages and worsened daily life. Educational level, endometriosis stages, years of symptoms, and eating habit changes linked to changes in daily life.

Conclusion: Our findings emphasize the importance of monitoring eating behaviors to prevent unhealthy habits and malnutrition in women with endometriosis. Further studies are needed to evaluate how different diets impact symptoms and enhance daily life for these individuals.

KEYWORDS

endometriosis, dietary changes, anti-inflammatory foods, eating habit, everyday life

1. Introduction

Endometriosis is the prevalent condition among non-malignant gynecological disorders, impacting approximately 10% of women in their reproductive years. It stands as one of the primary anatomical factors contributing to persistent pelvic pain (1). Endometriosis is commonly characterized as a chronic inflammatory condition that relies on estrogen and involves the presence of endometrium-like tissue functioning outside the uterus. Due to these characteristics, it is now recognized as a systemic disease rather than being confined solely to the pelvic region (1). Indeed, endometriosis frequently coexists with various other conditions including fibromyalgia, migraines, irritable bowel syndrome, mental health disorders, and immunological conditions like rheumatoid arthritis (2). Endometriosis is characterized by various symptoms including chronic pain, dysmenorrhea, dyschezia, dyspareunia, dysuria, fatigue, and reduced fertility. However, the precise causes and mechanisms underlying the development of endometriosis are not fully elucidated at present. The pathogenesis and pathophysiology of this condition remain areas of active research, and further investigations are necessary to achieve a comprehensive understanding of the disease (2, 3). The occurrence of endometriosis involves a complex interplay between endocrine, proinflammatory, and immunological processes (3). The current medical and surgical interventions available for endometriosis frequently prove insufficient in alleviating symptoms (1–3).

The presence of endometriosis can have a profound impact on a woman's physical and social wellbeing (4, 5), resulting in a significant burden of the disease, both in terms of its economic implications and its effect on quality of life (4). Furthermore, endometriosis leads to increased absenteeism from work or school (6). The condition exerts a significant influence on the mental and emotional wellbeing of women (7), as well as their social activities (8), and sexual relationships (9). Studies have indicated that endometriosis can diminish physical quality of life to a similar extent as experienced by cancer patients (8).

A recent systematic review and meta-analysis demonstrated that endometriosis has a detrimental effect on health-related quality of life comparable to that of chronic pain (10–12). Consequently, many women with endometriosis turn to non-medical methods to manage symptoms and enhance their everyday lives (13). Therefore, women with endometriosis often resort to lifestyle interventions such as rest, heat therapy, meditation, exercise, and dietary changes to manage their symptoms (3).

Dietary interventions, in particular, have shown promising results in improving endometriosis-related symptoms. Studies have indicated that a significant proportion of women with endometriosis (76%) employ self-management strategies, with nearly half of them (44%) opting for dietary changes (14). Another recent study revealed that 55.5% of participants reported that food influenced their endometriosis symptoms, and modifying their diet provided symptom relief (15). Dietary factors may play a role in the progression and development of endometriosis by influencing steroid hormone metabolism, the menstrual cycle, inflammation regulation, oxidative stress, and muscle contraction (16). As a result, diets and dietary modifications adopted by women with endometriosis have garnered increasing attention from researchers. The question of whether and how specific diets and lifestyles can influence the pathogenesis and progression of endometriosis continues to be investigated (16, 17).

The link between dietary factors and endometriosis has gained interest due to the recognition that diet can impact both physiological and pathological processes. Some authors suggest that dietary changes may have therapeutic potential in alleviating chronic inflammatory processes and reducing visceral pain perception (18, 19). Certain natural anti-inflammatory agents, such as Omega-3 polyunsaturated fatty acids (PUFAs) and squalene, a biofunctional lipid compound, have shown beneficial effects on chronic diseases (20–22).

Other diets, such as the Mediterranean Diet, low FODMAP (fermentable oligo-, di-, monosaccharides, and polyols) diet, and gluten-free diet, have also been investigated in relation to chronic inflammatory diseases (23, 24). A recent systematic review focusing on the impact of dietary changes on pain perception in relation to endometriosis demonstrated that diet had a positive influence on pain perception among women with endometriosis. Specifically, a high intake of PUFAs, a gluten-free diet, and a low nickel diet were associated with improved pain management in endometriosis (25) Additionally, adding nutrients with anti-inflammatory and antiestrogenic properties such as antioxidants curcumin, epigallocatechin gallate, quercetin, resveratrol, and inositol, found in fruits, vegetables, and fatty fish, while eliminating pro-inflammatory substances like lactose, saturated fats, and soy, has been suggested to alleviate endometriosis pain (15, 26–29).

Moreover, initial investigations into the effectiveness of probiotics in managing endometriosis in women have shown promising outcomes in terms of pain alleviation (30). Furthermore, studies have reported that the administration of Lactobacillus probiotics can ameliorated endometriosis-associated pain in females (31). Consequently, the existing data implies the significant impact of dietary supplements in inducing favorable alterations in the gut microbiota, which may play a role in promoting human health and lowering the risk of inflammatory conditions, including endometriosis.

Consequently, food choices may have an impact on disease progression and pain perception in endometriosis.

However, it is important to note that robust evidence regarding the relationship between nutrition, a healthy diet, and endometriosis treatment is limited, as are studies exploring the effect of the disease on food choices.

Thus, the aim of this study was to investigate the potential effects of the disease on dietary habits and daily activities in women following an endometriosis diagnosis.

2. Materials and methods

The Italian Dental Hygienists Association (AIDI) and the Technical Scientific Association of Food, Nutrition, and Dietetics (ASAND), in collaboration with the Clinical Nutrition Unit of the "Magna Graecia" University of Catanzaro, conducted an online survey to explore various aspects of daily life in women with endometriosis. This cross-sectional study collected data between 9 April and 27 June 2021. An anonymous national survey was administered using the Google Forms tool, targeting women over the age of 18 residing in Italy who self-reported a previous endometriosis diagnosis. Recruitment was carried out through direct survey links and invitations distributed via social media platforms such as Facebook, WhatsApp, Twitter, and Instagram, specifically through AIDI, ASAND, and the Italian Association of Endometriosis. The latter serves as a network to foster discussion, community, and support among women with endometriosis. The study received ethical approval from the Local Ethics Committee in the Calabria Region Central Area (code 355/2021/CE).

2.1. Questionnaire

We developed a semi-structured online questionnaire that focused on collecting self-reported sociodemographic data (age, educational level, employment status), the self-perceived impact of endometriosis symptoms on daily life, capturing self-reported disease-related information (years since diagnosis, stage, symptoms, delay in diagnosis, pharmacological treatment, associated autoimmune diseases), and documenting self-reported changes in eating habits following an endometriosis diagnosis (see Supplementary Table S1).

In our study, dietary change was defined as a self-reported modification in one's previous diet (15, 32–34). The impact of endometriosis symptoms on daily life was investigated through questions related to chronic fatigue, depression and anxiety, sleep disorders, reduced fertility or subfertility, decreased sexual satisfaction, reduced work capacity, diminished social interactions, difficulties in daily activity planning and execution, and pain management challenges (7–12, 35–38). Our questionnaire was developed adapting previous validated tools (7–12, 35–38). Participants provided informed consent via an anonymous online form at the beginning of the questionnaire. Participants were asked to self-report the stage of their endometriosis diagnosis, if known, according to the classification system of the American Society of Reproductive Medicine (ASRM), which includes four stages: Stage I (Minimal), Stage II (Mild), Stage III (Moderate), and Stage IV (Severe) (39). The questionnaire consisted of 31 items, primarily employing closed-ended questions with predefined answer options. Five questions allowed participants to provide open-ended responses and share personal opinions. The survey, on average, required 15–20 min to complete.

To validate our questionnaire, as reported in other studies (40), we conducted a factor analysis using Horn's parallel analysis for principal components, employing varimax rotation (32, 33, 40). An eigenvalue of 1 was used as a cut-off for determining the number of factors. In total, the explained variance accounted for 64.4% of the variance. To assess internal consistency, reflecting the degree to which the elements of the instrument measure the same construct, we employed Cronbach's α test. A Cronbach's α value exceeding 0.70 is indicative of good internal consistency, and our questionnaire achieved a Cronbach's α value of 0.72.

2.2. Statistical analysis

To find a correlation between changes in eating habits and the stage of endometriosis with an r value of 0.05, with a study power of 80% and a one-tailed alpha of 0.05, a sample size of 3,134 women with endometriosis was required. Upon closure of the online survey and cessation of data collection, the final database was downloaded as a Microsoft Excel sheet and subjected to data analysis. Open-ended questions were carefully reviewed, condensed, and coded for statistical analysis. Missing data were not imputed during the statistical analysis. The results are presented as absolute (n) and relative (%) frequencies for categorical variables. Pearson's correlation coefficient was utilized to identify any confounding variables associated with changes in eating habits and daily life, assuming normal distribution for continuous variables. Additionally, a Chi-square test was conducted to examine the changes in eating habits and daily life among participants following the diagnosis of endometriosis, stratified by disease stage. The same test was employed to assess dietary patterns and food choices among women with endometriosis who reported a deterioration in their quality of life. Statistical significance was set at $p < 0.05$ (two-tailed). All statistical analyses were performed using SPSS 25.0 for Windows (IBM Corporation, New York, NY, United States).

3. Results

During the survey, a total of 4,078 responses were collected and analyzed. Table 1 presents the demographic and clinical characteristics of women with endometriosis. The largest proportion of participants (45%) fell between the ages of 36 and 45, and 37% of women had a severe stage of the disease. Among the participants, 1,333 were undergoing hormonal treatment at the time of the interview, with 1,331 using oral contraceptive pills or vaginal contraceptive rings (see Table 1). The educational background of the respondents varied, encompassing both secondary school and university education (see Table 1). A delay in diagnosis exceeding 7 years was reported by 39% of the participants (see Table 1). Approximately 17% of women reported having autoimmune diseases, including Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disorder, and others (data not shown). Coeliac disease was reported by 1.2% of the participants.

3.1. Changes in eating habits after the diagnosis of endometriosis

After the diagnosis of endometriosis, the eating habits changed in 66.4% of the responders (Figure 1).

Some women reported following various dietary patterns after endometriosis diagnosis to improve their health and reduce symptoms (Figure 2). Most of the responders has chosen a gluten-free diet (15%), anti-inflammatory diet (8%), Mediterranean diet (7.1%), ketogenic diet (4%), and other dietary patterns (Figure 2).

Other responders reported a change in eating habits by increasing, or excluding the intake of specific foods or macronutrients or certain cooking methods (Figure 3). Most of the participants excluded dairy products (18.4%), foods with soy (6.7%), and foods with high content of saturated fats (8%) (Figure 3). Other participants instead reported an increase in consumption of vegetables and fruit (10%), cereals and legumes (6.6%), and fish (4.5%).

3.2. Impact of endometriosis symptoms on everyday life

Family and friends tend to minimize endometriosis symptoms for 46% ($n = 1872$) of responders (data not shown). In addition, the everyday Life worsened for 92% ($n = 3,767$) of the women interviewed due to the disease. In particular, women with endometriosis reported

TABLE 1 Demographic and clinical characteristics of women with endometriosis (n = 4,078).

Characteristics		n (%)
Age groups	Aged 18–25	332 (8.1)
	Aged 26–35	1,407 (34.5)
	Aged 36–45	1822 (44.7)
	Aged 45 and above	517 (12.7)
Educational level	High school graduate	2040 (50)
	University degree	2038 (50)
ARSM endometriosis stages	Minimal (stage I)	962 (23.6)
	Mild (stage II)	773 (19.0)
	Moderate (stage III)	831 (20.4)
	Severe (stage IV)	1,512 (37.1)
Years of symptoms (years)	< 1	55 (1.3)
	1–3	555 (13.6)
	4–10	1,357 (33.3)
	11–15	700 (17.2)
	16–20	565 (13.9)
	> 20	731 (17.9)
	Did not answer	115 (2.8)
Delay in diagnosis (years)	< 1	1,016 (24.9)
	1–3	877 (21.5)
	4–6	600 (14.7)
	> 7	1,585 (38.9)
Hormonal treatments	Progesterone-like medications	1,333 (32.7)
	Combined oestrogen/progestagen medications	1,331 (32.6)
	Menopause-inducing medications	80 (2.0)
Pain relief medication	Pain killers	237 (5.8)
	NSAIDs	217 (5.3)
	Opioids	23 (0.6)
	Nutritional supplements*	213 (5.2)
	PEA supplements	44 (1.1)

ARSM, American society for reproductive medicine; NSAIDs, non-steroidal anti-inflammatory drugs; PEA, palmitoylethanolamide. *Nutritional supplements (quercetin, curcumin, parthenium, nicotinamide, 5-methyltetrahydrofolate, and omega 3/6).

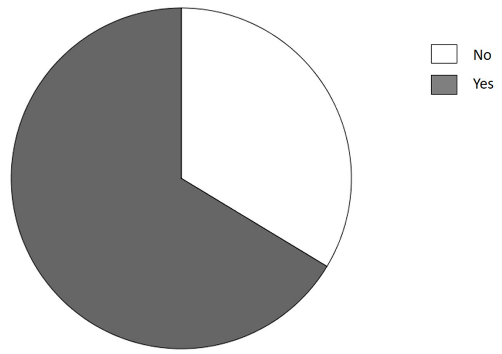

FIGURE 1
Changes in eating habits after diagnosis of endometriosis.

difficulty in managing pain and difficulty planning or carrying out daily activities (22%), reduction of working capacity and (12%), and reduction of social interactions (10%) (Figure 4). Furthermore, chronic fatigue and depression-anxiety were reported by 22% and 13% of women with endometriosis, respectively (Figure 4).

3.3. Predictors of changes in eating habits and the worsening of the everyday life

In women with endometriosis, Pearson's correlation showed that changes in eating habits correlated with endometriosis stages ($r = 0.10$, $p < 0.001$), years of symptoms ($r = 0.37$, $p = 0.018$), and changes everyday Life ($r = 0.14$, $p < 0.001$) (data not shown). Moreover, in this population, the worsening of the everyday Life was correlated with educational level ($r = -0.04$, $p = 0.002$), endometriosis stages ($r = 0.15$, $p < 0.001$), years of symptoms ($r = 0.13$, $p < 0.001$), and changes in eating habits ($r = 0.14$, $p < 0.001$) (data not shown).

In the logistic regression analysis, changes in eating habits were found to be associated with endometriosis stages and a decline in everyday life (Table 2). Moreover, changes in everyday life were significantly associated with all variables, including educational level, endometriosis stages, years of symptoms, and changes in eating habits (Table 2).

Thus, we analysed changes in eating habits based on the severity of the disease (Table 3). We found that women with stage IV of endometriosis they had greater adherence to the anti-inflammatory diet ($p < 0.001$) than those in stage I (Table 3). Moreover, in the severe stage, there is a higher prevalence of women who have eliminated the consumption of dairy products and/or lactose ($p < 0.001$), red and/or processed meat ($p = 0.003$), foods with high intake of saturated fats ($p < 0.001$), with simple sugar ($p = 0.03$), and fried foods ($p = 0.03$) than those with minimal stage of endometriosis (stage I) (Table 3). Furthermore, women with stage III and IV reported increased consumption of vegetables and fruit ($p = 0.04$), cereals and legumes ($p = 0.03$), and fish ($p = 0.02$) compared to women with stage II and I of endometriosis (Table 3).

We also found a higher prevalence of worsening of everyday Life in women with stage III and IV compared to women with stage III and II of endometriosis (Figure 5).

Finally, Table 4 shows the food choices of women with and without worsening of the quality of life due to endometriosis. A higher prevalence of women with worsening of the quality of life chose a gluten-free diet (15%), an anti-inflammatory diet (8%) and a ketogenic diet (4%) than women without worsening of the quality of life. In addition, a higher prevalence of women with worsening of the quality of life eliminated the consumption of dairy products and/or lactose (19%), red and/or processed meat (5%), foods with high intake of saturated fats (8%), and fried foods (4%) than those without worsening of the quality of life (Table 4). Furthermore, women with worsening of the quality of life reported increased consumption of vegetables and fruit (10%), cereals and legumes (7%), and fish (5%) compared to women worsening of the quality of life due to endometriosis (Table 4).

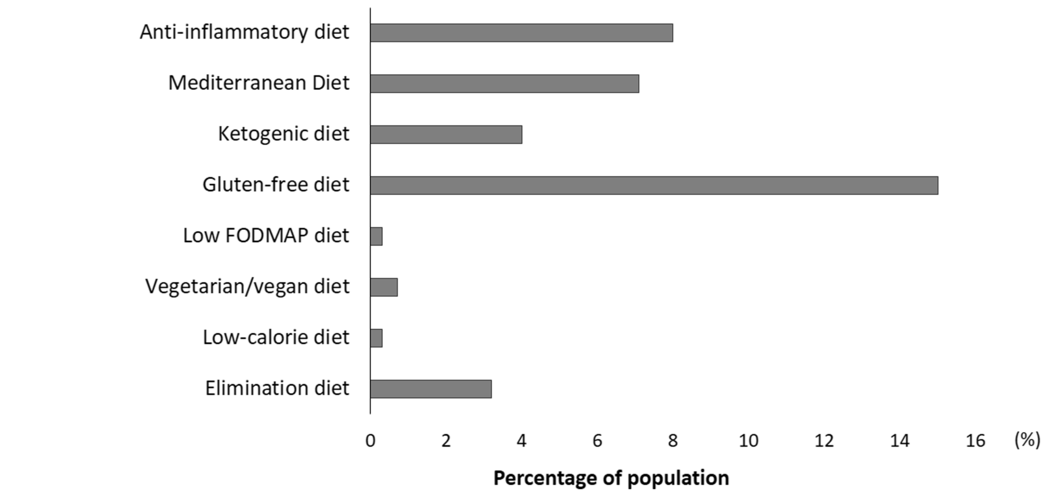

FIGURE 2
Dietary patterns followed by women with endometriosis.

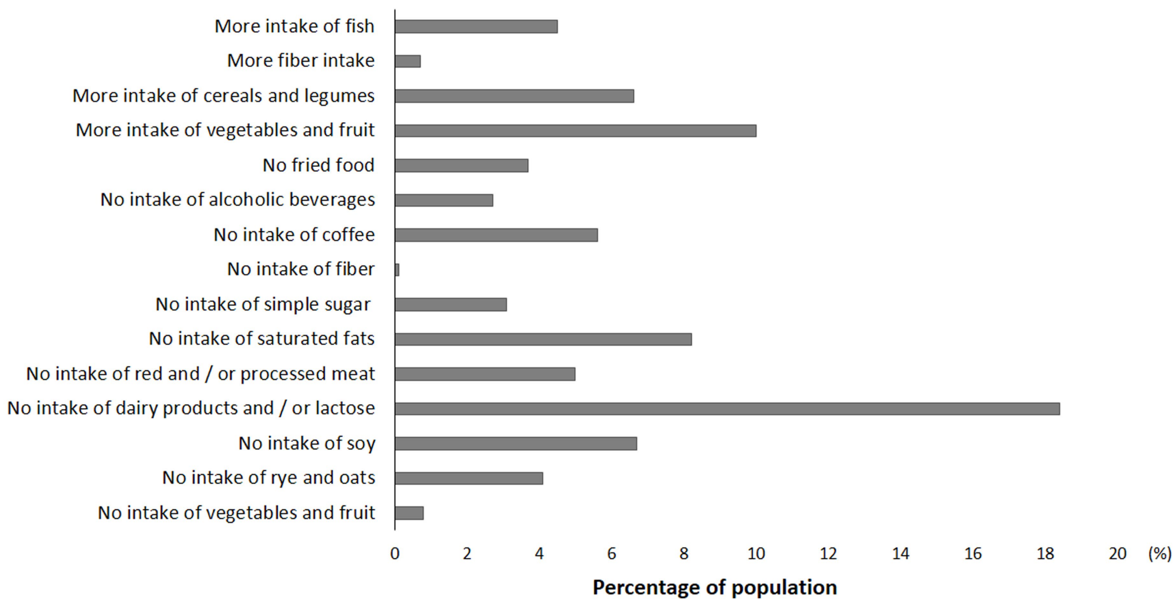

FIGURE 3
Food choices of women with endometriosis.

4. Discussion

The aim of this study was to investigate the potential effects of the disease on dietary habits and daily activities in women following an endometriosis diagnosis. The large cohort of 4,078 participants provides a robust basis for data analysis. The majority of women falling between the ages of 36 and 45 may reflect the typical age of diagnosis or when women actively seek medical assistance (4, 5). The prevalence of 37% of women with severe stage (stage IV) is a significant representation of those facing the most challenging issues associated with endometriosis (4, 5, 10–12). The delay in diagnosis exceeding 7 years for 39% of the participants is concerning and highlights the importance of timely and accurate diagnosis. Several studies have reported similar diagnostic delays to those observed in our population, with an average time from the onset of initial symptoms to a definitive diagnosis ranging from 4.4 years in the

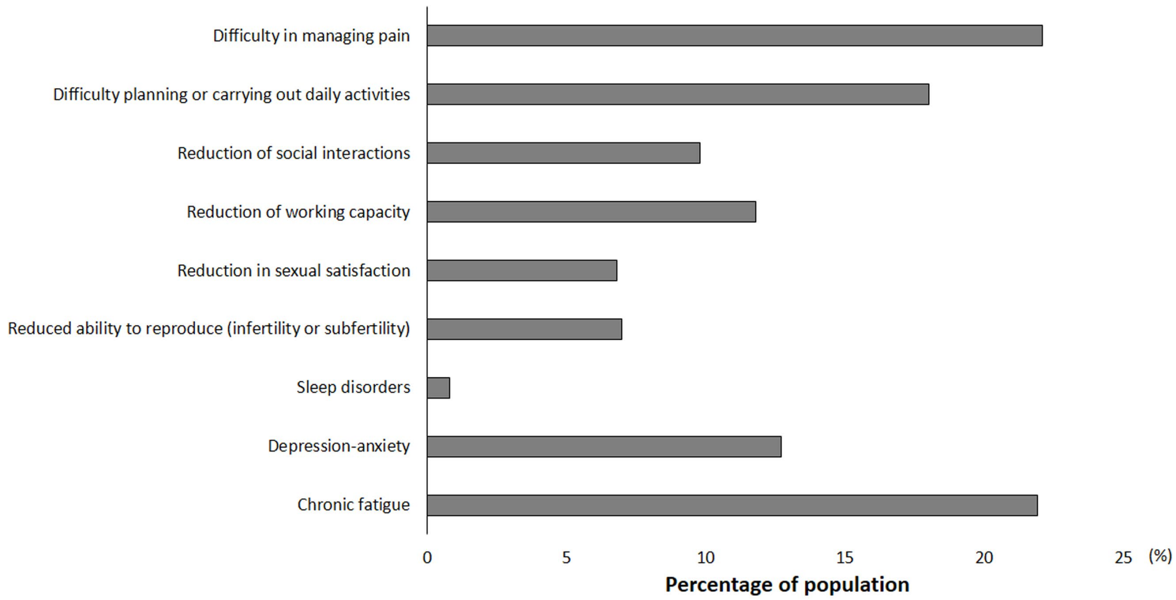

FIGURE 4
Impact of Endometriosis on everyday Life.

TABLE 2 Logistic regression analysis – demographic and clinical factors associated with the worsening of everyday life and changes in eating habits.

Dependent variable worsening of the quality of life	*B*	SE	*p*	OR	95% CI	
					LL	UL
Educational level	−0.32	0.12	0.009	0.72	0.57	0.92
Endometriosis stages	0.37	0.05	<0.001	1.45	1.30	1.61
Years of symptoms	0.24	0.04	<0.001	1.27	1.17	1.38
Changes in eating habits	0.96	0.12	<0.001	2.61	2.05	3.32

Dependent variable changes in eating habits*	*B*	SE	*p*	OR	95% CI	
					LL	UL
Endometriosis stages	0.14	0.02	<0.001	1.15	1.09	1.22
Worsening of the quality of life	0.96	0.12	<0.001	2.62	2.06	3.33

*Excluded variables: years of symptoms. *B*, unstandardized coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; LL, lower limit; UL, upper limit.

United States to 10.4 years in Germany (41, 42). The primary reasons for such delays include intermittent contraceptive use, self-treatment of pain with over-the-counter analgesics, and misdiagnosis.

The fact that 66.4% of women reported making changes in dietary habits after an endometriosis diagnosis suggests a significant impact of the disease on women's perception of nutrition and health (14). The reported dietary choices, such as gluten-free, anti-inflammatory, Mediterranean, and ketogenic diets, indicate that women are exploring diverse dietary approaches to address symptoms and improve their quality of life. The analysis of dietary choices based on the disease stage revealed some significant differences. Women with severe endometriosis (stage IV) appear to more frequently follow an anti-inflammatory diet while eliminating foods high in saturated fats and simple sugars. These findings may indicate an attempt to manage inflammation associated with severe endometriosis. Simultaneously, greater adherence to an anti-inflammatory diet might reflect a response to symptom severity and the need to address inflammatory processes. On the other hand, differences in dietary choices could also be influenced by women's increased awareness of the effect of nutrition on health. The findings of our study are in line with current understanding in the field.

A retrospective Italian study examined the effects of a gluten-free diet on endometriosis-associated symptoms (23). At the 12-month follow-up, 52% of patients re-ported statistically significant improvements in pain compared to baseline (23). Interestingly, approximately 30% of patients did not adhere to the gluten-free diet (23). A gluten-free diet may be beneficial for patients experiencing gastrointestinal-related abdominal pain, constipation, bloating, and suspected visceral hypersensitivity. However, adherence to such diets may be compromised due to financial constraints and inherent difficulties. Our study revealed that the anti-inflammatory diet was more commonly followed by women with severe-stage disease. Although popular, there is currently insufficient scientific evidence to support the role of this diet in managing endometriosis.

TABLE 3 Dietary models and foods choices among women with endometriosis according to stages of disease.

Variables	Stage I (n = 962)	Stage II (n = 773)	Stage III (n = 831)	Stage IV (n = 1,512)	p-value
Anti-inflammatory diet	5.3	7.6	7.7	9.7	<0.001
Mediterranean Diet	7.8	7.6	6.9	6.6	0.21
Ketogenic diet	3.3	3.8	4.0	4.6	0.11
Gluten-free diet	10.8	15.3	17.1	15.0	0.007
Low FODMAP diet	0.5	0.4	0.2	0.2	0.14
Vegetarian/vegan diet	0.6	0.8	0.8	0.7	0.79
Low-calorie diet	0.3	0.1	0.4	0.4	0.51
Elimination diet	2.0	3.8	3.6	3.4	0.10
No intake of vegetables and fruit	0.3	0.6	1.2	1.0	0.046
No intake of rye and oats	3.1	4.0	4.3	4.7	0.06
No intake of soy	5.7	6.5	7.6	7.1	0.15
No intake of dairy products and/or lactose	13.0	18.2	20.5	20.7	<0.001
No intake of red and/or processed meat	3.4	4.8	4.7	6.2	0.003
No intake of saturated fats	5.7	7.9	7.9	10.1	<0.001
No intake of simple sugar	2.5	2.5	3.1	3.8	0.035
No intake of fiber	0.2	0.1	0.0	0.2	0.93
No intake of coffee	4.3	6.0	5.9	6.1	0.08
No intake of alcoholic beverages	2.6	3.0	2.5	2.6	0.91
No fried foods	3.0	2.8	3.7	4.4	0.034
More intake of vegetables and fruit	8.6	10.1	9.3	11.3	0.045
More intake of cereals and legumes	5.6	5.8	6.7	7.6	0.032
More fiber intake	0.4	0.6	0.6	0.9	0.20
More intake of fish	3.5	3.6	5.4	5.1	0.029

Data are reported as a percentage (%).

A single-arm study conducted in Australia examined the effects of the Mediterranean diet on endometriosis-associated pain (43). Patients adhered to a specific diet that included fruits, fresh vegetables, fatty fish, white meat, soy products, whole grain products, magnesium-rich foods, and extra virgin olive oil. Furthermore, the Mediterranean diet includes the consumption of many spices. Significant pain relief, including improvements in general pain, dysmenorrhea, dyschezia, dyspareunia, and overall condition, was observed (43). The Mediterranean diet may alleviate endometriosis-related pain through synergistic mechanisms. Extra virgin olive oil and fish have been shown to exert anti-inflammatory effects (44, 45). Oleocanthal, found in extra-virgin olive oil, exhibits a molecular structure similar to that of ibuprofen and exerts a cyclooxygenase inhibition effect via the same mechanism (46). Furthermore, the antioxidant effects, abundant fiber content, and magnesium present in the Mediterranean diet may have positive effects on pelvic pain and inflammation (47, 48). Moreover, some spices such as onions, rosemary, chili peppers, ginger, turmeric, garlic, are commonly incorporated into the Mediterranean Diet and antinflammatory pattern. Recent preclinical and clinical studies have substantiated the effectiveness of these spices and their bioactive compounds in preventing and mitigating various chronic diseases, including arthritis, asthma, cancer, neurodegenerative disorders, and cardiovascular conditions (49, 50). These spices hold the potential to alleviate the inflammatory effects associated with endometriosis.

Our findings align with previous studies in which female participants reported that avoiding or limiting a wide range of nutrients, including dairy, gluten, soy, sugar, and coffee, helped alleviate their symptoms, while adding fruits or vegetables proved beneficial (51). Several epidemiological studies have associated a high consumption of fruits (52), omega-3 fatty acids (15), and dairy during adolescence (53) with a reduced risk of developing endometriosis. Conversely, high consumption of trans-unsaturated fats (15), red meat (16), and alcohol (54) have been associated with an increased risk, although it remains unclear whether these factors

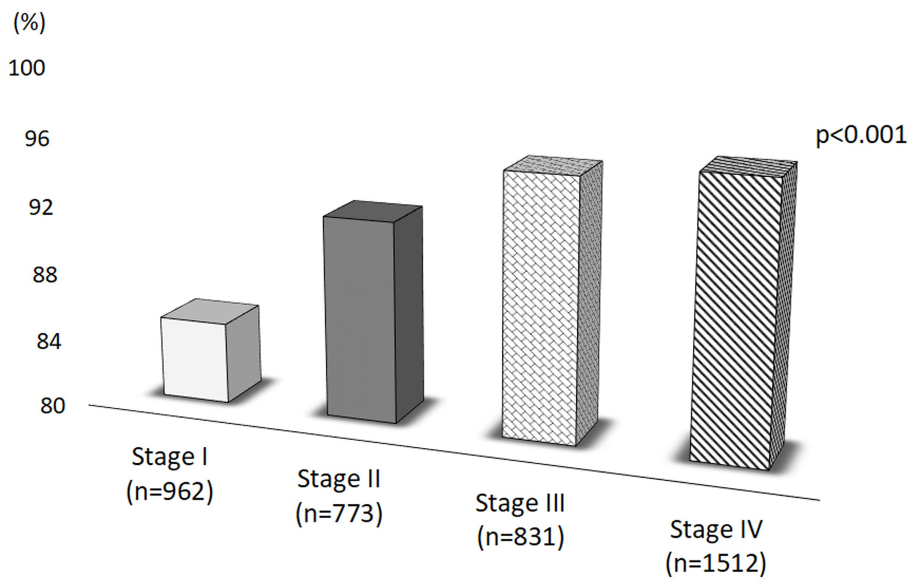

FIGURE 5
Worsening of everyday Life according to stages of disease.

also influence the symptoms of diagnosed endometriosis. Some participants in our study also adopted a ketogenic diet, which is high in fats, moderate in proteins, and very low in carbohydrates. This diet promotes the production of endogenous ketones as an alternative metabolic fuel source (55). Preclinical studies have demonstrated positive effects of the ketogenic diet on oxidative stress markers and inflammation, which are relevant to endometriosis (56–59). However, there is currently insufficient scientific evidence to support the use of this dietary protocol for endometriosis. A prospective controlled study demonstrated the anti-inflammatory effects of a nutraceutical containing vitamin B3, omega-3/6, quercetin, calcium salt, 5-methyltetrahydrofolate, parthenium, and turmeric in women with endometriosis (19). This study revealed significant reductions in pain symptoms and serum levels of CA-125, PGE2, and 17β-estradiol in the group treated with the nutraceutical (19). A small proportion (5%) of women in our questionnaire reported using this nutraceutical for pain relief. However, due to the unclear long-term safety of dietary antioxidant supplementation beyond 6 months, prolonged use cannot be recommended (60, 61).

Importantly, the correlation between dietary habit changes, endometriosis stage, and symptom duration suggests that some dietary adjustments may be adaptive responses to symptom severity or disease progression. The negative effect of the disease on women's everyday life is evident in the study's results and is consistent with findings from other scientific studies (7, 8, 10, 11, 15). Family and friends' minimizing attitude toward symptoms can contribute to increased emotional burden for women facing misunderstanding. The worsening of quality of life, as indicated by difficulties in managing pain and planning daily activities, highlights a range of physical and psychological challenges that women must confront, which aligns with observations in other studies (7, 8, 10, 11, 15). The prevalence of 22% for chronic fatigue and 13% for depression-anxiety underscores the importance of a comprehensive and integrated approach to endometriosis management.

The results from our study underscore the necessity of providing specific nutritional guidance to women with endometriosis. Currently, there are no established nutritional guidelines for this clinical condition, highlighting the need for clinical trials to identify the optimal nutritional strategies for alleviating endometriosis symptoms.

Our study possesses several strengths, including the use of an online survey, which facilitated the rapid recruitment of a sizeable sample of women. The participants exhibited diverse age ranges, educational backgrounds, and endometriosis stages according to the ASRM classification. However, our study also has limitations. Firstly, it is a cross-sectional study. Secondly, we relied on self-reported data and did not employ a food frequency questionnaire or food diary to assess macro- and micro-nutrient deficiencies. or explore the impact of these conditions using validated questionnaires (38). In addition, we categorized the age of the patients; however, we did not establish a maximum age cutoff within the scope of this study. Furthermore, we did not investigate anthropometric parameters or the effects of endometriosis diagnosis on the risk of malnutrition. Additionally, there may be a selection bias as the survey participants were members of the Italian endometriosis association, potentially indicating a higher level of health awareness compared to the general population. Nonetheless, despite these limitations, our study generates hypotheses for future investigations. Currently, there is limited research available on the effects of dietary modifications on endometriosis-associated symptoms, with only a small number of studies (19, 27, 41–43) addressing this topic. However, several dietary approaches have been proposed as potential strategies to mitigate the progression of endometriosis and improve clinical symptoms. Nonetheless, further

TABLE 4 Dietary models and Foods choices of women with endometriosis according to worsening of everyday Life.

Variables	Women without a worsening of the everyday life (*n* = 311)	Women with a worsening of the everyday life (*n* = 3,642)	*p*-value
Anti-inflammatory diet	4.8	8.1	0.037
Mediterranean Diet	4.5	7.4	0.06
Ketogenic diet	1.9	4.2	0.05
Gluten-free diet	9.0	14.9	0.003
Low FODMAP diet	0.6	0.3	0.26
Vegetarian/vegan diet	0.3	0.8	0.72
Low-calorie diet	0.3	0.3	1
Elimination diet	1.3	3.3	0.06
No intake of vegetables and fruit	0.3	0.8	0.51
No intake of rye and oats	1.3	4.4	0.007
No intake of soy	3.2	7.0	0.007
No intake of dairy products and/or lactose	8.4	19.2	<0.001
No intake of red and/or processed meat	1.9	5.2	0.009
No intake of saturated fats	5.1	8.4	0.041
No intake of simple sugar	1.3	3.3	0.06
No intake of fiber	0.0	0.2	1
No intake of coffee	2.3	5.9	0.005
No intake of alcoholic beverages	0.6	2.8	0.016
No fried foods	1.3	3.8	0.017
More intake of vegetables and fruit	5.5	10.4	0.004
More intake of cereals and legumes	3.5	6.9	0.023
More fiber intake	0.0	0.7	0.26
More intake of fish	1.9	4.7	0.022

Data are reported as a percentage (%).

studies are needed to investigate the efficacy of these dietary interventions.

5. Conclusion

In conclusion, our study provides evidence that dietary changes are commonly employed by women with endometriosis as a self-management tool. These women are utilizing various dietary modifications to alleviate their endometriosis symptoms. However, it remains unknown which specific dietary interventions are effective for women with different types of endometriosis or specific individual characteristics. The findings of our study highlight the importance of referring patients to nutritional counselling to prevent nutritional deficiencies. It is crucial to educate women about the objectives and rationale of the dietary intervention and to provide guidance on which nutrients to include or avoid. Future clinical trials investigating the efficacy of specific diets for women with endometriosis will help tailor individualized dietary approaches for optimal patient outcomes.

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 Local Ethics Committee in the Calabria Region Central Area. 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

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Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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.2023.1273976/full#supplementary-material

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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 27 November 2023
DOI 10.3389/fnut.2023.1273509

OPEN ACCESS

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RECEIVED 08 August 2023
ACCEPTED 13 November 2023
PUBLISHED 27 November 2023

CITATION
Hu P, Zhang S, Li H, Yan X, Zhang X and Zhang Q (2023) Association between dietary trace minerals and pelvic inflammatory disease: data from the 2015–2018 National Health and Nutrition Examination Surveys.
Front. Nutr. 10:1273509.
doi: 10.3389/fnut.2023.1273509

Association between dietary trace minerals and pelvic inflammatory disease: data from the 2015–2018 National Health and Nutrition Examination Surveys

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Objective: Pelvic inflammatory disease (PID) is a prevalent gynecological disorder. Dietary trace minerals play an important role in combating many chronic diseases including PID. However, it is unknown whether dietary trace minerals and PID are related. This study aimed to examine the relationship between dietary trace minerals (copper, iron, selenium, and zinc) and PID.

Methods: Data of women participants from the National Health and Nutrition Examination Survey (NHANES) 2015–2018 were enrolled in this cross-sectional investigation. Univariate and multivariate linear regression analyses of the relationship between dietary trace minerals and PID were performed, and restricted cubic spline (RCS) analyses were applied to visualize those relationships.

Results: In total, 2,694 women between the ages of 20 and 59 years participated in the two NHANES cycles. In the univariate analyses, a significant negative relationship was identified between PID and dietary copper intake [odds ratio (OR) = 0.40, 95% confidence interval (CI): 0.24–0.67, $p < 0.01$] but not with iron (OR = 0.96, 95% CI: 0.90–1.03, $p = 0.25$), selenium (OR = 1.0, 95% CI: 0.99–1.0, $p = 0.23$), and zinc (OR = 0.94, 95% CI: 0.86–1.03, $p = 0.17$) intake. Following the adjustment for age and race (model 1), a robust correlation was found between dietary copper intake and PID (OR = 0.23, 95% CI = 0.09–0.61, $p < 0.01$), as indicated by the fully adjusted model 2 (OR = 0.29, 95% CI = 0.09–0.90, $p = 0.03$). Simultaneously, a significant trend was found between copper intake and PID across the quintile subgroups (p for trends <0.05), suggesting a robust relationship. Furthermore, the RCS analysis demonstrated a linear correlation between PID and dietary copper intake (overall $p < 0.01$, non-linear $p = 0.09$).

Conclusion: Decreased dietary copper intakes are linked to PID. However, additional research is needed to fully investigate this relationship due to the constraints of the study design.

KEYWORDS

pelvic inflammatory disease, dietary trace minerals, dietary copper intake, National Health and Nutrition Examination Survey, cross-sectional study

1 Introduction

Pelvic inflammatory disease (PID) is a polymicrobial infection that generally occurs in the women's genital tract and often leads to the impairment of the endometrium, oviduct, and ovaries (1). The clinical manifestations of PID include long-term infertility, extrauterine pregnancies, and chronic pelvic pain (2). The cause of PID is associated with many factors, including race, age, and smoking status (3). Young people and African or Caucasian people are especially prone to PID (4). A study has estimated that 4 to 12% of women of reproductive age have PID worldwide (5). However, few studies on the epidemiological trends of PID among different areas of the world have been conducted due to challenges with the invasiveness and sensitivity of screening methods (6). In the United States, approximately 0.5 to 1 million cases of PID develop annually, and the average cost is up to $3,025 per episode for PID therapy (7, 8). At the same time, the majority of PID patients are prone to experience disease recurrence, resulting in additional burdens on society and healthcare systems (9). Hence, it is crucial to examine the risk factors associated with PID to enable early intervention.

Diets enriched with antioxidants (fruit and vegetables), vitamins (vitamins B6, A, C, E), and macronutrients (n-3 fatty acids) improve immune system functioning and eliminate free radical damage, which can help control chronic pelvic pain, including PID (10). Although trace minerals account for only a small part of the diet, they are essential to ensure normal function and health, and the excessive or inadequate consumption of trace elements is detrimental to the inherent metabolic balance of the body (11). Trace elements, including copper, iron, selenium, and zinc, are vital for maintaining metabolic balance, especially in cell function, DNA repair, and antioxidant defense (12). Previous studies have indicated that dietary trace minerals have powerful regulatory effects on the oxidative activation of protein kinase C, prostaglandin synthesis, and Ca^{2+} receptors which, in turn, increase chronic pain intensity (13). A study has revealed that copper is closely related to inflammatory responses in many chronic diseases, such as metabolic disorders and cancer (14). Additional studies have illustrated that the intake of dietary copper and selenium is linked to many diseases including gynecological tumors and metabolic syndrome (15–17). Meanwhile, dietary intake of iron and zinc was found to be negatively correlated with fibromyalgia, characterized by widespread muscle soreness, and other chronic symptoms such as fatigue, anxiety, and depression (18). However, the relationship between dietary trace elements and PID is not fully understood.

To this end, using data from the NHANES, the current study aimed to determine if dietary trace elements and PID were correlated after controlling for covariates.

2 Methods

2.1 Study design and participants

Based on the large sample size of the NHANES, data from 2015 to 2018 (two cycles: 2015–2016 and 2017–2018) before the coronavirus disease in 2019 were selected for analysis. Since PID occurs in women's genital tracts, only females were recruited. All women participants were initially interviewed at home using the sample person and family demographics questionnaires, followed by either another interview or health examination at a mobile examination center (MEC). During these MEC examinations, participants were screened for direct anthropometrics, height, weight, blood draws, and various other health-related tests (19). Before the study, all subjects provided written informed consent, and no external ethical approval was needed since the research was approved by the National Center for Health Statistics Ethics Review Board (https://www.cdc.gov/nchs/nhanes/irba98.htm, continuation of protocol #2011–17, protocol #2018–01). The analysis only included women participants whose data were complete. We excluded 15,749 participants with missing PID, 167 with missing dietary trace minerals, and 615 missing covariates from the 19,225 eligible individuals. This research eventually included 2,694 individuals aged 20–59 years from the entire US population. The original NHANES study was a random sampling trial, and our research adopted a cross-sectional method based on the NHANES database. The women's selection scheme is shown in Figure 1. At the same time, our study was weighted to allow the representation of the entire population in the US.

2.2 Measurement of PID

Based on a self-reported questionnaire of reproductive health, the diagnosis of PID was ascertained at the MEC by trained interviewers who used the built-in Computer-Assisted Personal Interview (CAPI) system, which enquired, 'Have you ever been treated for an infection in the fallopian tubes, uterus, or ovaries, also called a pelvic infection, pelvic inflammatory disease, or PID?'. A "PID group" was formed from participants who replied "yes" whereas a "without PID group" was formed from those who answered "no" (20).

2.3 Measurement of dietary trace minerals

The dietary intake data was acquired at the MEC through standard dietary interviews, called What We Eat in America (WWEIA), and types and amounts of food and beverages consumed during the 24-h period immediately prior to the interview were obtained. WWEIA interviews were randomly allocated to the participants on the day of the interview. Before they could start working independently in the MEC, all dietary interviewers were asked to complete a standardized training course and engage in practice interviews under supervision. Finally, the daily total intakes of trace minerals (copper, iron, selenium, and zinc) from foods and beverages were then collated to obtain daily trace intake data. By using the recommended dietary allowance (RDA) in women (0.9 mg/day for copper, 18 mg/day for iron, 55 mcg/day for selenium, and 11 mg/day for zinc) (21), values of dietary trace minerals over 10-fold of the RDA were excluded as outliers.

2.4 Assessment of covariates

Based on related studies (20, 22), regular period, democratic data (race, education level, age, marital status, and poverty), BMI, smoking status, diabetes mellitus (DM), and hypertension were treated as covariates. Regular period data were assessed through the reproductive health questionnaire that asked, 'Had regular periods in past

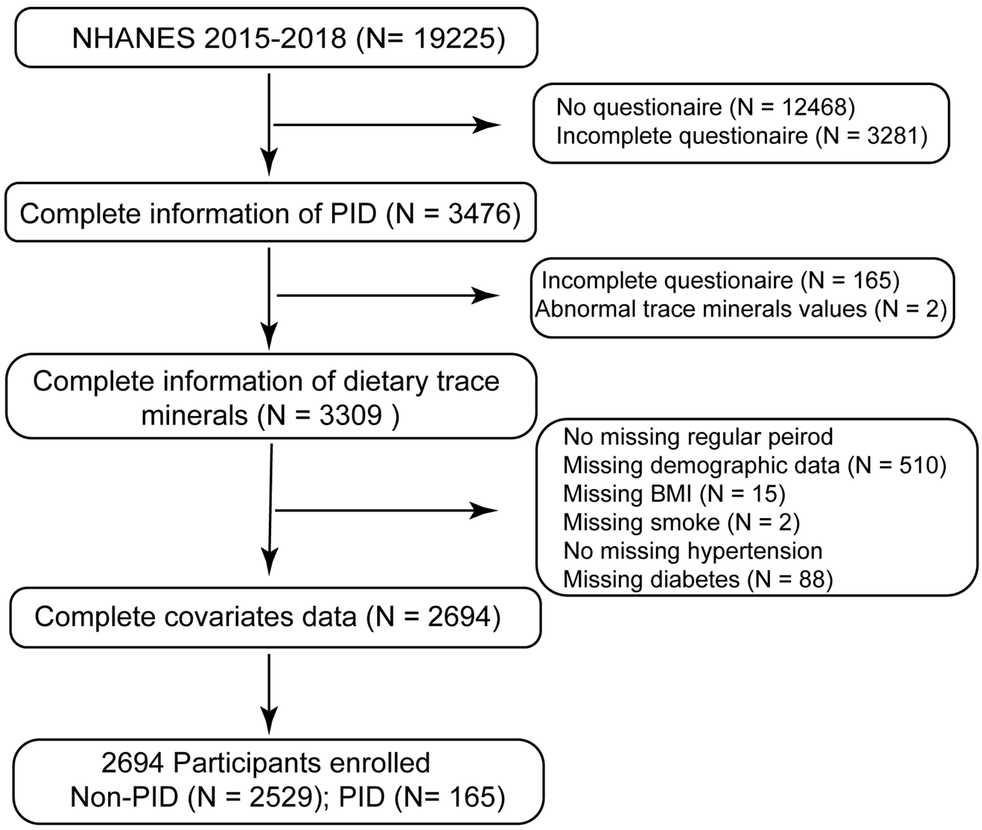

FIGURE 1
Screening procedure flowchart (NHANES 2015–2018).

12 months (eligible for participants aged 12 years older)?', and women who were pregnant or who had bleeding as result of medical issues, hormonal treatments, or surgical procedures were excluded. The CAPI method was used to collect information from in-depth interviews with participants in their homes conducted by trained interviewers. Participants in the survey answered these questions using hand cards depicting response options or information. The interviewer directed the respondent to the appropriate hand card during the interview, and the complete data of democratic covariates was obtained. Educational levels were classified as lower than high school, high school, and college, whereas marital status was classified as married, spinsterhood, divorced/separated, or widowed. Subsequently, the poverty income ratio (PIR) was divided into three groups: low (≤ 1), medium (1–3), and high (> 3) (22). The data of weight and height were obtained electronically from the measuring devices to minimize potential data entry errors, and the individual's body mass index (BMI) was obtained using the formula BMI = weight (kg)/height (m^2). After that, BMI was categorized into: obese (≥ 30.0 kg/m^2), overweight (25–29.9 kg/m^2), normal weight (18.5–24.9 kg/m^2), and underweight (< 18.5 kg/m^2) (23). The CAPI system was used to conduct in-home interviews by trained interviewers who administered a "smoking-cigarette usage" questionnaire to determine whether respondents smoked and then assigned to three classes of smoking status: never (no more than 100 cigarettes in whole life), former (over 100 cigarettes in whole life and quit smoking right now), and now (over 100 cigarettes in whole life and smoke some days or every day). After resting for at least 5 minutes, the blood pressure of participants was measured three consecutive times. Repeated attempts were made to measure blood pressure if the first one was incomplete or interrupted. All systolic and diastolic blood pressure measurements were performed in the MEC, and hypertension was diagnosed based on the threshold of systolic/diastolic blood pressure at 140/90 mmHg. Blood specimens were processed, stored, and shipped to a specific site for testing the glucose. Women's DM condition was classified as no DM, pre-DM (impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or combined IFG and IGT), and DM (24).

2.5 Statistical analysis

R (v4.2.1) and R Studio (v2022.07.1) were employed to analyze statistical data. Dietary weights were adopted to ensure the rigor and accuracy of the study under the least common denominator strategy of sampling weight guidance of the NHANES. Categorical variables are presented as proportions (n) and percentages (%), whereas continuous variables are presented as mean and standard error (SE). Categorical and continuous characteristics were analyzed using the chi-squared tests and *t*-tests, respectively. To verify the correlation between dietary trace minerals and PID, dietary trace minerals that were shown to be statistically significant in univariate logistic regression analysis were then subjected to multivariate logistic regression analyses. Adjustments for age and race were made to Model 1, whereas adjustments for all other covariates were made to Model 2 (regular period, demographics, BMI, smoking status, hypertension, and DM). Subsequently, restricted cubic splines (RCS) were adopted to assess the linear and non-linear associations, and these relationships were tested using quintile logistic regression analyses. Subgroup analyses and interaction tests were conducted to evaluate potential interactions, and RCS was administered to determine how dietary trace minerals correlated with PID after stratification of meaningful interaction terms. The criterion for statistical significance was established at a two-tailed *p*-value <0.05.

3 Results

3.1 Description of participants

According to the study's eligibility criteria, 2,694 female participants were enrolled, and the average age of the participants was 40 ± 0.4 years. Among these participants, 32.67% were non-Hispanic white, 23.01% were non-Hispanic black, 16.82% were Mexican American, and 27.51% were from other races. There were 2,529 (93.88%) participants without PID and 165 (6.12%) with PID. A detailed description of the women participants is provided in Table 1. Of those individuals with PID, the weighted mean concentration of dietary trace minerals was 0.95 mg/day (copper), 10.96 mg/day (iron), 89.9 mg/day (selenium), and 8.30 mg/day (zinc), respectively. There were 56 (54.79%) participants who were Non-Hispanic White, 96 (57.39%) had a college education, and 131 (86.8%) participants without diabetes. Participants with PID were more likely to have the following characteristics relative to those without the disorder: a lower copper intake ($p < 0.01$), irregular period ($p < 0.01$), older age ($p < 0.01$), non-married status ($p < 0.01$), better economic situation ($p < 0.01$), obesity or overweight ($p < 0.01$), history of no or current smoking status ($p < 0.01$), and hypertension ($p < 0.01$).

3.2 PID correlation with dietary trace minerals

The correlation between dietary copper intake and PID was substantially negative, as indicated in Table 2 (OR = 0.40, 95% CI: 0.24–0.67), whereas the same trend was not significant in iron (OR = 0.96, 95% CI: 0.90–1.03), selenium (OR = 1.0, 95% CI: 0.99–1.0), and zinc (OR = 0.94, 95% CI: 0.86–1.03). The correlation between dietary copper intake and PID was negative in a univariate analysis. Hence, multivariate logistic regression was used to delve deeper into the correlation between copper and PID. Dietary copper intake was shown to be significantly correlated with PID after adjusting for age and race (model 1) (OR = 0.41, 95% CI = 0.23–0.70). This association remained consistent in model 2 (OR = 0.51, 95% CI = 0.28–0.90) after adjusting for all covariates.

3.3 Relationship between PID and various quintiles of dietary copper intake

When divided into quintiles (Table 3), the quintile of copper intake (Q5 > 1.49 mg/day) served a protective role in PID, regardless of the unadjusted or adjusted models (crude model: OR = 0.23, 95% CI = 0.09–0.58; model 1: OR = 0.23, 95% CI = 0.09–0.61; model 2: OR = 0.29, 95% CI = 0.09–0.90). Simultaneously, a significant trend was observed between copper intake and PID across the quintile subgroups (*p* for trend <0.05), suggesting the robustness of this relationship. To visualize the correlation between dietary copper intake and PID, an RCS plot was generated (Figure 2), demonstrating an approximately linear correlation between the two variables (overall *p*-value <0.01, non-linear *p*-value = 0.09).

3.4 Subgroup analysis

To reduce heterogeneity, subgroup analyses were conducted, and the interaction between covariates and dietary copper intake was further examined (Figure 3). Here, nearly all ORs in the subgroup were lower than one except for the women participants in the underweight group, indicating a consistent negative relationship between copper intake and PID. Copper intake was positively related to PID in the underweight subgroup (OR = 1.61, 95% CI = 0.81–3.19), although without a statistically significant difference ($p = 0.15$). Interaction effects were also shown to be statistically significant for age (*p* for interaction = 0.01) and BMI (*p* for interaction = 0.01). To investigate the influence of meaningful interactions, RCS was conducted for better visualization in model 2 (all covariates were adjusted except for the grouping variable) (Figures 4, 5). Age-stratified analyses revealed a parabolic association between PID and copper intake (overall *p* value = 0.137, non-linear *p* value <0.05). In the age subgroup of 20–40 years old, the correlation between dietary copper intake and PID increased before the 1.19 mg/day point and then decreased gradually. In contrast, in the 41–59-year-old subgroup, a linear pattern of correlation was observed between dietary copper intake and PID (overall *p*-value <0.01, non-linear *p*-value = 0.13). After stratifying by BMI, copper intake was shown to significantly correlate with PID in the overweight subgroup (overall *p*-value = 0.01, non-linear *p*-value <0.01). The association between dietary copper intake and PID remained relatively stable until around 0.85 mg/day and then decreased rapidly. However, no significant *p*-values were observed in the underweight (overall *p*-value = 1.0, non-linear *p*-value = 0.99), normal weight (overall *p*-value = 0.17, non-linear *p*-value = 0.81), or obese subgroups (overall *p*-value*p* = 0.92, non-linear *p*-value = 0.80).

4 Discussion

PID is a chronic and recurrent disease that significantly impacts the well-being of patients, causing considerable suffering. Until now, few studies have been done on the dietary recommendations for women with PID. This is the first research to our knowledge to investigate the link between PID and dietary trace minerals. Based on the large sample size of the NHANES, dietary copper intake was shown to exhibit a significant negative linear relationship with PID; however, no difference was found in the correlation between other trace minerals (iron, selenium, and zinc) and PID. In addition, we found that age and BMI may have meaningful interactions between copper intake and PID. In the younger age subgroup, the relationship exhibited a curved pattern; however, in the older age subgroup, it showed a straight line. Similarly, a curved relationship was observed in the overweight subgroup.

TABLE 1 Characteristics of the women participants [mean and standard errors (SE); proportions (n) and percentage (%)].

Characteristics	Total	Without PID (*n* = 2,529)	PID (*n* = 165)	*p*-value
Copper (mg/day)	1.12 (0.02)	1.14 (0.02)	0.91 (0.05)	< 0.01
Iron (mg/day)	12.31 (0.21)	12.40 (0.23)	10.96 (0.98)	0.18
Selenium (mcg/day)	99.18 (1.28)	99.77 (1.32)	89.90 (6.94)	0.17
Zinc (mg/day)	9.52 (0.16)	9.60 (0.16)	8.30 (0.76)	0.10
Regular period (*n*, %)				0.01
No	875 (32.48)	798 (35.23)	77 (48.93)	
Yes	1819 (67.52)	1731 (64.77)	88 (51.07)	
Age (years)	40.23 (0.40)	40.03 (0.42)	43.40 (1.13)	0.01
Race (*n*, %)				0.32
Non-Hispanic White	880 (32.67)	824 (60.60)	56 (54.79)	
Non-Hispanic Black	620 (23.01)	567 (11.74)	53 (16.63)	
Mexican American	453 (16.82)	435 (10.38)	18 (6.59)	
Other races	741 (27.51)	703 (17.28)	38 (21.99)	
Marital (*n*, %)				0.02
Married	1,567 (58.17)	1,479 (62.58)	88 (55.29)	
Widowed	59 (2.19)	53 (2.08)	6 (5.35)	
Divorced/separated	416 (15.44)	374 (13.28)	42 (25.80)	
Spinsterhood	652 (24.2)	623 (22.06)	29 (13.56)	
Education (*n*, %)				0.20
Less high school	398 (14.77)	370 (9.15)	28 (13.52)	
High school	560 (20.79)	519 (21.45)	41 (29.10)	
College	1736 (64.44)	1,640 (69.40)	96 (57.39)	
Poverty (*n*, %)				< 0.01
Low	597 (22.16)	546 (16.44)	51 (24.96)	
Medium	1,133 (42.06)	1,054 (33.92)	79 (51.69)	
High	964 (35.78)	929 (49.64)	35 (23.35)	
BMI (*n*, %)				< 0.01
Underweight	55 (2.04)	54 (2.52)	1 (0.17)	
Normal weight	745 (27.65)	712 (30.97)	33 (12.48)	
Overweight	660 (24.5)	618 (24.21)	42 (36.63)	
Obese	1,234 (45.81)	1,145 (42.31)	89 (50.73)	
Smoke (*n*, %)				< 0.01
Never	488 (18.11)	433 (18.19)	55 (37.30)	
Former	1825 (67.74)	1757 (66.36)	68 (36.09)	
Now	381 (14.14)	339 (15.45)	42 (26.61)	
Hypertension (*n*, %)				< 0.01
No	1942 (72.09)	1851 (77.10)	91 (62.44)	
Yes	752 (27.91)	678 (22.90)	74 (37.56)	
Diabetes mellitus (*n*, %)				0.55
No	2,186 (81.14)	2055 (83.39)	131 (86.80)	
Pre-diabetes mellitus	156 (5.79)	147 (5.45)	9 (4.57)	
Diabetes mellitus	352 (13.07)	327 (11.15)	25 (8.63)	

The format of mean ± standard error (SE) is used to present continuous variables, whereas counts and percentages are used to present categorical variables. Categorical and continuous characteristics were analyzed using the chi-squared tests and *t*-tests, respectively.

Currently, dietary iron intake is mainly focused on pregnancy and anemia among women (25, 26). However, it has been shown that dietary iron intake exhibited no relationship with non-pregnancy diseases such as gynecological cancers (15). In our study, dietary iron intake was not significantly different between the PID and non-PID groups, as supported by insignificant results from logistic regression analysis. Selenium is now recognized as an important trace nutrient with anti-inflammatory function (27). Compared with the control group, in men, selenium supplementation improved inflammatory parameters (28). No significant link was found between selenium in the diet and PID in this study, which may be explained by sex differences and disease-specific factors. Zinc deficiency is closely related to an increased risk to pregnancy health because of its vital role in some enzymatic reactions (29), and bone mineral density is associated with zinc intake in a positive manner (30). However, in the present study, univariate analysis of dietary zinc intake and PID showed no significant relationship, suggesting avenues for future research. Compared to non-pregnant women, the urine levels of trace element silicon in pregnant women were higher, which might be accounted for by the differences in the gastrointestinal tract, kidney excretion, and metabolism in pregnant women (31). The trace elements metabolism also changed between gestational weeks (32). Consequently, as a non-pregnancy disease, PID might not be easily susceptible to changes in common trace elements.

Copper performs an integral function in the secretion of inflammatory products and is linked to many inflammatory diseases by regulating the nuclear factor kappa-B and mitogen-activated protein kinase pathways (14). Another study has shown that copper is capable of activating nicotinamide adenine dinucleotide phosphate hydrogen in mitochondria, thus mediating metabolic and epigenetic processes toward the inflammatory state (33). The dietary copper intake was demonstrated to be correlated with inflammatory disorders and serum estradiol levels in women (34, 35). Adequate copper intake is vital to maintain the

TABLE 2 Weighted univariate logistic analyses between dietary trace minerals and PID (odds ratios, 95% confidence intervals).

Dietary trace minerals	Univariate analysis (crude model)	
	95% CI	*p*
Copper (mg/day)	0.40 (0.24, 0.67)	< 0.01
Iron (mg/day)	0.96 (0.90, 1.03)	0.25
Selenium (mcg/day)	1.0 (0.99, 1.0)	0.23
Zinc (mg/day)	0.94 (0.86, 1.03)	0.17

TABLE 3 Weighted multivariate logistic analyses between quintiles of dietary copper intake and PID (odds ratios, 95% confidence intervals).

Dietary copper intake (mg/day)	Crude model		Model 1[a]		Model 2[b]	
	95% CI	*p*	95% CI	*p*	95% CI	*p*
Copper	0.40 (0.24, 0.67)	< 0.01	0.41 (0.23, 0.70)	< 0.01	0.51 (0.28, 0.90)	0.03
Q1 ≤ 0.63	Reference		Reference		Reference	
Q2 0.63–0.86	0.85 (0.40,1.81)	0.66	0.85 (0.39,1.85)	0.68	0.91 (0.39, 2.14)	0.80
Q3 0.87–1.09	0.67 (0.36,1.26)	0.20	0.69 (0.35,1.34)	0.26	0.83 (0.34, 2.03)	0.63
Q4 1.10–1.48	0.59 (0.28,1.27)	0.17	0.60 (0.27,1.34)	0.20	0.84 (0.32, 2.20)	0.68
Q5 > 1.49	0.23 (0.09,0.58)	< 0.01	0.23 (0.09,0.61)	0.01	0.29 (0.09, 0.90)	0.04
P for trend		< 0.01		< 0.01		0.04

There was no adjustment made to the crude model.[a]Age and race adjustments were made to Model 1.
[b]All covariates (age, regular period, demography, BMI, smoke, hypertension, and DM) were adjusted to Model 2.

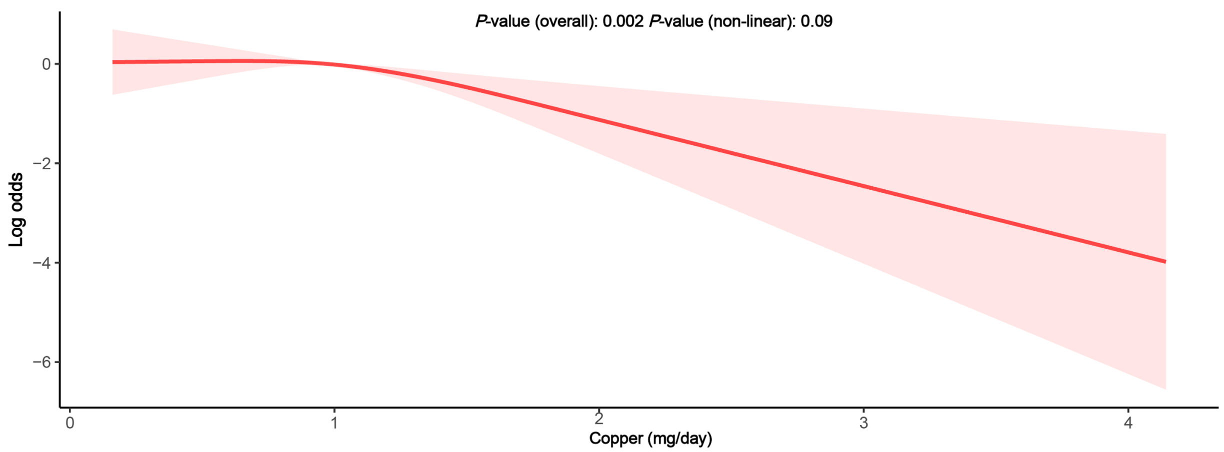

FIGURE 2
The RCS between dietary copper intake and the risk for PID.

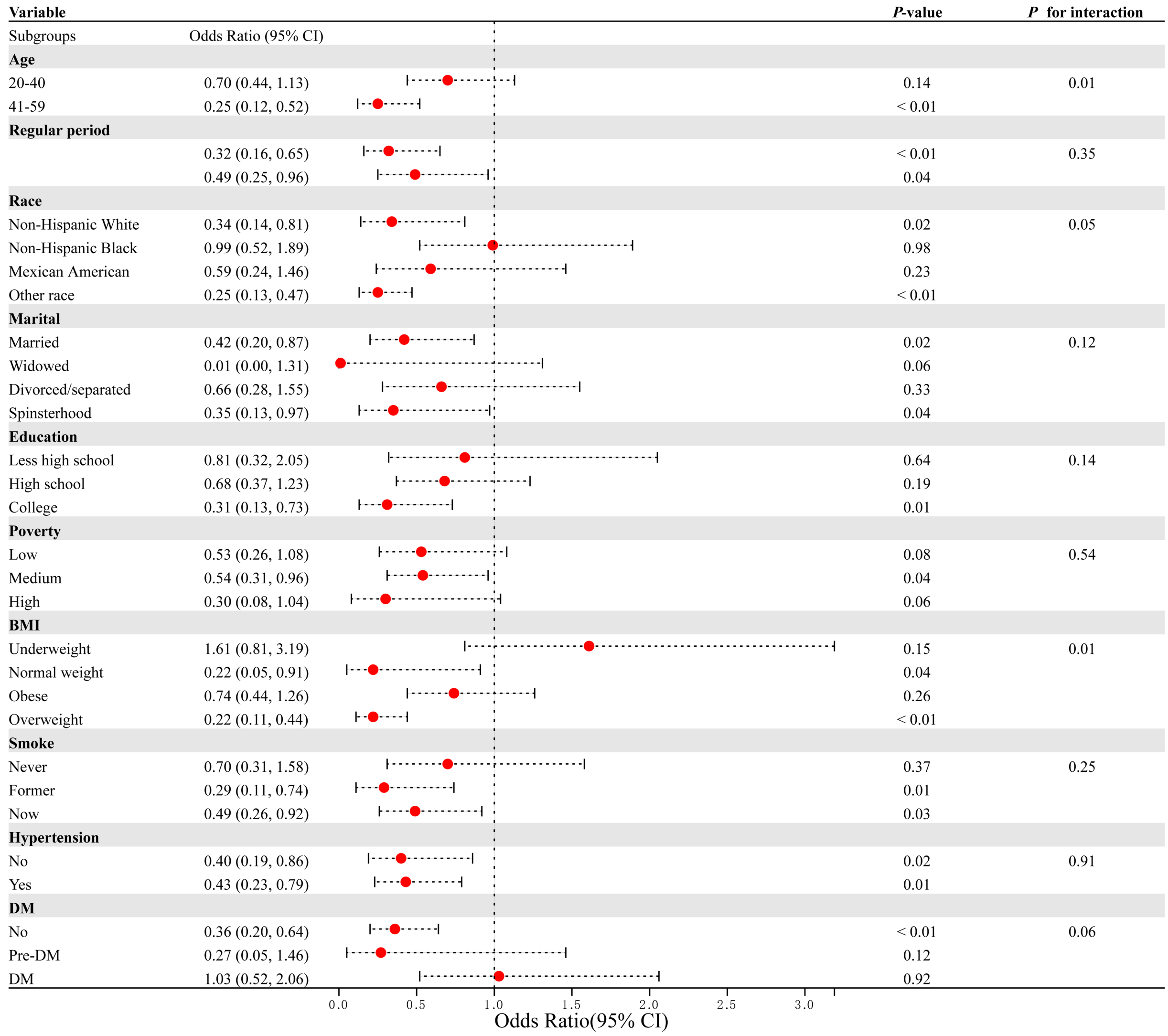

FIGURE 3
Subgroup analysis between dietary copper intake and the risk for PID.

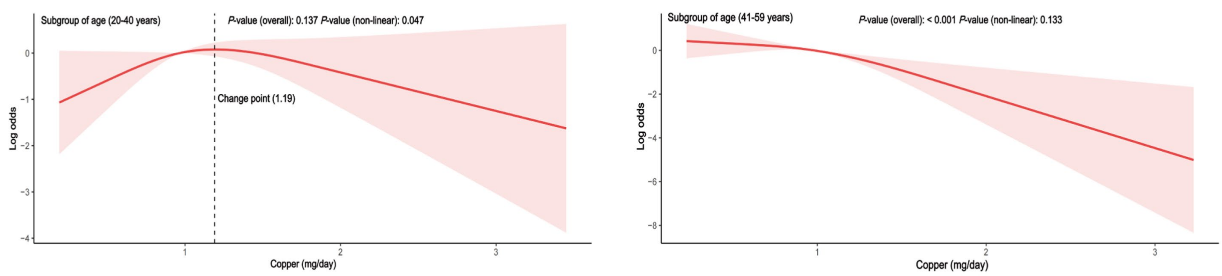

FIGURE 4
The RCS between dietary copper intake and the risk for PID in age-stratified subgroups (adjusted for all covariates except age).

antioxidant capacity of the body (36). Although, to our knowledge, no study has been conducted on dietary copper intake and PID, evidence has shown that using non-hormonal copper-containing intrauterine devices could effectively decrease pelvic pain, which highlights the importance of the copper mechanism in PID (37). Our data showed a consistent negative linear correlation between copper intake and PID, which remained stable across different models. Our findings imply that copper intake can aid in the fight against PID, which may contribute to its regulatory role in inflammation. However, a key consideration is that excessive copper intake may be harmful to health. Therefore, future research is needed to

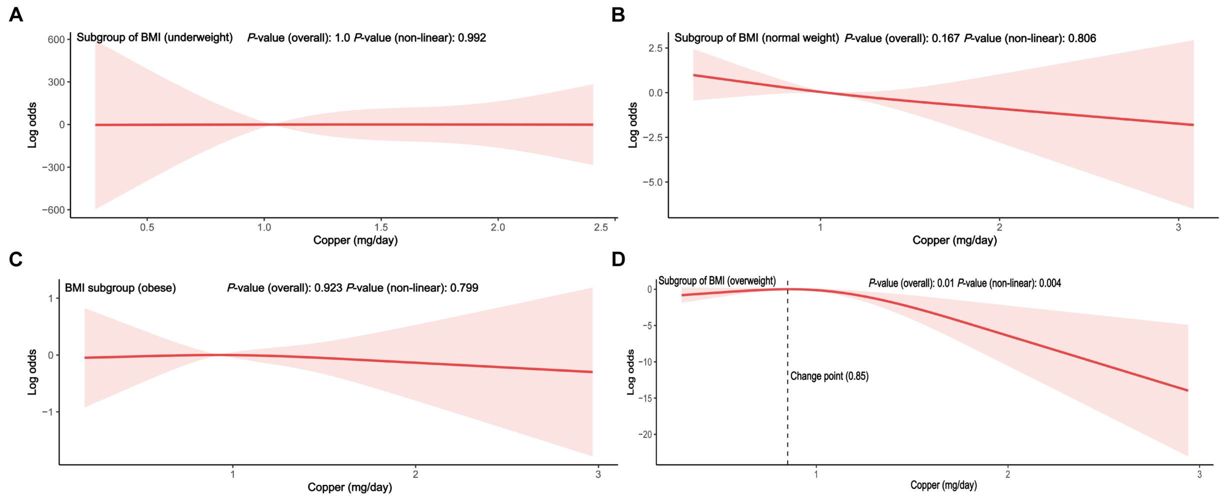

FIGURE 5
The RCS between dietary copper intake and the risk for PID in BMI stratified subgroup (adjusted for all covariates except BMI). **(A)** subgroup of underweight; **(B)** subgroup of normal weight; **(C)** subgroup of obesity; **(D)** subgroup of overweight.

determine the specific turning points of copper intake that are effective in preventing and managing PID.

Age and body weight were independently associated with pelvic disease, especially in older and obese women (38). In our study, age and BMI covariates were identified as interaction terms between copper intake and PID. In the younger age group, it appears that adequate copper intake (>1.19 mg/day), which exceeds the RDA, may have a protective effect against PID. However, in the older age group, the relationship between copper intake and PID is assumed to be linear from the beginning of copper intake. According to a disease burden analysis, women younger than 25 years old had a higher rate of PID than older women (39). Young women may be more susceptible to the modulatory effects of high estrogen and progesterone levels, which in turn makes them less susceptible to the influence of copper intake. Among the different BMI subgroups, only the overweight participants showed a significant non-linear relationship between copper intake and PID, while no significant correlations were found in other BMI subgroups. Although there was an initially positive correlation between copper intake and PID in the underweight subgroup, this relationship disappeared in the subsequent multivariate RCS, which could be due to the presence of confounding variables. Before reaching a copper intake of 0.85 mg/day (close to the RDA), the link between copper intake and PID in the overweight subgroup (≥30.0 kg/m^2) was flat and decreased rapidly when the RDA of copper was reached. A retrospective study has shown that obese PID patients were identified to be associated with an unfavorable clinical course (9). Thus, adequate copper intake may become even more important for older and overweight women with PID. Poultry was considered a valuable food for its abundance of minerals (specifically iron, zinc, and copper) and moderate energy (40). Therefore, intake of a certain amount of meat rich in copper may be beneficial for women with PID. However, the trace minerals consumed are not equivalent to the actual uptake of minerals, and the absorption efficiency may also be a critical factor. Before being absorbed, dietary copper (Cu^{2+}) was first reduced to cuprous copper, then absorbed by the intestinal epithelial cells, and finally transported to the liver for processing and activation (41). Thus, people with gastrointestinal disease or liver diseases may present a low absorption efficiency of dietary copper. Furthermore, copper imbalance was associated with liver pathological features, including oxidative stress and mitochondrial dysfunction, which in turn affect the copper absorption efficiency (42). Hence, future studies on dietary copper absorption efficiency and PID will be required to apply our findings to real-world situations.

To our knowledge, our research is the first to investigate whether PID is linked to dietary trace minerals. A significant negative relationship between PID and dietary copper intake was identified, though not in iron, selenium, and zinc. Additionally, multiple linear regression was used to verify the solid relationship between dietary copper intake and PID after adjusting for several covariates. Our study may have important implications regarding the setting of recommended dietary copper intake for women with PID. However, there were several limitations to this research. To begin with, this was a cross-sectional study; therefore, no causal relationship could be determined based on the accurate dietary trace intake recommendation for women with PID. Second, the diagnostic nature of the PID questionnaire inevitably introduced some degree of selection bias. Thirdly, although efforts were made to incorporate related confounding factors, we were unable to address all confounders. Finally, sampling errors inherent in the NHANES data cannot be ruled out. Given these limitations, large prospective cohort studies are necessary to validate the link between dietary copper intake and determine the recommended intake of dietary trace minerals for women with PID.

5 Conclusion

Overall, our study suggested that decreased dietary copper intakes are linked to PID. However, no significant link was found for other dietary trace minerals (iron, selenium, and zinc). To confirm our findings, more large-scale prospective investigations are needed.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by National Center for Health Statistics Ethics Review Board gave approval for the project (https://www.cdc.gov/nchs/nhanes/irba98.htm). 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

PH: Writing – original draft. SM: Conceptualization, Writing – original draft. HL: Data curation, Conceptualization, Writing – review & editing. XY: Data curation, Formal analysis, Software, Writing – review & editing. XZ: Conceptualization, Data curation, Supervision, Writing – review & editing. QZ: Supervision, Funding acquisition, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The investigation was supported by the National Natural Science Research Fund of China (grant no. 82305283 and 82305284), the Shanghai Committee of Science and Technology (23S21900400), and the Fifth Batch of National TCM Clinical Outstanding Talents Training Program (National TCM Personnel Education Letter (2022) No. 1).

Acknowledgments

The authors thank all NHANES participants, staff, and investigators. We thank Zhang Jing (Shanghai Tongren Hospital) for his 'nhanesR' assistance with the NHANES database. We thank Bullet Edits Limited for the linguistic editing and proofreading of 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.

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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 08 January 2024
DOI 10.3389/fnut.2023.1281971

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OPEN ACCESS

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RECEIVED 12 September 2023
ACCEPTED 18 December 2023
PUBLISHED 08 January 2024

CITATION
Liu X, Liu X, An H, Li Z, Zhang L, Zhang Y, Liu J, Ye R and Li N (2024) Folic acid supplements and perinatal mortality in China.
Front. Nutr. 10:1281971.
doi: 10.3389/fnut.2023.1281971

Folic acid supplements and perinatal mortality in China

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Introduction: Periconceptional use of multivitamins containing folic acid prevents external major birth defects, especially neural tube defects. We aimed to explore the effects of maternal folic acid supplementation alone on perinatal mortality with or without external major birth defects plus neural tube defects.

Methods: From the China-US Collaborative Project for Neural Tube Defects Prevention, we identified 222, 303 singleton pregnancies with detailed information on periconceptional folic acid use, defined as folic acid supplementary before the last menstrual date until to the end of the first trimester. Perinatal mortality included stillbirths after 20 weeks' gestation and early neonatal deaths within 7 days of delivery.

Results: Among the fetuses or infants of women who did not take folic acid, the rate of perinatal mortality was 2.99% and 1.62% at least 20 weeks' gestation in the northern and southern regions. Among the fetuses or infants of the women with periconceptional use of folic acid, the rates were 1.85% and 1.39% in the northern and southern region. The estimated relative risk for perinatal mortality [adjusted risk ratio (RR), 0.72; 95% confidence interval (CI), 0.61- 0.85], stillbirth (adjusted RR, 0.78; 95% CI, 0.64-0.96), early neonatal mortality (adjusted RR, 0.61; 95% CI, 0.45-0.82), and neonatal death (adjusted RR, 0.64; 95% CI, 0.49-0.83) in northern China was significantly decreased in association with periconceptional folic acid supplementation. Compared with northern, there was a lesser effect in southern China.

Conclusion: Periconceptional intake of 400μg folic acid daily reduces the overall risk perinatal mortality, as well as the risk from external major birth defects and neural tube defects, especially in northern China.

KEYWORDS

folic acid supplementation, perinatal mortality, stillbirth, early neonatal death, neonatal death

1 Introduction

Perinatal mortality is one of the most noticeable adverse pregnancy outcomes, and causes millions of deaths each year, especially in developing countries (1–3). Perinatal mortality is categorized into stillbirth and early neonatal death according to clinical manifestation. A total of 2.65 million babies is stillborn annually, with 98% occurring in low- and middle-income counties. The etiology of perinatal mortality is multifactorial but remains unclear.

Women's nutritional intake during pregnancy may play a vital role in maternal morbidity and mortality (4, 5), although few data exist on the effect of nutritional supplementation on perinatal mortality. A 2011 meta-analysis and a 2013 systematic review do not found protective effect of folic acid-fortified multivitamin on perinatal mortality (6, 7). However, they do not take folic acid supplements alone into consideration, and its potential role in preventing perinatal mortality remains unclear. Existing evidence supported that structural births defects, especially external major birth defects and neural tube defects, were common and contributed to perinatal mortality (8, 9). Further a systemic meta-analysis study showed folic acid supplementation could prevent against neonatal mortality by decreasing the incidence of neural tube defects (10); the most recent review of the correlation between folic acid and all-cause perinatal mortality was based on observational studies that cannot distinguish whether effects on perinatal mortality are mediated by external major birth defects and neural tube defects or are simply concurrent. However, the public health impact of the reduced perinatal mortality should be further evaluated by assessment of external major birth defects and neural tube defects.

The only antenatal supplement promoted by the Chinese Ministry of Health and United States Public Health Service is 400 μg of folic acid daily with no additional vitamins to prevent neural tube defects during the 1990s (11), which has been adopted by other countries (12). Several cohort studies have confirmed the effectiveness of this campaign (13–15). With the large and prospective birth cohort in China, we aimed to explore the association of periconceptional supplementation with folic acid alone and the risk of perinatal mortality overall or certain compositions thereof, and further to examine this association with or without major external birth defects and neural tube defects in this study.

2 Methods

2.1 Background of the cohort

The methods of the original study have been described previously (13, 16). Beginning in 1993, the Chinese Ministry of Health conducted a public health campaign to prevent neural tube defects in 21 counties in two southern provinces (Zhejiang and Jiangsu) and one northern province (Hebei). During this campaign, all couples planning to marry undergo a premarital examination in China. All women in the three provinces who were pregnant and who prepared to get marry were registered in a pregnancy monitoring system, which was linked to the detailed data about demographic information, folic acid supplement, and perinatal health care record. The perinatal health care record was designed to monitor the course and outcome of all the resident women. All women were advised to take a pill containing 400 μg of folic acid alone every day from the registration time to the end of the first trimester of pregnancy. If women consented to take folic acid, the pills were distributed at the time of registration. At the end of each month, the health workers recorded the dates of all menstrual periods and how many pills remained in each bottle. The original cohort comprised 247,831 women who registered with the pregnancy-monitoring system between October 1993 and September 1995 and who delivered by December 31, 1996. The project was approved by the institutional review boards of the Centers for Disease Control and Prevention and Beijing Medical University. All women who took pills provided verbal informed consent.

2.2 Definition of folic acid use

Women who took folic acid pills at any time from the registration period until the end of the first trimester of pregnancy were classified as folic acid users. Folic acid usage was divided into three patterns based on the usage period: (i) periconceptional use, defined as the initiation of folic acid supplementation before the last menstrual period and termination at the end of the first trimester; (ii) preconceptional use, defined as the initiation and termination of folic acid use before the last menstrual period; and (iii) postconceptional use, defined as the initiation of folic acid supplementation after the last menstrual period but within the first trimester. Women who did not agree to take folic acid or who were registered during the second trimester of pregnancy were considered to be non-users. Compliance was calculated for each woman by dividing the total number of pills taken by the total number of days between the initiation and termination of supplementation.

2.3 Case ascertainment of stillbirth, early neonatal deaths, neonatal deaths, and major external birth defects

The detailed data about fetuses or infants with stillbirth, early neonatal deaths, neonatal deaths, and external structural birth defects were obtained by a birth-defects surveillance system that was established in January 1993. The atlas contains detailed descriptions, photographs, and International Classification of Diseases, Ninth Revision, codes for 26 common birth defects (17). Birth defects that are not included in the atlas are coded as 'unknown'. The number and frequency of each type of major external birth defects excluded in the present study were provided in Supplementary Table 1. Three pediatricians independently reviewed the report and photographs and assigned diagnostic codes. Neonatal deaths were circumscribed as live births registered as having died within the first 28 days of life. We defined perinatal mortality as stillbirths (fetuses delivered at 20 weeks' gestation or later with no signs of life and recorded as occurring before the onset of or during labor) plus early neonatal deaths (deaths among liveborn infants occurring within 7 days of delivery) (18).

2.4 Statistical analysis

We compared the characteristics of maternal age, body mass index (BMI), ethnicity, education, occupation, and parity between women who took folic acid and those who did not. We compared the means of age and BMI using *t*-tests, and the distributions of categorical variables using chi-square tests. Using the logistic regression model, we estimated risk ratios (RRs) by dividing the incidence of perinatal mortality among women who took folic acid by that among women who did not; we also estimated risk reduction to observe the different effect of folic acid on perinatal mortality between the northern and southern China. Both unadjusted and adjusted RRs were derived after adjustment for potential confounders including maternal age at delivery (continuous), BMI (continuous), ethnicity, parity, education, and occupation. The participants were divided into three subgroups to compare the differences in effects of the timing and compliance of folic acid use on perinatal mortality. We used mean imputation to substitute missing values of those confounding variables in the logistic regression. Findings at $p < 0.05$ were considered significant. All analyses employed SPSS ver. 20.0 software (SPSS, Inc., Chicago, IL, USA).

3 Results

After the exclusion of pregnant women who were lost to follow-up or those for whom the status of the fetus or infant with respect to perinatal mortality was unknown, there were 222,303 singleton pregnant women (28,829 in the northern region and 193,474 in the southern region). The proportion of folic acid supplementation was higher in the north (58.9%) than the south (52.9%). The difference analysis results of demographic characteristics showed the women who took folic acid pills were approximately 2 years younger than those who did not, and were more likely to be primiparous, factory workers, and better educated in both regions (Table 1).

According to the results of logistic regression model, there were significant differences in the associations between folic acid supplementation with perinatal mortality occurrence in the north and south of China (Table 2). After adjusting for maternal age, BMI, education, occupation, ethnicity, and parity, folic acid supplementation significantly prevented perinatal mortality (adjusted RR: 0.72, 95% CI: 0.61–0.85) in northern China. A lesser preventive effect of folic acid on perinatal mortality (adjusted RR: 0.92, 95% CI: 0.85–0.99) was observed in southern China. Additional adjustment for gestational age and birth weight did not change the slight disproportion in the north and south of China (data not shown). When we further classified the cases of perinatal mortality into subgroups according to whether birth defect was unaccompanied by additional major external anomalies or neural tube defects, all differences were significant in northern and southern China.

We compared the differences in the associations between folic acid use and perinatal mortality by the timing and compliance of taking folic acid (Table 3). The prevention effect of periconceptional folic acid use in northern China (adjusted RR: 0.62, 95% CI: 0.51–0.75) was more obviously than that in southern China (adjusted RR: 0.90, 95% CI: 0.82–0.98). However, folic acid use before or during pregnancy was not associated with a reduced risk of perinatal mortality in either northern or southern China. The protective effect increased in magnitude with higher folic acid usage compliance. The risk reduction of ≥90% folic acid usage compliance tended to be 20% higher for women from northern China than for those from southern China.

Table 4 showed the effects of folic acid on the three main compositions of perinatal and neonatal death in northern and southern China. The lesser risk associated with folic acid pill use was more obvious in the north than the south. In the north, there was a 20 to 30% reduced risk of stillbirth, early neonatal death, and neonatal death among women taking folic acid pills. In the south, there were no significant associations between folic acid use and reduced risk of stillbirth (adjusted RR: 0.96, 95% CI: 0.87–1.07) and neonatal death (adjusted RR: 0.92, 95% CI: 0.83–1.02), except for early neonatal death (adjusted RR: 0.86, 95% CI: 0.77–0.97).

We compared the differences in preventive effect of folic acid supplementary on perinatal mortality between different regions. When compared with the south, there were significant risk reductions in all cases of perinatal mortality (Table 2), periconception use of folic acid, usage compliance ≥90% (Table 3), and perinatal mortality composition (Table 4) in the north. We additionally excluded the cases with major birth defects (Supplementary Tables S2, S3) or neural tube defects (Supplementary Tables S4, S5) from perinatal mortality, to analyze the effects of overall folic acid use (Supplementary Tables S3, S5), usage time and compliance (Supplementary Tables S2, S4). The results showed the preventive effects on perinatal mortality were larger in the northern region of China, periconceptional folic acid use, and higher compliance compared with the corresponding reference.

4 Discussion

In this large population-based cohort study, we observed a substantially decreased risk for perinatal mortality with or without

TABLE 1 Characteristics of women who enrolled in the pregnancy monitoring system according to folic acid use, China, 1993 to 1996.

Characteristic	North					South				
	Folic acid users (*n* = 16,974)		Nonusers (*n* = 11,855)		*P*	Folic acid user (*n* = 102,333)		Nonusers (*n* = 91,141)		*P*
	n	%	*n*	%		*n*	%	*n*	%	
Age (years, mean [SD])	24.52 (2.49)		26.90 (4.02)		<0.001	24.75 (2.42)		26.05 (3.74)		<0.001
Body mass index (kg/m^2, mean [SD])	21.15 (2.01)		21.12 (1.52)		0.118	20.33 (2.13)		20.67 (1.86)		<0.001
Primiparous	16,222	95.57	7,359	62.08	<0.001	93,853	91.71	65,400	71.76	< 0.001
Han ethnic group	16,525	97.35	11,665	98.40	<0.001	101,366	99.06	90,330	99.11	0.205
Education					<0.001					<0.001
High school or higher	1,513	8.91	887	7.48		11,450	11.19	8,674	9.52	
Junior high school	12,920	76.12	9,255	78.07		64,105	62.64	49,977	54.83	
Primary school or lower, or unknown	2,541	14.97	1713	14.45		26,778	26.17	32,490	35.65	
Occupation					<0.001					<0.001
Farmer	14,669	86.42	10,853	91.55		54,416	53.18	60,789	66.70	
Factory worker	1,619	9.54	743	6.27		42,230	41.27	25,927	28.45	
Other or known	686	4.04	259	2.18		5,687	5.56	4,425	4.86	

SD, standard deviation.

10.3389/fnut.2023.1281971

TABLE 2 Association of folic acid use with perinatal mortality in China, 1993 to 1996 per 1,000 births.

Folic acid use	North			South			Risk reduction[c]		
	All cases of perinatal mortality	All cases without major external birth defects	All cases without neural tube defects	All cases of perinatal mortality	All cases without major external birth defects	All cases without neural tube defects	All cases of perinatal mortality	All cases without major external birth defects	All cases without neural tube defects
	No. (Rate, %)	No. (Rate, %)	No. (Rate, %)	No. (Rate, %)	No. (Rate, %)	No. (Rate, %)	RD (95% CI)	RD (95% CI)	RD (95% CI)
None	11,855 (29.9)	11,668 (21.1)	11,779 (24.5)	91,141 (16.2)	90,405 (12.9)	91,063 (15.5)			
Use	16,974 (18.5)	16,871 (15.9)	16,952 (17.5)	102,333 (13.9)	101,594 (11.0)	102,271 (13.3)			
RR 95% CI	0.61 0.53, 0.71	0.75 0.63, 0.89	0.71 0.60, 0.84	0.86 0.80, 0.92	0.85 0.78, 0.92	0.86 0.80, 0.93	0.33 (0.18, 0.49)	0.13 (−0.05, 0.30)	0.19 (−0.02, 0.36)
Adjusted RR 95% CI	0.72 0.61, 0.85	0.80 0.66, 0.97	0.79 0.66, 0.94	0.92 0.85, 0.99	0.90 0.83, 0.98	0.92 0.85, 0.99	0.24 (0.05, 0.43)	0.11 (−0.11, 0.34)	0.16 (−0.05, 0.36)
P[b]	<0.001	0.026	0.008	0.027	0.019	0.037	0.015	0.323	0.141

No., number of pregnancies; RR, risk ratio; CI, confidence interval; RD, risk differences.
[a]Adjusted for maternal age (continuous), BMI (continuous), education, occupation, folic acid use, ethnicity, and parity.
[b]Adjusted RR.
[c]Risk reduction of perinatal mortality in the north when compared with that in the south.

TABLE 3 Timing of, and compliance with, folic acid supplementation and risk of perinatal mortality in China, 1993 to 1996 per 1,000 births.

Folic acid use	All cases of perinatal mortality in the north				All cases of perinatal mortality in the south				RD[c] (95% CI)
	No.	Rate[a]	Crude RR (95% CI)	Adjusted RR (95% CI)[a]	No.	Rate[a]	Crude RR (95% CI)	Adjusted RR (95% CI)[a]	
Timing[b]									
Periconception	11,983	15.9	0.53 (0.44, 0.63)	0.62 (0.51, 0.75)	54,410	13.5	0.83 (0.76, 0.91)	0.90 (0.82, 0.98)	0.37 (0.16, 0.58)
Preconception	3,395	25.6	0.85 (0.67, 1.08)	1.00 (0.78, 1.28)	32,725	14.0	0.87 (0.78, 0.96)	0.92 (0.83, 1.03)	−0.09 (−0.35, 0.18)
Postconception	1,568	23.0	0.76 (0.54, 1.08)	0.88 (0.62, 1.25)	15,132	14.4	0.89 (0.77, 1.03)	0.95 (0.82, 1.10)	0.05 (−0.34, 0.43)
Compliance									
<70%	1,663	19.2	0.64 (0.44, 0.92)	0.73 (0.50, 1.06)	4,352	16.3	1.01 (0.80, 1.28)	1.08 (0.85, 1.37)	0.38 (−0.02, 0.78)
70% to <90%	3,839	19.0	0.63 (0.49, 0.81)	0.73 (0.56, 0.95)	12,945	14.2	0.88 (0.75, 1.03)	0.94 (0.81, 1.10)	0.24 (−0.07, 0.56)
≥90%	11,472	18.2	0.60 (0.51, 0.72)	0.71 (0.59, 0.86)	85,036	13.7	0.85 (0.78, 0.91)	0.91 (0.84, 0.98)	0.24 (0.02, 0.46)

No, number of pregnancies; RR, risk ratio; CI, confidence interval; RD, risk differences.
[a]Adjusted for maternal age (continuous), BMI (continuous), education, occupation, ethnicity, and parity.
[b]The analysis excluded 28 and 66 women in the northern and southern regions, respectively, for whom the timing of folic acid use could not be classified.
[c]Risk reduction of perinatal mortality in the north when compared with perinatal mortality risk in the south after adjusting the potential confounders.

external major birth defects plus neural tube defects, especially neonatal deaths, among pregnant women who took folic acid supplements during the periconceptional period compared with those who did not. The protective association for perinatal mortality and neonatal deaths tended to be greater in the north than the south, and greatest among women with greater compliance with folic acid supplementation. Our study provides further support for the hypothesis that folic acid supplementation prevents perinatal mortality in populations with low folate concentrations.

There was a marked difference in the risk of perinatal mortality between the north and the south. The protective effect was greater among women in northern China than southern China. One possible explanation for this geographic difference is that diets in the north were more likely to be folate deficient. Based on the overall higher socioeconomic status and generally greater availability of fresh vegetables in the southern region, diets in the south were likely richer in folate than those in the north. As a whole, the southern region (which is adjacent to Shanghai) is one of the wealthiest regions in

TABLE 4 Association of folic acid use with perinatal mortality composition in China, 1993 to 1996 per 1,000 births.

Folic acid use	North			South			Risk reduction[c]		
	Stillbirth	Early neonatal death	Neonatal death	Stillbirth	Early neonatal death	Neonatal death	Stillbirth	Early neonatal death	Neonatal death
	No. (Rate, %)	No. (Rate, %)	No. (Rate, %)	No. (Rate, %)	No. (Rate, %)	No. (Rate, %)	RD (95% CI)	RD (95% CI)	RD (95% CI)
None	11,855 (20.2)	11,616 (9.9)	11,616 (12.6)	91,141 (9.2)	90,305 (7.0)	90,305 (8.9)			
Use	16,974 (13.1)	16,752 (5.5)	16,752 (7.0)	102,333 (8.2)	101,498 (5.7)	101,498 (7.7)			
RR 95% CI	0.64 0.54, 0.77	0.55 0.42, 0.73	0.55 0.43, 0.71	0.89 0.81, 0.98	0.82 0.73, 0.91	0.87 0.79, 0.96	0.32 (0.11, 0.53)	0.39 (0.10, 0.68)	0.45 (0.18, 0.72)
Adjusted[a] RR 95% CI	0.78 0.64, 0.96	0.61 0.45, 0.82	0.64 0.49, 0.83	0.96 0.87, 1.07	0.86 0.77, 0.97	0.92 0.83, 1.02	0.20 (0.02, 0.39)	0.34 (0.01, 0.67)	0.36 (0.04, 0.68)
P[b]	0.018	0.001	0.001	0.464	0.012	0.097	0.034	0.041	0.029

No., number of pregnancies; RR, risk ratio; CI, confidence interval; RD, risk differences.
[a]Adjusted for maternal age (continuous), BMI (continuous), education, occupation, ethnicity, and parity.
[b]Adjusted RR.
[c]Risk reduction of perinatal mortality composition in the north when compared with perinatal mortality risk in the south.

China and has a more temperate climate with a longer growing season than the northern region. In 2003, our colleagues randomly selected one county and one city in the north and south from the same regions as this study and examined the first-trimester folate concentration in blood samples. Women in the north (440.0 nmol/L) had less than half the red blood cell folate levels of women in the south (910.4 nmol/L) (19). This is supported by data from a cross-sectional study showing a significantly higher frequency of folate deficiency in the north (40%) compared with the south (6%), based on plasma and red-blood-cell folate concentrations (20).

We estimate that folic acid supplementation has the potential to prevent about 20% of perinatal mortality, partly due to visible congenital malformations. A large prospective cohort study in China showed that periconceptional supplementation with folic acid alone reduces the occurrence of neural tube defects (13), and similar findings have been reported around the world (21, 22). As shown by a meta-analysis based on eight population-based observational studies, folic acid food fortification could give an estimated reduction in neural tube defect incidence of 46%, and then prevent 13% of neonatal deaths associated with visible congenital defects (9). Moreover, we found folic acid was significantly correlated with decreased risk of 26 common visible congenital birth defect and central nervous system defect (Supplementary Table S6). The preventive effect on external major birth defect in the present study were consistent with previous findings (14, 23, 24). We further found the preventive effect for central nervous system defect was stronger than neural tube defect. That means folic acid supplementary also has potential role in other varieties of nervous system defect except for neural tube defect, but the extents to which need more intervention studies to verify.

A healthy nutrition status during pregnancy was correlated with infant morbidity and mortality, partly resulting from congenital malformations (25, 26). But women who supplemented with multiple micronutrients containing folic acid or iron-folic acid could not significantly reduce the risk of perinatal mortality based on our team's *post hoc* analysis study (27) and other two trials in Nepal (28, 29). We previously have found folic acid supplements have a potential possibility to promote fetal growth with increasing birth weight and gestation duration (25). However, we did not find that gestational age and birth weight could affect the preventive effect of folic acid supplement on perinatal mortality. There has been well-established evidence on the benefit of folic acid for external birth defect reduction (30, 31). As for internal birth defect, it's also confirmed that folic acid supplementary can effectively prevent against congenital heart defect, respiratory system and digestive system defect, and then reduce the occurrence of perinatal mortality (32–34). It can be speculated the reduced risk of perinatal mortality associated with folic acid may be partly mediated by low incidence of internal birth defect. More additional evidence is needed to clarify possibly indirect role of fetal growth and nutrition status among women who supplement with folic acid in prevention of perinatal mortality. The association of specific compositions of perinatal mortality have been inconsistent, potentially because of the small numbers of cases and different study designs, populations, and methods of classifying cases (27, 35, 36). We found a significant preventive effect of folic acid on peri- and early neonatal mortality in both northern and southern China. Different preventive effects of folic acid on different compositions of perinatal mortality with or without external major birth defects were observed. These observations suggest that the folate-mediated, single-carbon metabolic pathways through which folic acid acts to reduce perinatal mortality risk may be nonspecific and that folic acid protects against perinatal mortality in part by suppressing external major birth defects. Our finding that maternal folic acid supplementation reduces the risk of perinatal mortality with or without other anomalies/neural tube defects is consistent with this notion. In this evaluation, women were not randomly selected to take or not to take folic acid pills. Therefore, the women who took them may have differed systematically from those who did not in factors that influence the birth order. Compared with the women who took folic acid, those who did not were more likely to have been pregnant before. Our results emerged into unobvious association between folic acid supplementation and stillbirth or neonatal death after taking into account potential confounders. Stratification according to the number of previous pregnancies, however, did not change the results.

The strengths of our evaluation were its use of a population-based prospective cohort design, with nearly complete ascertainment of outcomes, and that we prospectively documented the monthly recording of folic acid use during the period of gestation before the pregnancy outcome was known. Second, the only intervention was folic acid supplementation, so the results reflect the effect of folic acid alone. The dose of folic acid was 0.4 mg, and we identified effects associated with this dose. At the time, few women in the study area could afford multiple vitamins, and there was little market supply of multiple vitamins. The study period was before implementation of the national folic acid supplementation program, and so the results may reflect the effect of folic acid concentrations. Furthermore, we adopted an appropriate prospective surveillance system for birth defects, which was established before the evaluation commenced and identified all affected fetuses and infants. The well-organized monitoring system included all births at 20 complete gestational weeks (including live births, stillbirths, and pregnancy terminations) and all structural congenital anomalies irrespective of gestational week (13). This will facilitate more precise estimations of birth defects than those provided by hospital-based surveillance systems, because some external structural birth defects are terminated following prenatal diagnosis before 28 gestational weeks in China (37). This study used quality controls to ensure data quality by establishment of diagnoses on the basis of photographs taken at birth and reviews of detailed written descriptions by several clinicians. The sample size was large enough to detect both overall and subgroup effects. Detailed data on folic acid use, as well as clinical records of pregnancy outcomes and external birth defects, allowed us to examine the associations among patterns of folic acid consumption, perinatal mortality compositions, and specific external major birth defects.

The main limitation of the data obtained from this public health campaign is the lack of randomization of folic acid supplementation. All women are advised to take 400 μg folic acid every day, and whether to follow the advice is up to their own ideas. However, we found additional adjustment for other demographic factors did not change the present results appreciably, meaning that the lack of randomization of folic acid supplementation induces few systematic differences between women who took folic use and those who did not. Second, maternal behaviors, such as smoking, drinking alcohol, or taking other nutritional supplements, have been confirmed to be potential confounders for perinatal mortality (38, 39). However, data on these risk factors were not collected at the time of the campaign. Further studies are needed to collect the relevant information to analyze their potential impact. Third, almost all participants in our study were of Han (China's predominant ethnic group) ethnicity, as well as different diet patterns, living environment and lifestyles in the north and south may have been at play, which should be given a high-priority in future research.

5 Conclusion

We conclude that daily maternal consumption of 400 μg of folic acid without other vitamins had reduced peri- and neonatal mortality in China, especially in the northern region, and has potential to decrease major external birth defects and neural tube defect. Our findings support the importance of folic acid supplementary during pregnancy to enhance effective intervention of perinatal mortality. The results should be interpreted cautiously due to the limitations in this study. In the future, there is an urgent need for deep understandings of the role of folic acid in internal birth defect, the potential effect of other confounders, and the pathophysiology of adverse outcomes; all these will facilitate to reveal the mechanisms of fetus death and birth defect associated with folic acid.

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 the Ethics Committee of the United States Centers for Disease Control and Prevention and the Peking University Health Science Center (grant no. U01DD000293). 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

XJL: Conceptualization, Writing – original draft. XWL: Data curation, Software, Writing – review & editing. HA: Data curation, Writing – review & editing. ZL: Supervision, Writing – review & editing. LZ: Visualization, Writing – review & editing. YZ: Validation, Writing – review & editing. JL: Software, Writing – review & editing. RY: Supervision, Writing – review & editing. NL: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (grant nos. 81903327 and 82173527), Beijing Natural Science Foundation (grant nos. 7234401, 7222245, and 7194285), Postdoctoral Science Foundation of China (grant no. 88014Y0226), National Clinical Research Center for Obstetrics and Gynecology (Peking University Third Hospital) (no. BYSYSZKF2021001), the startup funding from the "Incubation" Program of China and Peking University Health Science Center (grant no. BMU2017YB003), and Young Elite Scientist Sponsorship Program by CAST (YESS) (grant no. 2018QNRC001). The original project was supported by a cooperative agreement between the US Centers for Disease Control and Prevention and Peking University (grant no. U01 DD000293).

Acknowledgments

We would like to thank all the participants, staff members and volunteers involved in the original trial.

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.2023.1281971/full#supplementary-material

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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 13 March 2024
DOI 10.3389/fnut.2024.1303822

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OPEN ACCESS

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RECEIVED 28 September 2023
ACCEPTED 29 February 2024
PUBLISHED 13 March 2024

CITATION
Sims CR, Saben JL, Martinez A, Sobik SR, Crimmins MR, Bulmanski JE, Turner D, Furst A, Jansen LT, Bode L and Andres A (2024) A Mediterranean diet plan in lactating women with obesity reduces maternal energy intake and modulates human milk composition – a feasibility study. *Front. Nutr.* 11:1303822.
doi: 10.3389/fnut.2024.1303822

A Mediterranean diet plan in lactating women with obesity reduces maternal energy intake and modulates human milk composition – a feasibility study

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Introduction: Maternal obesity is associated with increased concentrations of human milk (HM) obesogenic hormones, pro-inflammatory cytokines, and oligosaccharides (HMOs) that have been associated with infant growth and adiposity. The objective of this pilot study was to determine if adherence to a Mediterranean meal plan during lactation modulates macronutrients and bioactive molecules in human milk from mothers with obesity.

Methods: Sixteen healthy, exclusively breastfeeding women with obesity (body mass index ≥30kg/m^2) enrolled between 4 and 5months postpartum. The women followed a 4-week Mediterranean meal plan which was provided at no cost. Maternal and infant anthropometrics, HM composition, and infant intakes were measured at enrollment and at weeks 2 and 4 of the intervention. Thirteen mother-infant dyads completed the study. Additionally, participants from an adjacent, observational cohort who had obesity and who collected milk at 5 and 6months postpartum were compared to this cohort.

Results: Participants' healthy eating index scores improved (+27units, p<0.001), fat mass index decreased (−4.7%, p<0.001), and daily energy and fat intake were lower (−423.5kcal/day, p<0.001 and-32.7g/day, p<0.001, respectively) following the intervention. While HM macronutrient concentrations did not change, HM leptin, total human milk oligosaccharides (HMOs), HMO-bound fucose, Lacto-N-fucopentaose (LNFP)-II, LNFP-III, and difucosyllacto-N-tetrose (DFLNT) concentrations were lower following the intervention. Infant intakes of leptin, tumor necrosis factor (TNF)-α, total HMOs, HMO-bound fucose, LNFP-III and DFLNT were lower following the intervention. Specific components of the maternal diet (protein and fat) and specific measures of maternal diet quality (protein, dairy, greens and beans, fruit and vegetables) were associated with infant intakes and growth.

Discussion: Adherence to a Mediterranean meal plan increases dietary quality while reducing total fat and caloric intake. In effect, body composition in women with obesity improved, HM composition and infants' intakes were modulated.

These findings provide, for the first time, evidence-based data that enhancing maternal dietary quality during lactation may promote both maternal and child health. Longer intervention studies examining the impact of maternal diet quality on HM composition, infant growth, and infant development are warranted.

KEYWORDS

human milk, obesity, Mediterranean meal plan, human milk oligosaccharides, infant growth, healthy eating index, maternal diet

1 Introduction

In the United States, more than 50% of women enter pregnancy with either overweight or obesity (1). Pre-gravid obesity has been associated with changes in the macronutrient (2) and bioactive composition of human milk (HM) (2–4), which may impact infant health (5). HM from women with obesity has higher energy, fat, and protein content compared to milk from mothers with normal weight throughout lactation (2, 6, 7) and obesity-associated elevations in HM hormones (8, 9), pro-inflammatory cytokines (10, 11) and HM oligosaccharides (HMOs) (4), are positively associated with infant growth and adiposity (2, 4, 9). Therefore, obesity-associated alterations in HM composition may play a role in early-life nutritional programing of infant adiposity.

Dietary interventions during the postnatal period may provide a window to temper the effects of obesity on HM composition. It has been shown in observational studies that a higher Mediterranean diet score is associated with lower HM saturated fatty acid concentrations and with increased monounsaturated fatty acids and total antioxidant capacity (12, 13). However, very few dietary intervention studies have been conducted in breastfeeding women that have also analyzed components of HM. A crossover study, employing four different dietary paradigms (galactose vs. glucose and high carbohydrate vs. high fat) during lactation, showed an association between dietary energy source and HMO concentrations (14). Another study, aimed at decreasing maternal energy, fat, and sugar intake over 2 weeks postpartum, found that HM insulin, leptin and adiponectin were reduced by 10–25% following the dietary intervention (15). Together these studies suggest that dietary interventions can modulate HM composition. As such, the Mediterranean diet has shown efficacy in decreasing body mass index (BMI) (16, 17), circulating obesogenic hormones (17), adipokines (18), and systemic inflammation (16, 19) in non-pregnant/non-lactating women with obesity. However, it is yet unknown whether similar results can be attained in lactating women or if these changes may affect human milk content.

In this within-subject pilot intervention trial, we aimed to determine if adherence to a Mediterranean meal plan during lactation could modulate the macronutrient and bioactive (hormone, HMO, and cytokine) content of HM from women with obesity.

2 Materials and methods

2.1 Participants and study design

The within-subject intervention study took place at the Arkansas Children's Nutrition Center in Little Rock, Arkansas between April 2019 and February 2020. Healthy women with obesity who were exclusively breastfeeding were recruited from the surrounding community. Of the 90 participants screened, 28 were eligible and of those, 16 enrolled between 4 and 5 months postpartum (Supplementary Figure S1). Three participants did not complete all study visits (19%), resulting in 13 participants for the current analysis. Inclusion criteria were: BMI = 30–50 kg/m^2, ≥ 18 years of age, singleton pregnancy, intent to continue breastfeeding exclusively until at least 6 months postpartum, and child being able to be fed expressed milk from a bottle. Exclusion criteria included: pre-existing conditions (e.g., diabetes, hypertension, heart disease); use of recreational drugs, tobacco, or alcohol; food allergies, intolerances or preferences incompatible with meal plan; and the use of medications or supplements that are contraindicated for lactating mothers. Maternal age, race and ethnicity, and infant sex were self-reported. Assessments took place at enrollment (pre), 2 weeks and 4 weeks following the start of the dietary intervention (Wk2 and Wk4, respectively). To examine the impact of time on milk composition and infant intakes, participants from an adjacent, observational cohort from the same study center (2, 4, 20) were matched to the participants of the within-subject intervention study based on maternal BMI and HM sample availability at postpartum months 5 and 6. From the adjacent, observational study, there were only 10 participants that had a BMI above 30 and collected milk samples at both 5 and 6 months postpartum, therefore, all 10 were used to compare with the participants from this within-subject study. To learn about the observational study sample used, please refer to our group's previous publications on this cohort (2, 4, 20).

2.2 Ethics statement

Written, informed consent was obtained from all participants prior to study procedures. All study procedures were approved by the Institutional Review Board of the University of Arkansas for Medical Sciences (Protocol #: 228407). This trial was registered at clinicaltrials.gov (NCT03744429).

2.3 3-day food records

Habitual maternal dietary intake was assessed prior to the initiation of the dietary intervention using 3-day food records (two weekdays, one weekend day) and analyzed with the Nutrition Data System for Research (Nutrition Coordinating Center, University of Minnesota, MN) software by trained interviewers. Participants recorded all food, beverages, supplements, and medications that they consumed during the 3 day period.

2.4 Dietary intervention

Participants met with a registered dietitian at the initial study visit to receive education about the dietary intervention based on the Mediterranean diet (21) and weekly thereafter to monitor adherence to the meal plan. Motivational interviewing, active listening, and goal setting techniques were used to help participants comply with the intervention. The goals of the counseling sessions were to identify and resolve barriers to adherence as well as provide encouragement and support. The initial session educated on the study intervention and tracking dietary intake while subsequent sessions reviewed compliance to problem solve challenges and celebrate successes. The macronutrient distribution (20–35% of calories from fat, 45–65% carbohydrates, 10–35% protein) and provided caloric intake met the Dietary Guidelines for Americans recommendations (22). All lunches and dinners (2/day, in the form of fresh packaged meals) were provided weekly to the participants throughout the 4 weeks by Trifecta Nutrition (Sacramento, California). Breakfast (breakfast sandwiches and oatmeal, 1/day) and snacks (walnuts, granola bars, Greek yogurt, and fruits, 2/day) were provided by the research team. Participants were also provided with extra virgin olive oil to add to their meals and were instructed to buy 1% low fat milk to drink or combine with fruits as a smoothie. Participants recorded all food, beverages, supplements, and medications that they consumed and where they made substitutions in the meal plan for the entirety of the trial. Dietary intake was analyzed using the Nutrition Data System for Research. Healthy Eating Index (HEI) and Mediterranean Diet scores were derived from published guidelines (23–25). The overall intervention dietary composition is summarized in Supplementary Table S1 and an example of a week's menu is shown in Supplementary Table S2. Intervention compliance was calculated as the participants HEI score of consumed meals divided by the HEI score of the prescribed meals multiplied by 100.

2.5 Anthropometrics and body composition

Maternal and infant anthropometrics and maternal body composition were measured at each visit. Maternal weight and height and infant weight and length were measured as previously described (2). Weight-for-length, weight-for-age and length-for-age z-scores were calculated based on the World Health Organization Child Growth Standards (26, 27). Maternal BMI was calculated as kg/m^2. Maternal fat mass (FM) and fat free mass (FFM) were measured using air displacement plethysmography (Cosmed BodPod®, Concord, CA). Infant fat mass and lean mass were measured using quantitative nuclear magnetic resonance (EchoMRI-AH, Echo Medical Systems, Houston, TX). FM and FFM index (FMI and FFMI, respectively) were calculated as FM (kg)/m^2 and FFM (kg)/m^2.

2.6 Plasma analysis

Maternal blood was collected following an overnight fast at the pre-intervention and Wk4 visits only. Plasma was processed and stored at −80°C. Leptin, insulin, C-reactive protein (CRP), interleukin (IL)-6, IL-8, and TNF-α concentrations were measured using high-performance electrochemiluminescence immunoassays (Meso Scale Diagnostics, Rockville, MD). Cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) concentrations were measured using a clinical analyzer (Randox Laboratories, Kearneysville, WV).

2.7 24-h human milk collection

Participants collected HM over 24-h, prior to each visit. Mothers were given the option to either feed their infant the expressed milk from a bottle or to feed baby from one breast and pump the other breast during the 24-h collection period. If only one breast was pumped, mothers were instructed to alternate the nursed breast and the pumped breast at each feed and record accordingly. At each feed, the mothers were asked to gently invert the expressed HM and aliquot 4 mL of HM into the provided polypropylene tubes. HM was stored at 4°C until the full 24-h collection was complete. Afterwards, the 24-h samples were pooled and stored intact at-80°C.

2.8 Human milk composition and infant intakes

Macronutrients (fat, protein, and carbohydrates) were measured in milk from all visits using a Miris HM Analyzer (Miris, Uppsala, Sweden) according to manufacturer's instructions, from which caloric content was derived. Leptin, insulin, CRP, IL-6, IL-8, and TNF-α concentrations were measured in milk from all visits using high-performance electrochemiluminescence immunoassays (Meso Scale Diagnostics, Rockville, MD). Concentrations of HMOs (nmol/mL) were measured in milk from the pre-intervention and Wk4 visits only. by high-performance liquid chromatography on an amide-80 column (2 μm particle size, 2 mm ID, 15 cm length) with fluorescent detection, as previously described (14). The absolute quantification of the 19 most abundant HMOs (4) was determined using the non-HMO oligosaccharide raffinose as an internal standard added to all milk samples at the beginning of analysis. Infant intakes were estimated using test weighing, which is considered a useful and precise method for assessing milk intake (28–30), at each visit to obtain a single-feed milk intake volume multiplied by regular, daily feeding frequency as reported by the mothers.

2.9 Statistical analyses

Demographic data was summarized using mean and standard deviation for continuous variables and counts (percentages) for categorical variables. Comparisons were made using linear mixed-effect models constructed with random intercepts for each participant followed by type 2 analysis of variance for measurements with no Wk2 values or using linear mixed-effects models constructed with random intercepts for each participant followed by contrasts of estimated marginal means using the *lme4*, *car* and *modelbased* R packages (31–33). Repeated measures correlations were performed to assess the relationship between dietary components and human milk content using the *rmcorr* R package (34) and were FDR-adjusted. Power analysis determined that n = 13 participants would allow consideration of an effect size greater than 1.6 g/100 mL for HM fat, 248 pg/mL for leptin, 0.16 pg/mL for TNF-α and 92 ng/mL for CRP. Significance was set at alpha ≤0.05. Data analyses were performed using R (version 4.1.0) (35). Extreme outliers were removed if they were 3 times above the upper quartile or 3 times below the lower quartile for all measurements.

TABLE 1 Baseline characteristics of lactating women with obesity ($n = 13$) upon enrollment.

	Mean (SD) or *N* (%)
Maternal age (y)	32.8 (3.8)
Maternal height (cm)	163.9 (5.4)
Maternal race	
African American Non-Hispanic	2 (15%)
White Hispanic	1 (8%)
White Non-Hispanic	10 (77%)
Maternal education	
High school/specialized training	3 (23%)
Partial college/college degree	7 (54%)
Graduate Training/Degree	3 (23%)
Household income ($)	
<$40,000	5 (38%)
$40,000 - $70,000	5 (38%)
>$70,000	3 (23%)
Infant sex	
Female	5 (38%)
Male	8 (62%)

3 Results

3.1 Mother and infant baseline characteristics

Participants were on average 32.8 ± 3.8 years of age and 77% of participants were of non-Hispanic, White descent (Table 1). All participants had obesity at enrollment (mean BMI: 35.9 ± 5.0 kg/m^2, FM: 46.1 ± 12.3 kg, and FMI: 17.1 ± 4.3 kg/m^2). Infants showed expected growth with increases in weight and length parameters over the 4-week study (Supplementary Table S3). Of all the measured characteristics, only baseline plasma IL-8 was significantly different between the participants that completed the intervention (2.6 ± 1.1 pg/mL) and those that did not (4.3 ± 1.4 pg/mL).

3.2 Maternal diet quality and metabolic health following dietary intervention

The dietary intervention was started at 4.8 ± 0.28 months postpartum and ended at 5.7 ± months postpartum. The dietary intervention yielded 83.7 and 84.0% compliance to the meal plan at Wk2 and Wk4, respectively. Participants' HEI increased by 70.5 and 71.0% (+27 and + 27.2 units, $p < 0.001$, respectively) and Mediterranean diet scores increased by 87.1 and 90.6% (+7.4 and + 7.7 units, $p < 0.001$, respectively) whereas daily energy intake was 26.5 and 17.9% and lower (−629 and-424 kcal/d, $p < 0.001$, respectively) at Wk2 and Wk4 of the intervention (Table 2). While on the meal plan, participants' daily intake was significantly lower for total fat (−37.0% and − 33.0%, $p < 0.001$, respectively), saturated fat (−56.0% and − 52.0%, $p < 0.001$, respectively), polyunsaturated fat (−37.0% and − 34.0%, $p = 0.01$, respectively), ω6:ω3 ratio

TABLE 2 Maternal dietary characteristics before (Pre) and during (Wk2 and Wk4) Mediterranean dietary intervention that was provided from 5 to 6 months postpartum to 13 lactating women with obesity.

	Pre	Wk2	Wk4	*p* value
2015 Healthy eating index score	38.3 (5.1)^a	65.3 (7.6)^b	65.5 (6.7)^b	**<0.001**
Compliance to meal plan (%)	—	83.7 (9.7)	84.0 (8.5)	0.96
Mediterranean diet score	8.5 (2.6)^a	15.9 (3.5)^b	16.2 (3.2)^b	**<0.001**
Energy (kcal)	2368.0 (433.1)^a	1739.3 (299.1)^b	1944.5 (333.5)^b	**<0.001**
Total fat (g)	99.6 (23.3)^a	62.7 (11.2)^b	66.9 (12.0)^b	**<0.001**
Total carbohydrates (g)	288.8 (82.9)^a	220.2 (52.6)^b	251.5 (62.6)^{ab}	**0.009**
Total protein (g)	85.7 (17.1)	84.5 (12.9)	95.6 (10.8)	**0.029**
Sodium (mg)	4055.7 (1008.3)^a	1542.7 (307.7)^b	1847.6 (578.8)^b	**<0.001**
Whole grains (oz. equivalents)	2.0 (1.3)^a	3.2 (0.9)^b	3.7 (1.2)^b	**<0.001**
Refined grains (oz. equivalents)	6.3 (2.6)^a	1.3 (0.5)^b	1.6 (0.7)^b	**<0.001**
Saturated fatty acids (g)	34.5 (10.7)^a	15.2 (2.3)^b	16.7 (3.5)^b	**<0.001**
Polyunsaturated fatty acids (g)	25.4 (9.2)^a	15.9 (3.9)^b	16.8 (4.8)^b	**<0.001**
ω-6 Fatty acids (g)	22.1 (8.2)	12.6 (3.0)	13.1 (4.0)	**<0.001**
ω-3 Fatty acids (g)	2.5 (0.9)	2.8 (0.8)	2.9 (0.9)	0.36
ω-6:ω-3	8.9 (1.6)^a	4.6 (0.8)^b	4.6 (1.3)^b	**<0.001**

Maternal dietary characteristics are summarized as mean (SD). Intervention compliance was calculated as the participants Healthy Eating Index (HEI) score of consumed meals divided by the HEI score of the prescribed meals multiplied by 100. Comparisons were made using linear mixed-effect models followed by contrasting estimated marginal means and values with different superscripts are significantly different. The bolded values are those that were significantly different ($p < 0.05$).

(−48.3% and − 48.3%, $p < 0.001$), refined grains (−79.0% and − 75.0%, $p < 0.001$, respectively), and sodium (−62.0% and − 54.0%, $p < 0.001$, respectively). Intake of whole grains significantly increased (+60.0% and + 85.0%, $p < 0.001$, respectively). Daily protein intake was significantly different over the duration of the study (Table 2; $p = 0.029$), however, all post-hoc comparisons were non-significant ($p > 0.05$). Daily carbohydrate intake was significantly higher during the intervention at Wk2 compared to pre-intervention ($p = 0.015$).

Following the intervention, maternal weight (−2.7%, $p < 0.001$; Supplementary Table S3), BMI (−2.8%, $p < 0.001$; Figure 1A) and FMI (−5.0%, $p < 0.001$; Figure 1B) significantly decreased by Wk4. FFMI did not change by Wk4 (−0.5%, $p = 0.39$, Figure 1C). Maternal plasma cholesterol levels (total [−12.8%, $p < 0.001$; Figure 1D], HDL [−7.6%, $p = 0.002$; Figure 1E], and LDL [−17.2%, $p < 0.001$; Figure 1F]) were also significantly decreased, even after adjusting for maternal weight loss during the intervention. No significant differences were observed in plasma hormone or cytokine levels between visits (Supplementary Table S3). As expected during the 4-week period, infant length (4.5%, $p < 0.001$), weight (10.6%, $p < 0.001$), fat mass (16.7%, $p < 0.001$), lean mass (9.3%, $p < 0.001$) and FMI (4.3%, $p < 0.001$) increased; however, FFMI, WFA, LFA and WFL did not differ ($p > 0.05$; Supplementary Table S3).

3.3 Changes in human milk bioactive molecule concentrations and daily infant intakes

HM collections occurred 5.4 ± 4.5 days before the beginning of the dietary intervention, 0.77 ± 1.5 days before the Wk2 visit and 1.3 ± 2.5 days after finishing the dietary intervention. Following the 4-week intervention, mean HM leptin concentrations significantly decreased by 37.1% ($p < 0.001$, Figure 2; Supplementary Table S4), even after adjusting for maternal weight loss during the intervention. HM total energy ($p = 0.77$) and macronutrient levels (fat: $p = 0.75$, carbohydrate: $p = 0.60$, and protein: $p = 0.78$) did not change, nor did HM concentrations of insulin ($p = 0.28$), CRP ($p = 0.78$), IL-6 ($p = 0.25$), IL-8 ($p = 0.37$), as shown in Supplementary Table S4. HM concentrations of TNF-α ($p = 0.11$) were not significantly different between time points, albeit levels decreased in 9 out of the 13 participants (Figure 2).

The mean total HMO concentrations decreased by 6.3% ($p = 0.036$) and mean concentrations of HMO-bound fucose (−8.7%, $p = 0.001$), lacto-N-fucopentaose-II (LNFP II, −10.7%, $p = 0.048$), lacto-N-fucopentaose-III (LNFP III, −38.7%, $p = 0.041$), and difucosyllacto-N-tetrose (DFLNT, −59.4%, $p = 0.003$) were significantly lower following the dietary intervention (Figure 3; Supplementary Table S4). After adjusting for maternal weight loss, concentrations of total HMOs ($p = 0.075$), HMO-bound fucose

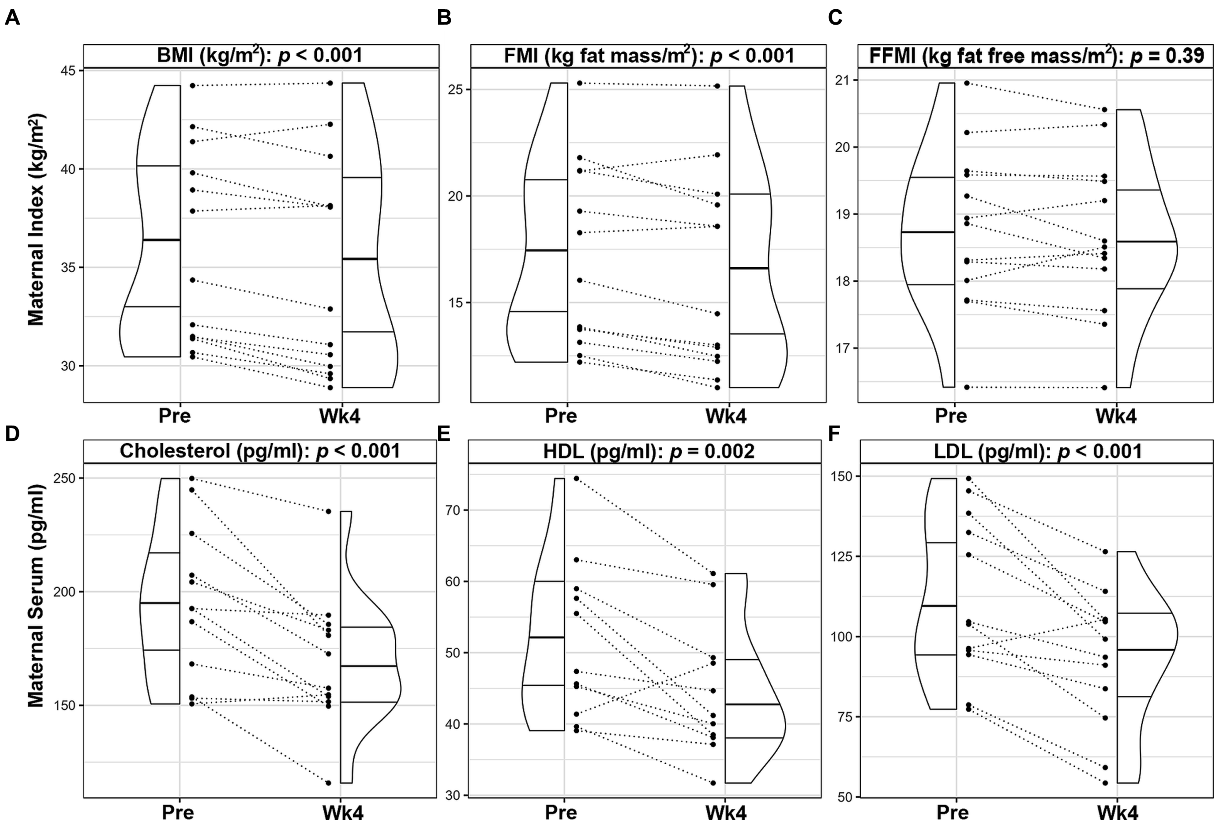

FIGURE 1
Changes in maternal outcomes of lactating women with obesity following a 4-week Mediterranean dietary intervention. Paired plots showing changes in maternal body mass index [BMI, **(A)**], fat mass index [FMI, **(B)**], fat free mass index [FFMI, **(C)**], cholesterol **(D)**, high density lipoprotein [HDL, **(E)**], and low-density lipoprotein [LDL, **(F)**] between pre-intervention (Pre) and the end of the intervention (Wk4). Dotted lines connect the Pre and Wk4 measures for each participant. Quantiles within the density plots are indicated by the solid horizontal lines.

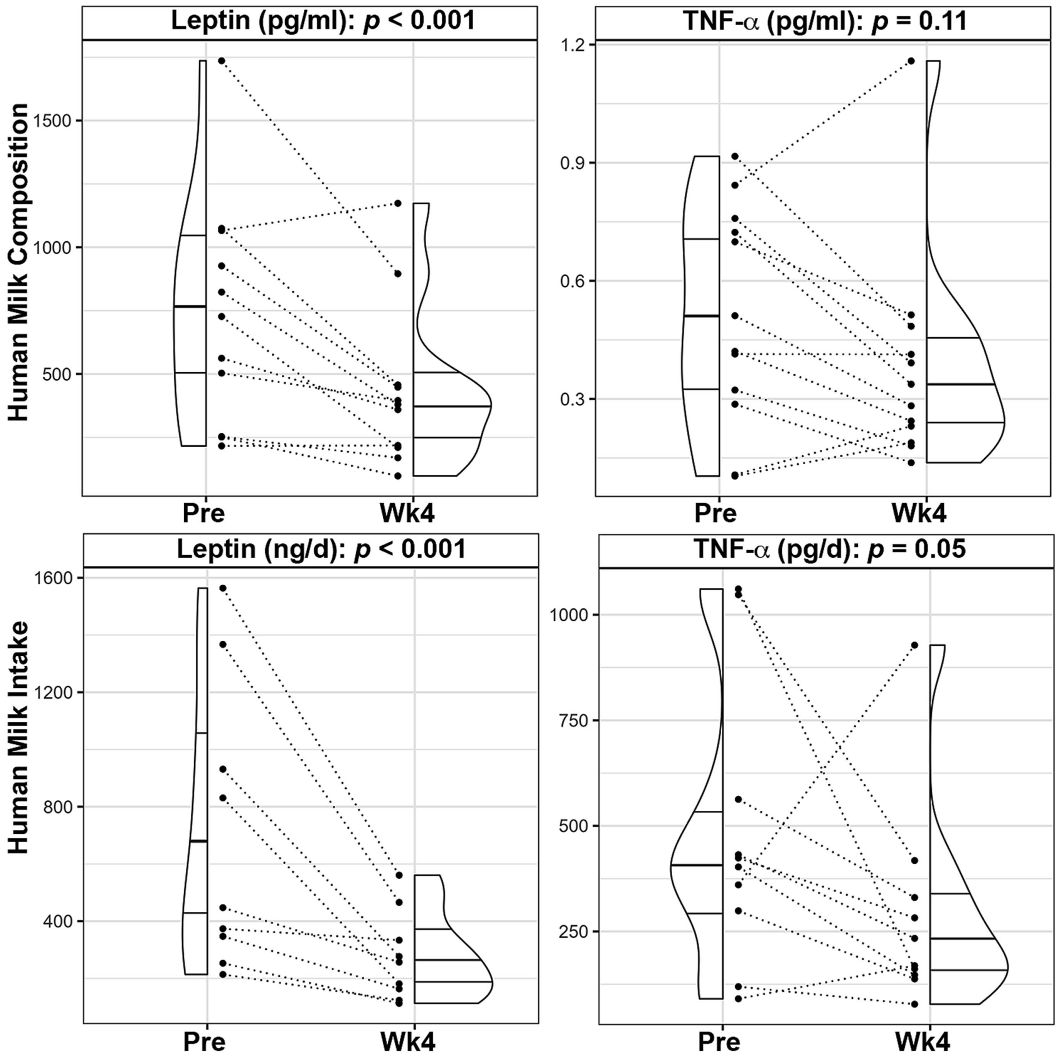

FIGURE 2
Changes in leptin and TNF-α composition and infant intake following a 4-week Mediterranean dietary intervention. Paired plots showing changes in human milk leptin and tumor necrosis factor α (TNF-α) between pre-intervention (Pre) and the end of the intervention (Wk4). Dotted lines connect the Pre and Wk4 measures for each participant. Quantiles within the density plots are indicated by the solid horizontal lines.

($p = 0.005$), LNFP-III ($p = 0.043$), and DFLNT ($p = 0.005$) remained lower following the intervention.

Mean total HM volume intakes were not significantly different prior to and after the intervention (881.4 ± 310.9 mL vs. 708.0 ± 209.2 mL, $p = 0.17$; Supplementary Table S3). Consistent with lower concentrations, infants' mean intake of HM leptin (−59.6%, $p < 0.001$) and TNF-α (−38.5%, $p = 0.05$), were significantly lower over the course of the intervention (Figure 2; Supplementary Table S4). Similarly, infants' mean intake of total HMOs (−24.0%, $p = 0.05$), HMO-bound fucose (−25.5%, $p = 0.029$), LNFP III (−50.4%, $p = 0.019$) and DFLNT (−61.9%, $p = 0.003$) were decreased following the dietary intervention (Figure 3; Supplementary Table S4).

3.4 Effect of time on lactation outcomes, a comparison with an observational cohort

To understand the potential impact of time on HM composition and infant intakes, we examined HM parameters and infant intakes from the within-subject study compared with those of an observational cohort of lactating women with obesity at the same months postpartum. There were no demographic differences between the two cohorts (Supplementary Table S5). There were no differences between the studies in HM concentrations of fat, protein, energy, insulin, IL-6 or CRP, or infants' total milk intake and daily intakes of carbohydrates, protein, energy, insulin, TNF-α, IL-6, or CRP (Supplementary Table S6). There were also no differences in infant weight-for-age, length-for-age or weight-for-length Z-scores or FFMI between cohorts nor did these parameters change with time (Supplementary Table S6). Infant fat mass index was also not different between cohorts, however we did observe that it increased with time, as would be expected in healthy growing infant cohorts.

We found that human milk carbohydrate concentrations were higher in the within subject study compared to the observational cohort (5 mo: 7.5 ± 0.29 g/100 mL vs. 7.2 ± 0.29 g/100 mL, 6 mo: 7.6 ± 0.22 g/100 mL vs. 7.1 ± 0.27 g/100 mL; $p < 0.001$) whereas concentrations of human milk leptin (5 mo: 694.4 ± 463.6 pg/mL vs. 1037.8 ± 532.4 pg/mL, 6 mo: 436.7 ± 324.1 pg/mL vs. 963.4 ± 669.5 pg/

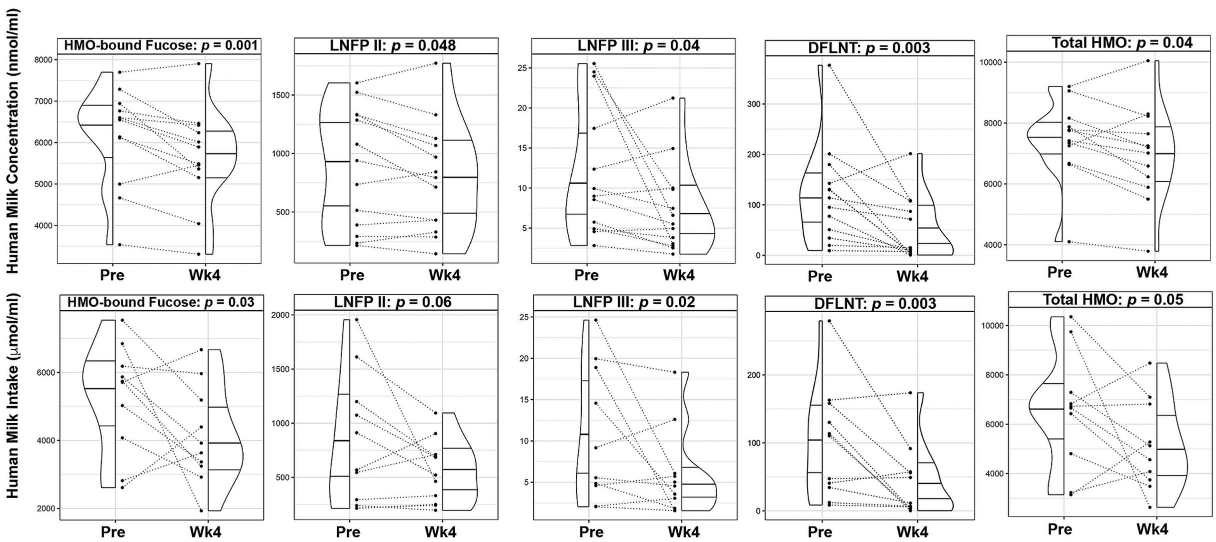

FIGURE 3
Changes in human milk oligosaccharide composition and infant intake following a 4-week Mediterranean dietary intervention. Paired plots showing changes in composition and intake of human milk oligosaccharide (HMO)-bound fucose, Lacto-N-fucopentaose (LNFP) II, LNFP III, Difucosyllacto-N-tetrose (DFLNT), and Total HMOs between pre-intervention (Pre) and the end of the intervention (Wk4). Dotted lines connect the Pre and Wk4 measures for each participant. Quantiles within the density plots are indicated by the solid horizontal lines.

mL; $p = 0.019$), TNF- α (5 mo: 0.52 ± 0.27 pg/mL vs. 0.88 ± 0.72 pg/mL, 6 mo: 0.38 ± 0.27 pg/mL vs. 1.12 ± 0.89 pg/mL; $p = 0.011$), and IL-8 (trending - 5 mo: 177.7 ± 78.3 pg/mL vs. 176.7 ± 134.7 pg/mL, 6 mo: 146.8 ± 107.1 pg/mL vs. 365.8 ± 328.4 pg/mL; $p = 0.06$) were lower in the within subject study compared to the observation cohort (Figure 4; Supplementary Table S6). Interestingly, we found a significant interaction between time and cohorts for IL-8 HM concentrations (Supplementary Table S6; $p = 0.012$). This was likely a result of the observed increase over time in the observational cohort (delta = 161.3 pg/mL) compared to an observed decrease over time in the within subject cohort (delta = −30.9 pg/mL, Figure 4; Supplementary Table S6).

3.5 Association of maternal diet components with human milk composition and daily infant intakes

To determine if specific dietary components had a direct relationship with HM or infant outcomes, we performed repeated measures correlations (Figure 5). After FDR-adjustment, no components of maternal diet were associated with HM composition. Several dietary components showed significant, negative associations with infant daily intake of leptin (Figure 5) including maternal dairy HEI score ($r_{rm} = -0.76$, $p_{rm\ adjusted} = 0.004$), total HEI score ($r_{rm} = -0.70$, $p_{rm\ adjusted} = 0.014$), total fruit HEI score ($r_{rm} = -0.65$, $p_{rm\ adjusted} = 0.021$), total vegetable HEI score ($r_{rm} = -0.68$, $p_{rm\ adjusted} = 0.019$), and greens and beans HEI score ($r_{rm} = -0.72$, $p_{rm\ adjusted} = 0.01$). Conversely, maternal fat intake as a percentage of daily calories was positively associated with infant daily intake of leptin ($r_{rm} = 0.65$, $p_{rm\ adjusted} = 0.021$).

There were also negative associations between maternal dairy HEI score and infant intakes of TNF-α ($r_{rm} = -0.62$, $p_{rm\ adjusted} = 0.019$), IL-6 ($r_{rm} = -0.57$, $p_{rm\ adjusted} = 0.031$), and Lacto-N-hexaose (LNH, $r_{rm} = -0.81$, $p_{rm\ adjusted} = 0.019$).

Maternal total protein intake was negatively associated with infant intakes of the HMOs 6′Sialyllactose (6′SL, $r_{rm} = -0.72$, $p_{rm\ adjusted} = 0.036$), Lacto-N-tetrose (LNT, $r_{rm} = -0.74$, $p_{rm\ adjusted} = 0.03$) and Sialyl-lacto-N-tetraose b (LSTb, $r_{rm} = -0.76$, $p_{rm\ adjusted} = 0.021$).

Adjusted linear mixed effects models were used to investigate the relationships between HEI score components and infant intakes while adjusting for total HEI score (Table 3). The adjusted β coefficients were less than 25% different for the following models: dairy HEI score and daily infant intake of TNF-α (14.5%), and greens and beans HEI score and daily infant intake of leptin (16.5%). Together, these data suggest that the observed relationship between dietary components of maternal HEI scores and infant intakes of human milk components were not dependent on total HEI scores.

4 Discussion

The growing evidence that having overweight and obesity modulates HM composition in ways that can promote infant adiposity (2, 4, 5, 9) warrants the development of interventions that may temper these effects. In this study, we tested the effect of a 4-week Mediterranean meal plan, implemented at 5 months postpartum in women with obesity and demonstrated for the first time that the intervention improved maternal HEI scores and plasma lipid profiles, reduced maternal BMI and fat mass, decreased HM concentrations and infants' intakes of leptin, TNF-α, LNFP II, LNFP-III, DFLNT, total HMOs and HMO-bound fucose. While we observed differences in the concentrations of HM leptin, maternal circulating levels of leptin did not change, indicating other potential avenues for maternal dietary interventions to alter HM composition such as altering leptin production locally in the mammary gland (36). Additionally,

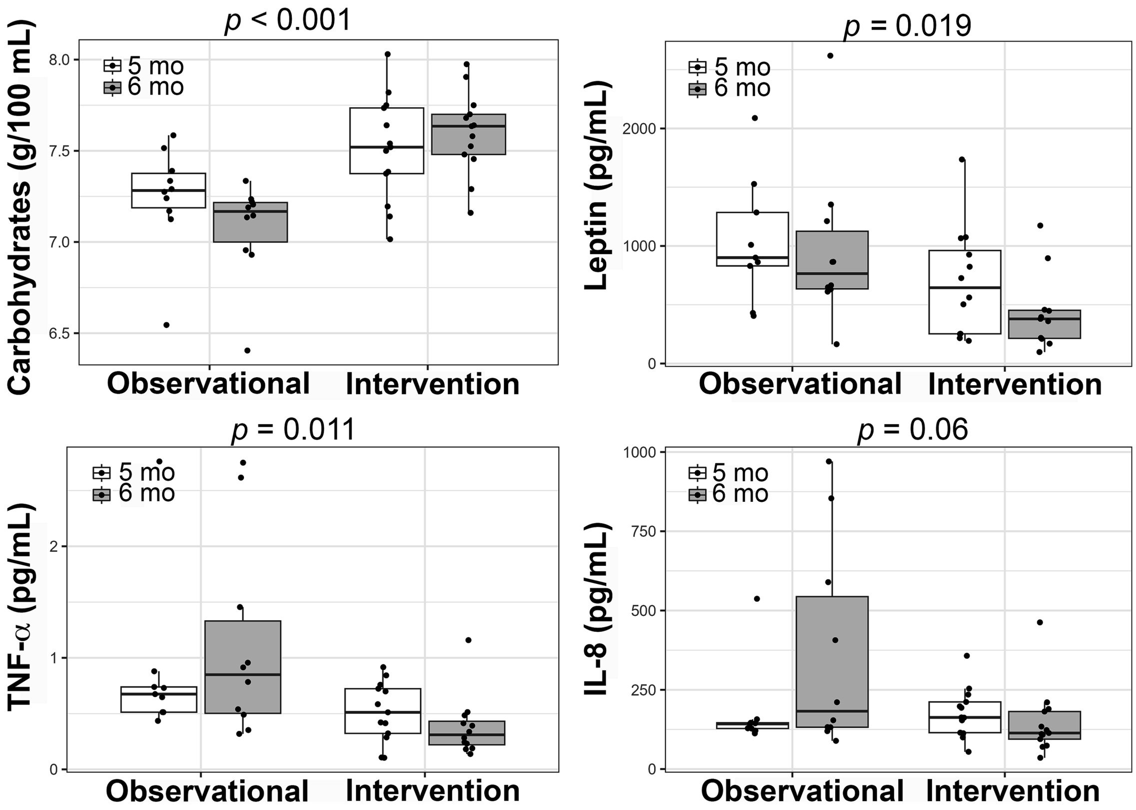

FIGURE 4
Comparison of changes in human milk composition between the within-subjects intervention and an adjacent, observational cohort. Boxplots showing the changes from 5 to 6 months postpartum in each of the studies for carbohydrate, leptin, tumor necrosis factor-α (TNF-α), and interleukin-8 (IL-8) concentrations. Linear mixed-effects models were used to compare the studies and the *p*-values are presented.

we identified individual dietary components (e.g., protein, fat) and HEI score components (e.g., dairy, total fruit) that were significantly associated with intakes of bioactive molecules in HM. These findings provide compelling evidence that dietary interventions during lactation can mitigate obesity-associated alterations in HM composition that may ultimately affect early-life nutritional programing of infant health while promoting maternal health.

4.1 Maternal diet and maternal outcomes

In non-pregnant/non-lactating women with obesity, adherence to a Mediterranean diet has been shown to decrease BMI (16, 17), circulating obesogenic hormones (17), adipokines (18), and systemic inflammation (16, 19). Findings from this study suggest that similar results can be attained in lactating women with obesity, which is of importance to prevent postpartum weight retention and optimize maternal and child health (37). Several randomized controlled trials have demonstrated the efficacy of caloric restriction and/or exercise on weight loss and body composition during the postnatal period, although they failed to evaluate their impact on HM composition or infant health (38). By proxy, replacing habitual post-partum maternal diet with a Mediterranean dietary pattern in our study population resulted in a reduced caloric intake while meeting dietary guideline recommendations. Consistent with our findings, caloric restriction resulted in significant weight loss and improved body composition that was sustained for up to 1 year in some studies (38, 39). Stendell-Hollis et al. also demonstrated that 4 months of a Mediterranean diet or a MyPyramid diet were effective in reducing postpartum maternal weight, fat mass, and plasma TNF-α levels (40). Low-fat diets, and diets that are high in fiber decreased HDL levels in adults with normal weight and overweight/obesity, similar to what we observed in lactating women (41, 42). Future studies will need to elucidate the unique contributions of energy deficit vs. maternal dietary quality to changes in HM composition and their benefits to the child.

4.2 Maternal diet and human milk bioactives

Women with obesity have elevated pro-inflammatory chemokines (2, 11), leptin (2, 3), and insulin (2, 8) HM content compared to peers with normal weight. Importantly, infants' intakes of HM insulin and CRP were significantly and positively associated with their fat mass index (2). It is believed that obesity-related systemic and local (mammary gland microenvironment) inflammation (43) may contribute to elevations in pro-inflammatory cytokines that have been observed in HM from women with obesity (2, 11). While much research has focused on how maternal obesity influences bioactives in HM (10), few studies exist describing the relationships between maternal dietary intake and HM bioactives. In animal models of obesity, caloric restriction has led to decreases in mammary gland

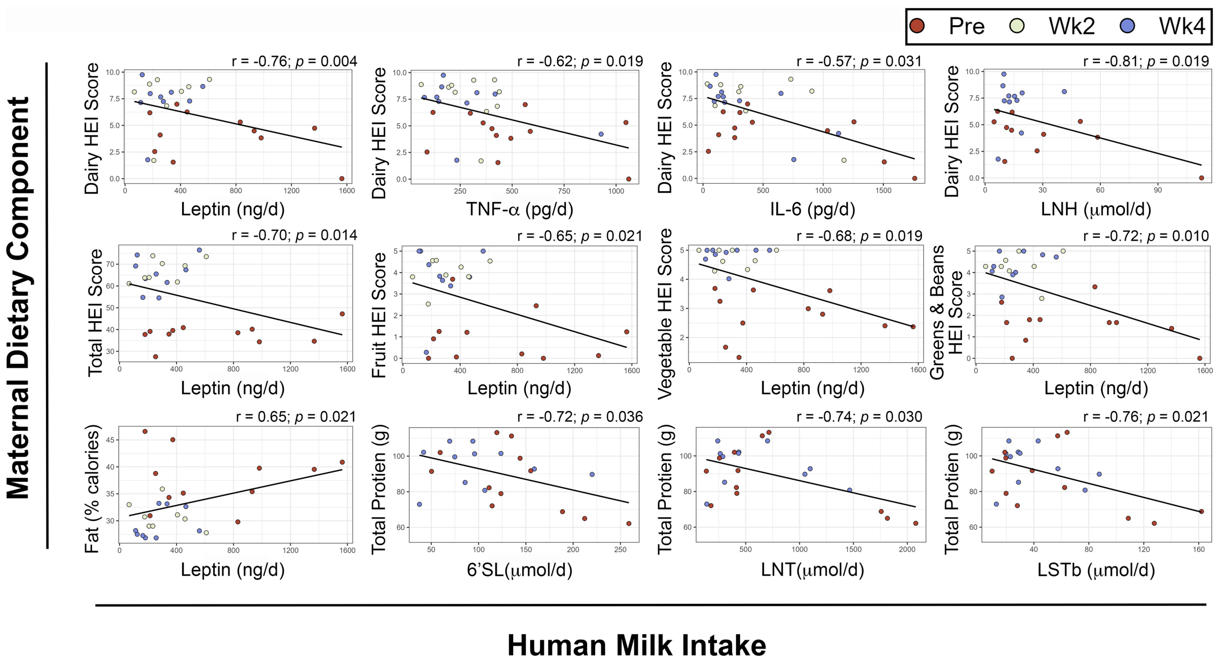

FIGURE 5
Repeated measures correlations between maternal diet components and infant intake of human milk components. Scatterplots showing relationships between maternal dietary components and infant intakes of human milk components. Maternal dietary intake was analyzed using the Nutrition Data System for Research. Infant intakes were estimated at each visit using test weighing and feeding frequency reported by the mothers. FDR-adjusted p-values are presented. HEI: Healthy Eating Index, 6′SL: 6′Sialyllactose, LNT: Lacto-N-tetrose, LSTb: Sialyl-lacto-N-tetraose b, IL: Interleukin LNH: Lacto-N-hexaose, TNF-α: Tumor Necrosis Factor α.

TABLE 3 Summaries of raw and adjusted Healthy Eating Index models.

HEI Component	Infant Intakes	Raw ß	Adjusted ß*	% Difference between raw and adjusted ß
Dairy HEI score	IL-6 (pg/d)	−105.17	−134.65	28.04
Dairy HEI score	Leptin (ng/d)	−85.22	−60.17	29.39
Dairy HEI score	LNH (μmol/d)	−5.84	−7.50	28.39
Dairy HEI score	TNF-α (pg/d)	−50.60	−43.27	14.48
Greens and beans HEI score	Leptin (ng/d)	−122.91	−102.67	16.47
Total vegetable HEI score	Leptin (ng/d)	−160.83	−117.79	26.76
Total fruit HEI score	Leptin (ng/d)	−95.95	−40.88	57.39

HEI, Healthy Eating Index; IL, Interleukin; LNH, Lacto-N-hexaose; TNF-α, Tumor Necrosis Factor α. The bolded values are those that had % differences less than 25%. *Model adjusted for Total HEI Score.

inflammation (43, 44). Our study expands on these findings and demonstrates a reduction in HM pro-inflammatory cytokines (TNF-α and IL-8) from women with obesity who underwent a Mediterranean dietary intervention. In agreement with our current data, improved maternal dietary quality and reduced caloric intake led to lower HM insulin and leptin levels (17). Critically, infant intakes of these HM components were also reduced following the 4-week intervention. In accordance with our study, a previous investigation reported reduced caloric intake for 2 weeks did not result in changes in concentrations or infant intakes of HM macronutrients or in changes in infant weight-for-length, weight-for-age, or length-for-age z-scores, despite changes in infant intakes of leptin and insulin (15). With such an acute intervention, changes in infant growth that could be attributed to HM components would not necessarily be expected. Therefore, future studies that can implement dietary interventions throughout the postnatal period are critical to understanding the potential positive impact such dietary interventions may have on HM composition and subsequent offspring body composition.

We and others have also shown positive associations between maternal obesity and HMO content (4, 45). These associations are important because HMOs are among the most predominant bioactive components in HM, supporting infant gut development (46, 47) and the prevention of infectious diseases (47). However, recent evidence also suggests that some HMOs that are elevated in HM from women with obesity are associated with infant growth (greater weight-for-length Z-scores) and fat accretion (4, 48, 49). While LNFP III was not associated with maternal obesity in our previous study (4), it showed a strong positive association with infant fat mass at 2 months of age (4).

This is important because in the current study, HM concentrations and infant intakes of LNFP III were significantly lower following the dietary intervention. Similarly, previous studies have found significant positive associations between HMO concentrations (disialyllacto-N-tetraose, LNFP II, total HMO concentrations, and total HMO-bound fucose) and infant fat mass at 5–6 months of age (48, 49), many of which were significantly reduced following the Mediterranean diet intervention in this study. It is important to recognize that HMO concentrations change over lactation (50, 51) and change in relation to maternal BMI (4). While these pilot data present compelling evidence for dietary influences on HMOs, our study did not include a prospective control group to test sufficiently the effect of dietary intervention vs. time on HMO concentrations nor did we have time-matched retrospective data on HMO concentrations in our observational cohort.

Previous studies have shown that maternal consumption of fruit, whole grains, and specific fatty acids have been associated with individual HMO concentrations (51–53). Our data are not completely aligned with these previous reports. It is possible that these discrepancies are related to differences in the analyses of dietary intake data (e.g., food frequency questionnaires vs. daily food records), in the timing of sample collection, or in the analytical approaches of the studies. Comparable to our data, Azad et al. reported no significant association between maternal HEI score and HMO concentrations (51). However, Azad et al. did find a weak but significant negative association between maternal total protein intake and LSTb concentrations consistent with the infant intake data presented herein. LSTb showed a strong, positive association with infant fat mass as well as weight-for-length and weight for age Z-scores in our previous study (4), suggesting that maternal protein intake may be a modifiable factor that can be used in future intervention studies to improve infant body composition. A recent short-term crossover study employing four different dietary paradigms (galactose vs. glucose and high carbohydrate vs. high fat) demonstrated a significant association between maternal dietary energy source and the concentrations of HMOs (14) further supporting the notion that interventions focused on specific dietary components may benefit infant health through alterations to HMOs.

4.3 Limitations and strengths

Caution should be taken when interpreting these results because of the small sample size of mainly non-Hispanic White lactating women and the lack of a concurrent control group for comparison. Yet, given the US population-wide exclusive breastfeeding rates at 6 months of 24.9% (54), this study assesses the feasibility of Mediterranean diet pattern implementation in an exclusively breastfeeding cohort of women with obesity. Therefore, reporting data from 13 participants of this population provides foundational knowledge for future Mediterranean diet intervention designs. There is a clear need to conduct randomized control trials to confirm our pilot-study findings and to use standardized methodology to increase reproducibility and rigor of future research. A second limitation is the confounding effect of calorie restriction that occurred by replacing habitual dietary patterns with the Mediterranean diet plan in this study. While this prevents us from exclusively attributing the assessed effects to the change in diet quality, it provides insights to the prevailing nutrient poor, calorie dense habitual diets in the assessed cohort. Furthermore, participants consumed an average of 1841 kcal/d during the intervention, which is in-line with DGA for sedentary women ages 19-50y, as an additional 450–500 kcal/d intake during breastfeeding is only recommended for women aiming to maintain post-partum weight (22). Third, the effects of storage at 4°C of the HM during the 24-h collection at the participants' homes were not investigated. Despite these limitations, this pilot study provides unique results that healthy dietary habits can influence maternal health, HM composition, and children's HM intakes during the postpartum period in women with obesity. There were several significant strengths to this study, including: (1) greater than 80% adherence to the dietary intervention that resulted in significant improvements in maternal diet quality and body composition in only 4 weeks, (2) significant changes in human milk bioactive components and (3) measuring infant HM intakes and acquiring representative milk samples over 24-h to use best practices in estimating infants' exposures. Future studies will need to evaluate a more diverse population, larger cohort, and a longer length of intervention while maintaining isocaloric intakes and body weight from baseline.

4.4 Conclusion

This study is the first to demonstrate the feasibility of implementing a Mediterranean meal plan in lactating women with obesity while examining its impact on human milk composition, infant intake, and infant anthropometrics. This in-depth investigation allows for a better understanding of the dynamic of the breastfeeding triad of mother/milk/infant and how a healthy diet could improve maternal and child health.

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 University of Arkansas for Medical Sciences Institutional Review Board. 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 participant.

Author contributions

CS: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization. JLS: Writing – review & editing, Writing – original draft. AM: Writing – review & editing, Investigation, Formal analysis, Conceptualization. SS: Writing – review & editing, Writing – original draft. MC: Writing – review & editing, Investigation. JB: Writing – review & editing, Investigation, Formal analysis. DT: Writing – review & editing, Investigation, Formal analysis. AF: Writing – review & editing, Investigation. LJ: Writing – review & editing, Writing – original draft. LB: Writing – review & editing, Investigation, Conceptualization. AA: Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The United States Department of Agriculture Agricultural Research Service (USDA ARS) funded the Arkansas Children's Nutrition Center through project plans #6026-51000-010-05S and #6026-51000-012-06S. Arkansas Children's Research Institute/Arkansas Biosciences Institute provided funding through grant GR037121. The National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases partially supported CS and AA through grant R01DK107516. The funding agencies had no role in the design, analysis, interpretation, or presentation of the data and results.

Acknowledgments

We thank the participants and the clinical research team at ACNC for their dedication and hard work in producing and collecting the samples and data presented in this manuscript.

Conflict of interest

JLS is an editorial board member of Frontiers in Pediatrics – Pediatric Obesity.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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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.2024.1303822/full#supplementary-material

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Glossary

6'SL	6'Sialyllactose
BMI	Body mass index
CRP	C-reactive protein
DFLNT	Difucosyllacto-N-tetrose
FFM	Fat free mass
FFMI	Fat free mass index
FM	Fat mass
FMI	Fat mass index
HDL	High density lipoprotein
HEI	Healthy eating index
HM	Human milk
HMO	Human milk oligosaccharides
IL	Interleukin
LDL	Low density lipoprotein
LNFP	Lacto-N-fucopentaose
LNH	Lacto-N-hexaose
LNT	Lacto-N-tetrose
LSTb	Sialyl-lacto-N-tetraose b
TNF-α	Tumor necrosis factor-α
Wk	Week

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 21 March 2024
DOI 10.3389/fpubh.2024.1337822

OPEN ACCESS

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RECEIVED 24 November 2023
ACCEPTED 27 February 2024
PUBLISHED 21 March 2024

CITATION
Mislu E, Kumsa H, Arage MW, Shitie A and Adimasu A (2024) Effective breastfeeding techniques and associated factors among lactating women: a community-based study, north east Ethiopia.
Front. Public Health 12:1337822.
doi: 10.3389/fpubh.2024.1337822

Effective breastfeeding techniques and associated factors among lactating women: a community-based study, north east Ethiopia

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Background: Effective breastfeeding techniques, which include proper attachment, positioning, and suckling, offer a range of benefits for both the mother and the infant. These techniques ensure efficient milk transfer, reduce the risk of infections, support optimal infant weight gain, enhance maternal comfort, and foster a strong emotional bond. This study aimed to identify the magnitude and factors associated with effective breastfeeding techniques among lactating women in the Legambo district of South Wollo, Ethiopia, in 2022.

Methods: A community-based cross-sectional study was conducted from September to November 2022. Samples were selected using a multi-stage sampling method from 18 wards (kebele). Data were collected using an interviewer-administered structured questionnaire and an observational checklist. The collected data were entered into Epi-Data and then exported to SPSS version 25.0 for analysis. Descriptive statistics and bivariate and multivariable logistic regression analyses were performed to identify the magnitude and associated factors. Variables with a p-value less than 0.05 on multivariable analysis were considered independent factors associated with the outcome variable.

Results: Six hundred and ten lactating women were included for observation and interviewed, resulting in a 96.2% response rate. The magnitude of effective breastfeeding technique practice was found to be 25.9% (95% CI: 22.47–29.57%). Factors associated with effective breastfeeding technique practice included being a working woman (AOR = 1.70; 95%CI: 1.07–2.72), age between 26 and 30 years (AOR = 0.37; 95%CI: 0.16–0.84), urban residence (AOR = 1.59; 95%CI: 1.06–2.39), initiating breastfeeding 1 to 2 h after birth (AOR = 0.27; 95%CI: 0.16–0.43), and initiating breastfeeding after 2 h of birth (AOR = 0.34; 95%CI: 0.17–0.67). Additionally, not receiving breastfeeding education (AOR = 0.46; 95%CI: 0.30–0.72) and experiencing current breast problems (AOR = 0.28; 95%CI: 0.28–0.75) were also found to have a significant association with effective breastfeeding technique practice.

Conclusion: Only one in four women demonstrated effective breastfeeding techniques, indicating that their practice was below the WHO's recommendations. Therefore, it is crucial to consider the identified variables to improve the practice of effective breastfeeding techniques.

KEYWORDS

effective breastfeeding techniques, good attachment, good positioning, good suckling, breastfeeding

Introduction

Breastfeeding is the practice of feeding a child directly from the breast or through expressed milk by hand or with a pump (1, 2). It is a natural and essential practice that provides optimal nutrition and promotes the overall health and development of infants (1–3). The World Health Organization (WHO) and the Ethiopian Federal Ministry of Health recommend initiating breastfeeding within the first hour of a baby's life and exclusively breastfeeding for the first 6 months. After 6 months, breastfeeding should be continued along with appropriate complementary feeding for up to 2 years and beyond (1, 2). Implementing these recommendations has the potential to prevent approximately 820,000 deaths of children under the age of 5 annually in low- and middle-income countries, where the burden of under-five mortality is high (4).

Breastfeeding has numerous short-term and long-term benefits for the mother and the child. It decreases the risk of infection, sudden infant death syndrome, asthma, food allergies, and diabetes for the baby while also improving cognitive development and decreasing the risk of obesity in adulthood (4–6). For the mother, breastfeeding offers benefits such as a decrease in postpartum hemorrhage, depression, and facilitation of involution. In the end, it also reduces the risk of breast cancer, cardiovascular disease, diabetes, metabolic syndrome, and rheumatoid arthritis (6–8).

Effective breastfeeding technique is a process of breastfeeding that occurs when the baby and mother show readiness for it, and the baby is appropriately positioned, has good attachment, and has good suckling (9, 10). Effective breastfeeding techniques are essential for women to feed their babies without pain, in a simple, safe, and time-saving manner (9). Proper attachment, positioning, and suckling during breastfeeding offer a range of benefits for both the mother and the infant. These components ensure efficient milk transfer, prevent nipple soreness and discomfort, reduce the risk of infections, support optimal infant weight gain, and enhance maternal comfort (10, 11).

Furthermore, practicing effective breastfeeding techniques fosters a strong emotional bond between the mother and the baby (9). Physical closeness, eye contact, and skin-to-skin contact during breastfeeding stimulate the release of oxytocin, a hormone that promotes feelings of love, nurturing, and attachment. This bonding experience contributes to the emotional wellbeing of both the mother and the infant (12). Emphasizing and supporting this aspect of breastfeeding is crucial to enhance successful breastfeeding outcomes and improve the overall health and wellbeing of both the mother and infant (10–12).

Promoting effective breastfeeding practices is of utmost importance in Ethiopia, where infant mortality rates remain a significant concern. However, there is a notable disparity in the prevalence and factors associated with effective breastfeeding techniques among different populations. Furthermore, most previous studies have been conducted in institutional settings. Therefore, this study aims to bridge these gaps by investigating the magnitude and factors associated with effective breastfeeding among lactating women in the Legambo district of South Wollo, Ethiopia, in 2022. The findings from this study will provide valuable insights to develop targeted interventions aimed at improving breastfeeding outcomes and enhancing the overall health and wellbeing of both mothers and infants, reducing healthcare costs, and fostering a sustainable environment in the region.

Materials and methods

Study setting

A community-based cross-sectional study was conducted in Legambo District, South Wollo Zone, from September to November 2022. The district is situated 450 km away from Bahir Dar, the capital city of the Amhara region, and 601 km from Addis Ababa, the capital city of Ethiopia. Legambo District comprises 41 wards, of which 38 are rural wards (kebeles) and three are urban wards. The district is equipped with 1 general hospital, 9 health centers, and 39 health posts (13).

Study population

The study included all lactating women who had given birth in the past 6 weeks and were living in selected wards of the district.

Eligibility criteria

All postnatal women who were breastfeeding during the study period were included. However, mothers of infants with serious illnesses that affect breastfeeding, such as inability to suck, lethargy, and unconsciousness, were excluded.

Sample size determination

The sample size was calculated using the single population proportion formula, assuming a 95% confidence interval, a 5% margin of error, and an estimated magnitude of effective breastfeeding of 48% based on a previous study in Gondar town (14). The margin of error was set at 1.5.

The formula used was: Sample size = [(Z1-α/2)2*P(1-P)]/d2.

where:

Abbreviations: AOR, adjusted odds ratios; COR, crude odd ratio; CI, confidence interval; WHO, World Health Organization; EBF, exclusive breastfeeding; PNC, postnatal care.

- (Z1-α/2) is the standard normal variation.
- P is the proportion in the population (48%).
- d is the margin of error (0.05).

The calculated sample size without considering design effect and non-respondents was 384. Taking into account a design effect of 1.5 and a 10% non-response rate, the final sample size was determined to be 634 postnatal mothers.

Sampling procedure

A multi-stage sampling method was employed. Initially, 18 wards (16 rural and 2 urban) were selected from the total using the lottery method. The target sample size was then proportionally allocated to each of the selected wards. Finally, study participants were recruited using a simple random sampling method, with the registration book at health posts serving as the sampling frame.

Operational definition

- *Effective breastfeeding technique*: The achievement of at least two criteria from positioning, three criteria from attachment, and two criteria from suckling while breastfeeding their infant (15).
- *Breast problems*: A woman who had one or more of the following six conditions: inverted nipple, flat nipples, cracked nipples, engorgement, mastitis, and breast abscess.
- *Poor, average, and good positioning*: Women who fulfill none or only one, any two, and all four/three out of four criteria were considered as poor, average, and good positioning, respectively (15). The criteria were as follows: the baby's head and body are in line; the baby is held close to the body; the baby's whole body is supported with the arm along their back; and the baby approaches breast nose to the nipple so that it comes to the breast from underneath the nipple (15).
- *Poor, average, and good attachment*: Women who fulfilled none or only one criterion, any two criteria, and all four/three criteria out of four criteria for infant attachment were considered as poor, average, and good attachment, respectively (15).
- *Poor suckling*: Women who do not achieve any or only one of the three criteria (slow and regular suckling, deep suckling, and sometimes pausing) (15).
- *Deep suckling*: A suckling demonstrated by visible or audible swallowing after every one or two sucks (14).
- *Good knowledge about the benefits of breastfeeding*: Women who correctly answered seven or more out of 13 questions were considered to have good knowledge about the benefits of breastfeeding (16).

Data collection tools and procedure

Data were collected using an interviewer-administered structured questionnaire and an observational checklist. The questionnaire included socio-demographic, obstetric, breastfeeding, and breast problem-related questions. The observational checklist was used to assess the woman's and baby's position, attachment, and suckling during breastfeeding, following the WHO's breastfeeding checklist (14, 17). The data collection tools were developed after reviewing relevant literature to address important variables related to the main objective (12, 16, 18–22). Ten trained female bachelor (BSc.) degree midwives and two supervisors were employed as data collectors. They observed the breastfeeding practice of each mother for 4 min and recorded it on the observation checklist form. Written informed consent was obtained from all participants before the interview and observation, and confidentiality was assured throughout the study process.

Data quality control

To ensure data quality, both the data collectors and supervisors received 2 days of training before data collection. Language experts translated the English version of the questionnaire into the local language (Amharic). Additionally, a pre-test was conducted on 5% (32 mothers) of the sample size before the actual data collection. The tool was modified and corrected based on the pre-test results. Each questionnaire was checked for completeness before data entry, and the data were then edited, coded, and entered into Epi Data version 4.6.1. Double entry was performed, and entry errors were checked and corrected accordingly.

Data processing and analysis

The data were analyzed using SPSS version 25.0. Descriptive statistics such as frequency, percentage, mean, and standard deviation were calculated and presented in tables, figures, and text. Bivariate and multivariable logistic regression analyses were conducted to identify factors associated with effective breastfeeding. Variables with p-values less than 0.25 in the bivariate analysis were included in the multivariable logistic regression to examine the relative effect of confounding variables and variable interactions. Variables with p-values less than 0.05 in the multivariable analysis were considered independent factors associated with the outcome variable. The omnibus test of model coefficients and the Hosmer and Lemeshow goodness-of-fit test were used to assess model fitness, with p-values of 0.000 and 0.851, respectively. Variance inflation factor (VIF) and tolerance tests were also conducted to check for multicollinearity among the explanatory variables, with the highest VIF at 1.18 and the lowest tolerance test at 86.7%.

Results

Socio-demographic characteristics of study participants

Six hundred and ten lactating women were observed and interviewed for effective breastfeeding, with a response rate of 96.2%. The participants' mean age (±SD) was 25.69 (±6.014) years. The majority of respondents, 471 (77.2%), were housewives, 327 (53.6%) were rural dwellers, and 545 (89.3%) were married. Only 115 (18.8%) had a secondary or higher degree of education (Table 1).

TABLE 1 Socio-demographic characteristics of study participants in Legambo District, North-East Ethiopia, 2022 ($n = 610$).

Variables	Frequency	%
Age of the mothers		
<20	67	11.0
20–25	278	45.6
26–30	162	26.6
˃30	103	16.9
Residence		
Rural	327	53.6
Urban	283	46.4
Level of education		
No formal education	266	43.6
Primary education	229	37.7
Secondary education	80	13.1
More than secondary	35	5.7
Marital status		
Married	545	89.3
Not married	65	10.7
Occupation		
Housewife	471	77.2
Working	139	22.8

Obstetrics characteristics of the respondents

Three-hundred and eighty (62.3%) of the total participants were multipara, and 56 (9.2%) gave birth at home. Seventy-five percent (456%) of the study participants received prenatal care (ANC). In terms of mode of delivery, 517 (84.8%) were spontaneous vaginal deliveries. Infants were born at term in 534 (87.5%) of the cases, and 554 (90.8%) of postpartum women had no history of breast problems (Table 2).

TABLE 2 Obstetrics characteristics of the participants for the study conducted in Legambo District, North East Ethiopia, 2022 ($n = 610$).

Variables	Frequency	Percent (%)
Parity		
Primipara	230	37.7
Multipara	380	62.3
Place of birth		
Home	56	9.2
Health institution	554	90.8
Mode of delivery		
Vaginal delivery	517	84.8
Cesarean delivery	93	15.2
GA in complete weeks		
Preterm	104	17.0
Term	506	83.0
Previous history of breast problems		
Yes	56	9.2
No	554	90.8
ANC follow-up		
Yes	456	74.8
No	154	25.2
PNC follow-up		
Yes	500	81.97
No	110	18.03
GA-Gestational age		

Breastfeeding characteristics of the study participants

Merely 74 (12.1%) of the total participants began breastfeeding within an hour after birth, whereas 236 (61.3%) of them got health education on the topic. Approximately 38.2% of the total participants were postpartum nursing mothers who mixed-fed their kids at the time of the interview with other foods and liquids in addition to breast milk (Table 3).

Magnitude of effective breastfeeding

In this study, 358 (58.7%), 337 (55.2%), and 416 (68.2%) women demonstrated good positioning, attachment, and suckling, respectively. The practice of effective breastfeeding techniques was identified among 158 women, which accounts for a magnitude of 25.9% with a 95% confidence interval ranging from 22.47 to 29.57%. The remaining 452 (74.1%) women exhibited ineffective breastfeeding practices.

Factors associated with effective breastfeeding

Bi-variable and multivariable logistic regressions were performed. In the bi-variable analysis, 14 variables (occupation, age of mothers, residence, marital status, place of birth, parity, gestational age, mode of delivery, previous breast problem history, receiving BF education, breastfeeding experience, type of feeding, current breast problem, and BF initiation time) had p-values less than 0.25. These 14 variables were adjusted to each other on the multivariable logistic regression to identify the AOR with their 95% confidence interval. In the multivariable logistic regression analysis, age, residence, and occupation of the mothers, breastfeeding initiation time, receiving BF education, and current breast problem retained their association with effective breastfeeding at a p-value less than 0.05 (Table 4).

Discussion

The magnitude of effective breastfeeding among lactating women in the study area was 25.9% (95% CI: 22.47, 29.57). This result is consistent with a study conducted in Madhya Pradesh, India (31.4%)

TABLE 3 Breastfeeding characteristics of the participants for the study conducted in Legambo District, North East Ethiopia, 2022 (n = 610).

Variables	Frequency	Percent (%)
Received BF education		
No	236	38.7
Yes	374	61.3
Time of breastfeeding initiation		
Within 1 h	174	28.5
2–3 h	384	63
First day (4–24 h)	49	8
At or After 24 h	3	0.5
Type of feeding		
Exclusive breastfeeding	377	61.8
Mixed feeding	233	38.2
Previous breastfeeding experience		
Yes	295	48.4
No	315	51.6
Mother knowledge on benefits of BF		
Good knowledge	346	56.7
Poor knowledge	264	43.3
Source of information on breastfeeding		
Friends and family	341	55.9
Healthcare providers	160	26.2
Audiovisual*	109	17.9
Breast problem		
Yes	316	54.3
No	294	45.7

Audiovisual*: Radio, TV, Newspaper, and Internet.

(23). However, it is lower than the findings of studies conducted in Southeast Nigeria (49%) (24), Gondar town health facilities (48%) (14), Harar city (43.4%) (25), South Ari district 36.5% (26), and Gidan district, Ethiopia (42.9%) (16). This difference could be attributed to the fact that the current study was community-based, and the district had a higher proportion of rural population than urban areas (27). Additionally, the educational levels of the participants in this study were generally lower, and a significant proportion of them were housewives. This factor might have affected the knowledge and practice of breastfeeding among the participants. Factors such as cultural beliefs, lack of awareness, and inadequate support systems could also contribute to the lower prevalence of effective breastfeeding observed in this study (28, 29).

In contrast, the magnitude of effective breastfeeding in this study is higher than that reported in a study conducted in a resettlement colony of Delhi (7.5%) (30). This difference might be attributed to several factors, including poor knowledge about the importance and benefits of effective breastfeeding, lack of breastfeeding-friendly workplaces, lack of support from family members, and harmful traditional practices. Additionally, limited access to healthcare, including comprehensive breastfeeding education and counseling programs, as well as inadequate postnatal and prenatal care for women living in resettlement areas, may contribute to this disparity (31, 32).

This study also found that working women had 1.7 times higher odds of practicing effective breastfeeding than housewives. Similar results were reported in studies conducted in Puducherry, India (33) and rural areas of Gandhinagar, India (34). This could be due to factors such as lower educational levels, reduced opportunities to attend breastfeeding-related health education sessions provided by healthcare providers, and vulnerability to traditional practices that discourage effective breastfeeding. Moreover, social isolation, lack of support from family members, lack of confidence in breastfeeding, and limited exposure to effective breastfeeding role models might result in lower effective breastfeeding practices among housewives.

Similarly, women residing in urban areas had 1.59 times higher odds of practicing effective breastfeeding techniques than those in rural areas. This could be attributed to higher educational levels, better access to breastfeeding advice, more exposure to breastfeeding role models, and access to healthcare services for any concern related to breastfeeding in urban areas.

Women aged between 26 and 30 years had 63% lower odds of practicing effective breastfeeding techniques than women aged 35 years and above. This finding is consistent with studies conducted in Southeast Nigeria (24), Puducherry, South India (33), and Gidan district, Ethiopia (16). The lower odds among younger women might be attributed to a lack of experience, lack of role models, lack of awareness about the benefit of effective breastfeeding, lack of time management due to multiple responsibilities, and their vulnerability to traditional practices.

The odds of practicing effective breastfeeding techniques were 54% lower among women who did not receive education on breastfeeding compared to those who did. This finding is also supported by studies conducted in Southeast Nigeria (24), Puducherry in South India (33), Vadodara in western India (35), and South Ari district (26), Harar city (25), Arbaminch Zuria (36), and Gondar town in Ethiopia (14). This might be because education creates awareness and promotes behavioral modifications, enabling women to understand the importance of proper breastfeeding techniques. Education also helps women anticipate challenges they may face during breastfeeding and equips them with strategies to overcome them. Moreover, it encourages women to seek support from family members, prioritize breastfeeding, and develop self-esteem, contributing to improved breastfeeding practices (18, 37, 38).

Women who initiated breastfeeding within 2 h had 73% lower odds of practicing effective breastfeeding than those who initiated breastfeeding within the first hour after giving birth. Similarly, women who breastfed after 2 h had 66% lower odds. The possible explanation for this might be that women who initiate breastfeeding later may have missed opportunities for guidance and support from healthcare professionals at the time of delivery, leading to a lack of knowledge about breastfeeding. Additional factors that can contribute to delayed initiation and lower rates of effective breastfeeding include breast problems, home deliveries, and complicated deliveries that require medical interventions. These factors can disrupt the natural process of early breastfeeding initiation and make it more challenging for women to establish effective breastfeeding practices (39–41).

Furthermore, women with current breast problems had 54% lower odds of practicing effective breastfeeding than women without

TABLE 4 Bi-variable and multivariable analysis of factors associated with effective breastfeeding techniques among postnatal lactating mothers in Legambo District, North East Ethiopia, 2022 (n = 610).

Variables		Effective breastfeeding		COR (95%CI)	AOR (95%CI)	p-value for AOR
		No	Yes			
Occupation	Housewife	360 (76.4%)	111 (23.6%)	Ref.	Ref.	
	Working	92 (66.2%)	47 (33.8%)	1.65 (1.09–2.49)	**1.70 (1.07–2.72)***	**0.024**
Age of mothers	≤ 20	48 (70.6%)	20 (29.4%)	0.94 (0.42–2.10)	0.60 (0.23–1.50)	0.278
	20–25	173 (71.2%)	70 (28.8%)	0.91 (0.47–1.78)	0.76 (0.36–1.61)	0.477
	26–30	140 (80.5%)	34 (19.5%)	0.55 (0.27–1.12)	**0.37 (0.16–0.84)***	**0.018**
	30–35	57 (75%)	19 (25%)	0.75 (0.34–1.68)	0.69 (0.28–1.68)	0.415
	≥35	34 (69.4%)	15 (30.6%)	Ref.	Ref.	
Residence	Rural	255 (78%)	72 (22%)	Ref.	Ref.	
	Urban	197 (69.6%)	86 (30.4%)	1.54 (1.07–2.22)	**1.59 (1.06–2.39)***	**0.024**
Marital status	Married	399 (73.2%)	146 (26.8%)	Ref.	Ref.	
	Not married	53 (81.5%)	12 (18.5%)	0.61 (0.32–1.19)	0.50 (0.24–1.05)	0.068
Place of birth	Home	47 (87.0%)	7 (13.0%)	0.39 (0.17–0.90)	0.50 (0.20–1.27)	0.148
	HI[a]	405 (72.8%)	151 (27.2%)	Ref.	Ref.	
Parity	Primi	180 (78.6%)	49 (21.4%)	Ref.	Ref.	
	Multi	272 (71.4%)	109 (28.6%)	1.47 (1.00–2.16)	0.78 (0.47–1.28)	0.327
Gestational age	Preterm	44 (84.6%)	8 (15.4%)	0.49 (0.22, 1.07)	1.12 (0.45–2.74)	0.800
	Term	408 (73.1%)	150 (26.9%)	Ref.	Ref.	
Delivery mode	Vaginal	388 (75%)	129 (25%)	Ref.	Ref.	
	CS	64 (68.8%)	29 (31.2%)	1.36 (0.84–2.20)	1.58 (0.89–2.72)	0.115
Hx[b] of breast problem	Yes	33 (58.9%)	23 (41.1%)	2.16 (1.22–3.81)	0.83 (0.42–1.63)	0.601
	No	419 (75.6%)	135 (24.4%)	Ref.	Ref.	
Breastfeeding initiation time	<=1 h	98 (57%)	74 (43%)	Ref.	Ref.	
	1–2 h	295 (81.5%)	67 (18.5%)	0.30 (0.20–0.45)	**0.27 (0.16–0.43)*****	**0.000**
	>2 h	59 (77.6)	17 (22.4%)	0.38 (0.20–0.70)	**0.34 (0.17–0.67)****	**0.002**
Receiving BF education	No	190 (80.9%)	45 (19.1%)	0.54 (0.37–0.81)	**0.46 (0.30–0.72)****	**0.001**
	Yes	262 (69.9%)	113 (30.1%)	Ref.	Ref.	
BF experience	Yes	209 (70.8%)	86 (29.2%)	1.38 (0.96–1.99)	1.05 (0.70–1.59)	0.792
	No	243 (77.1%)	72 (22.9%)	Ref.	Ref.	
Breast problem	Yes	272 (82.2%)	59 (17.8%)	0.39 (0.27–0.57)	**0.46 (0.28–0.75)****	**0.002**
	No	180 (64.5)	99 (35.5%)	Ref.	Ref.	
Feeding type	EBF	270 (71.6%)	107 (28.4%)	Ref.	Ref.	
	Mixed	182 (78.1%)	51 (21.9%)	0.70 (0.48–1.03)	0.83 (0.53–1.31)	0.439

Keys: *Statistically significant at p-values < 0.05; **at p-values < 0.01; ***at p-values < 0.001.
HI[a], health institution; Hx[b], history; Ref., Reference group.

breast problems. This finding is consistent with studies conducted in South Ari district (26), Harar city (25), and Gondar town (14) in Ethiopia. The possible reasons might be that women who do not practice effective breastfeeding may develop breast problems, or having breast problems may hinder their ability to practice effective breastfeeding (42).

Similar studies conducted in different parts of the world identified variables such as maternal level of education (24–26), parity (17, 26, 34, 35), antenatal care (16, 24), baby's birth weight (34, 43), preterm birth (34, 43), early initiation of complementary feeding (36), poor knowledge on breastfeeding (36), postnatal visit (16, 25), previous breastfeeding experience (25), and place of delivery (16, 26) for having association with effective breastfeeding practice. However, these were not identified in the current study.

While interpreting the findings from this study, it is important to consider the limitations of the current study. These include the possibility that female participants may have behaved differently because they were aware of being observed despite attempts to conceal the checklists. Additionally, the outcome of effective breastfeeding practice in the neonate was not addressed in this study, such as weight gain, growth and development, malnutrition, respiratory and diarrheal diseases, and maternal–infant bonding.

Conclusion and recommendations

Only one in four women demonstrated effective breastfeeding techniques, indicating their practice was below the WHO's recommendation. Maternal age, women's occupation, lack of education about breastfeeding, and experiencing breast problems were found to be significantly associated with ineffective breastfeeding practice. Therefore, providing education on breastfeeding through promoting educational programs during the antenatal and postnatal periods and early management of breast problems will benefit women in practicing effective breastfeeding techniques. It is also better for future researchers to consider interventional studies by using breastfeeding counselors.

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 Ethical review board of Wollo University College of medicine and Health Sciences (Ref. No CMHS/004/13). 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

EM: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. AS: Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis. HK: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. MA: Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Data curation. AA: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors would like to thank all respondents and data collectors who participated in this study.

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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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 30 April 2024
DOI 10.3389/fnut.2024.1334428

Check for updates

OPEN ACCESS

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RECEIVED 07 November 2023
ACCEPTED 08 April 2024
PUBLISHED 30 April 2024

CITATION
Gogojewicz A, Pilaczyńska-Szcześniak Ł, Popierz-Rydlewska N, León-Guereño P and Malchrowicz-Mośko E (2024) Assessment of nutritional status and health behaviors in yoga-trained women versus exercisers.
Front. Nutr. 11:1334428.
doi: 10.3389/fnut.2024.1334428

Assessment of nutritional status and health behaviors in yoga-trained women versus exercisers

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Introduction: Recreational physical activity is becoming more popular due to the increased public awareness about the beneficial effects on health status and quality of life. The aim of the study was to assess the nutritional status and health behaviors of women who regularly practice yoga as a form of physical recreation and to compare them with those who had not practiced before and had just signed up for yoga classes. A total of 143 women took part in this study.

Methods: The nutritional status was assessed based on the obtained anthropometric measurements. The following indicators were calculated: Body Mass Index (BMI) and waist-to-hip ratio (WHR), determining the visceral accumulation of fat tissue. Health behaviors were assessed using a standardized five-point scale Health Behavior Inventory (HBI).

Results: There were significant differences in the value of the general health behavior index, the sten scale, and the subscale regarding proper eating habits in the study groups compared to women who had not practiced yoga before (control group). Health behaviors indicators, particularly proper eating habits, are significantly higher in women participating regularly in yoga exercises, indicating a higher awareness among yoga practitioners.

Conclusion: It can be suggested that yoga participation as a recreational physical activity can be an appropriate option for pursuing healthy habits.

KEYWORDS

yoga, health behaviors, nutritional status, physical activity, healthy lifestyle

1 Introduction

Recreational forms of physical activity are becoming very popular (1–3). There is increasing awareness of the beneficial impact of physical activity on mental and physical health and on improving the quality of life. In recent years, the number of people practicing it regularly has increased due to its health benefits (4–7). Lifestyle and related health behaviors are important factors determining health (8). Health behavior is any intentional action taken by an individual whose aim is to maintain or increase health potential, regardless of its effectiveness (9). Health behaviors cause specific positive or negative health effects in people implementing them (10). Personal habits related to physical activity, healthy habits, healthy eating and motivation are of interest to contemporary researchers (11). In recent years, yoga has been one of the most popular forms of physical activity. Yoga is an ancient Indian system of philosophy, a mind–body discipline encompassing an array of philosophical precepts, mental attitudes, and physical practice. The most popular hatha yoga covers many different styles. In the most popular Iyengar or Ashtanga practitioners in asanas focus on the detailed positioning of bodies. Both styles of yoga are rich in asanas, and ashtanga also focuses on breathing control during practice (12). Research from other authors confirms the pleiotropic effect of yoga on the human body, including the circulatory system, and alleviates the effects of diseases of the musculoskeletal system (13–18). Yoga improves lung function, strength of respiratory and expiratory muscles as well as skeletal muscle strength and endurance (19). Yoga is also recommended for patients with non-communicable disease such as cancer (20). Currently, it is also one of the most frequently used therapies for people with depressive disorders (21).

The role of yoga in ecology and nutrition for sustainable healthy living is very important as well (22, 23). Yoga can support overweight people in eating healthier and increasing physical activity, which ultimately leads to a lower BMI (24). Chin-Cheng et al. (25) indicated in the studies among students in Yogalates class the effectiveness of multimedia-assisted learning. Perhaps it is worth knowing that this type of teaching model is included in the physical education programs, which influenced the use of functions after inclusion and the formation of activity habits (25). Yoga can also be an excellent form of activity in improving the physical fitness of children in early childhood (26). Studies suggest that yoga participation can be associated with mindful eating and the adoption and maintenance of other positive health-related outcomes such as regular physical activity and weight management (27). The results of the Watts et al. (28) study confirm that yoga is a promising intervention aimed at improving the health of overweight people. Regular yoga practice can support the development of physical activity habits and healthy eating patterns, which in turn is associated with greater body awareness (28).

At the same time, however, yoga has also been criticized for sometimes overly expecting yoga practitioners to pay excessive attention to diet and food quality. Some studies suggest that yoga teachers should avoid excessive reference to a healthy diet, which is component of yoga practice (29). In Domingues and Carmo's (30) study, interest in a healthy diet among the population of yoga practitioners was one of the strongest predictors of orthorexia nervosa. People who often control their body weight and use techniques common among yogis, such as cleansing, detox, fasting or vegetarian diets, are particularly susceptible to eating disorders (30). In a study conducted by Erkin and Gol (31) among yogis practicing in Turkey, it was found that the vast majority of yoga practitioners are at risk of orthorexia, and some factors, such as marital status and the presence of chronic diseases, significantly influence the tendency to mental orthorexia in yoga practitioners. Even though yoga provides several benefits, it is not clear whether the practice of yoga is associated with proper nutritional and health habits. Yoga can provide many health benefits, and studies comparing the effects of yoga and other forms of activity indicate that yoga may be as or even more effective than other physical activities in improving various indicators of health outcomes. Future research is therefore needed to examine the differences between yoga and other forms of physical activity in terms of their impact on physical and mental health (32).

Therefore, the objective of the present study is to assess the nutritional status and health behaviors of women practicing yoga as a form of physical recreation, and to compare them with those who had not practiced before and just signed up for yoga classes.

2 Materials and methods

2.1 Participants, design and procedure

The study involved women aged 30–59, members of yoga clubs and fitness clubs from the Greater Poland Voivodeship. Of the 143 respondents, 68 regularly practiced yoga and 75 had no previous experience with yoga. Women from the control group used other forms of recreation, such as walking, swimming, aerobics, aqua fitness and Nordic walking. Both groups had similar training experience and duration (at least 2 years). Both groups were homogeneous in terms of anthropometric characteristics. The respondents who participated in the study had been attending yoga classes or other kinds of classes (aerobic, Nordic Walking, etc.) at least twice a week regularly for 90 min for two years or more.

The yoga classes were conducted by qualified instructors. The leading style was Ashtanga Yoga, one of the forms of Hatha and Iyengar Yoga, the most popular in Poland. This practice is characterized by great attention to the precision of body positioning in the asana. Great importance is attached to proper breathing in positions. The Iyengar method uses many different yoga aids, e.g., blocks and straps, to help practitioners correctly position their bodies (33).

Yoga instructors provided their groups with information about the planned research. Leaflets describing the research were left at the places of classes. Interested persons received detailed information about the purpose and method of research carried out by the research supervisor. Participants were allowed to familiarize themselves with all testing procedures and provided written informed consent before the study. The study protocol was reviewed and approved by the Bioethics Committee at the Poznan University of Medical Sciences (reference number 824/10) and was performed in accordance with the Declaration of Helsinki.

2.2 Variables and instruments

2.2.1 Nutritional status

Body weight and height were measured on an in a fasting state using a certified Radwag device (Radom, Poland) with an accuracy of 0.01 kg and in the case of body height 0.5 cm. Waist and hip circumference were measured according to World Health Organization (WHO) recommendations (34) using a non-stretchable measuring tape. Based on the obtained measurement results, the following indices were calculated: BMI and WHR. The BMI classification recommended by the WHO was used to interpret the results (34).

2.2.2 Health behaviors

Health behaviors were assessed using the five-point scale Health Behavior Inventory (HBI) by Juczyński (35). This questionnaire is a Polish, standardized tool for measuring the overall intensity of health practices. Questionnaire contains 24 statements describing health-related behaviors, which are divided into 4 categories: proper eating habits, preventive behaviors, health practices and positive mental attitude. The statements were assessed, respectively, using a five-point response scale: 1-almost never, 2-rarely, 3-from time to time, 4-often, 5-almost always. The obtained points were summed up. The general index of the intensity of health behaviors measured by the HBI scale ranges from 24 to 120 points. The higher the score, the greater the intensity of the declared health behaviors. The obtained number of points was converted to the sten scale. Low scores are (1–4 sten), average (5–6 sten) and high (7–10 sten). The reliability of the HBI is Cronbach's $\alpha = 0.85$, and its four subscales range from 0.60 to 0.65.

2.3 Statistical analysis

The obtained data were subjected to statistical analysis using the Statistica version 13.3 (TIBCO Software Inc., Palo Alto, CA, United States). Data are presented as means, standard deviations (SD), minimum and maximum (min ÷ max). The Shapiro–Wilk test was used to check the data for normal distribution. Comparisons of normally distributed variables between the two groups were assessed using Student's t test and the Mann–Whitney test was used for non-normally distributed variables. A p-value <0.05 was considered significant.

3 Results

Table 1 shows a comparative analysis of anthropometric characteristics indicates the lack of statistically significant differences, which proves the high similarity of both groups in terms of somatic structure. All women declared good health condition.

The average value of BMI and WHR for the study and control groups is within the reference values. However, the analysis of the distribution of BMI values revealed that in the assessed groups there were women whose BMI exceeded 25 kg/m^2.

The research results showed that study groups' the average health behaviors and proper eating habits differ significantly between the study groups (Table 2). Women who regularly participate in yoga classes are characterized by a significantly higher value of the health behavior index, the raw score of which for the study group was on average 90.2 ± 12.74 points, and in the control group 84.7 ± 10.82 ($p < 0.01$). Proper eating habits are significantly higher in the group of women participating regularly in yoga exercises as well.

The results presented in Table 2 show that although the group of women attending yoga classes regularly obtained higher results in all tested subscales compared to the control group, significant differences were observed only in the case of proper eating habits.

The research results indicate that in the group of women exercising yoga regularly, health behaviors assessed with the sten scale turned out to be significantly higher ($p = 0.0177$) compared to the control group (Figure 1).

4 Discussion

The aim of the study was to assess the nutritional status and health behaviors of women who regularly practice yoga as a form of physical recreation, and to compare them with those who had not practiced it before. The average value of BMI and WHR for the study and control groups resulted within the reference values. However, the analysis of the distribution of BMI values revealed that in the assessed groups there were women whose BMI exceeded 25 kg/m^2. According to Gokal

TABLE 1 Descriptive statistics of somatic parameters.

Variables	Yoga group (n = 68)	Control group (n = 75)	p-value
	x ± SD (min ÷ max)		
Height (cm)	164.6 ± 6.40 (154 ÷ 180)	165.6 ± 5.59 (153 ÷ 179)	0.2139
Body mass (kg)	61.9 ± 7.01 (50 ÷ 80)	63.3 ± 7.89 (50 ÷ 81)	0.4188
BMI (kg/m^2)	22.9 ± 2.43 (18.6 ÷ 28.5)	23.1 ± 2.83 (18.8 ÷ 29.7)	0.7648
Waist circumference (cm)	78.0 ± 6.85 (65 ÷ 93)	76.6 ± 8.19 (59 ÷ 102)	0.0501
Hip circumference (cm)	100.0 ± 6.21 (90 ÷ 116)	98.6 ± 6.66 (82 ÷ 112)	0.1719
WHR	0.79 ± 0.05 (0.66 ÷ 0.92)	0.78 ± 0.06 (0.67 ÷ 0.93)	0.1046

Data are presented as mean ± SD, minimum and maximum. BMI – body mass index; WHR – waist-to-hip-ratio.

TABLE 2 Set of behavior health traits (BHT) of the studied and control group.

Variables	Yoga group (n = 68)	Control group (n = 75)	p-value
	x ± SD (min ÷ max)		
Health behavior index	90.2 ± 12.74 (62 ÷ 119)	84.7 ± 10.82 (61 ÷ 103)	**0.0169**
Positive mental attitude	3.82 ± 0.681 (2 ÷ 5)	3.72 ± 0.665 (1.84 ÷ 5)	0.4306
Preventive behaviors	3.76 ± 0.639 (2,17 ÷ 5)	3.59 ± 0.63 (1.67 ÷ 4.84)	0.1363
Proper eating habits	3.98 ± 0.620 (2,34 ÷ 5)	3.53 ± 0.696 (1.67 ÷ 5)	**0.0001**
Health practices	3.49 ± 0.675 (1.67 ÷ 5)	3.29 ± 0,62 (1.84 ÷ 4.67)	0.1332

Data are presented as mean ± SD, minimum and maximum. Statistically significant.

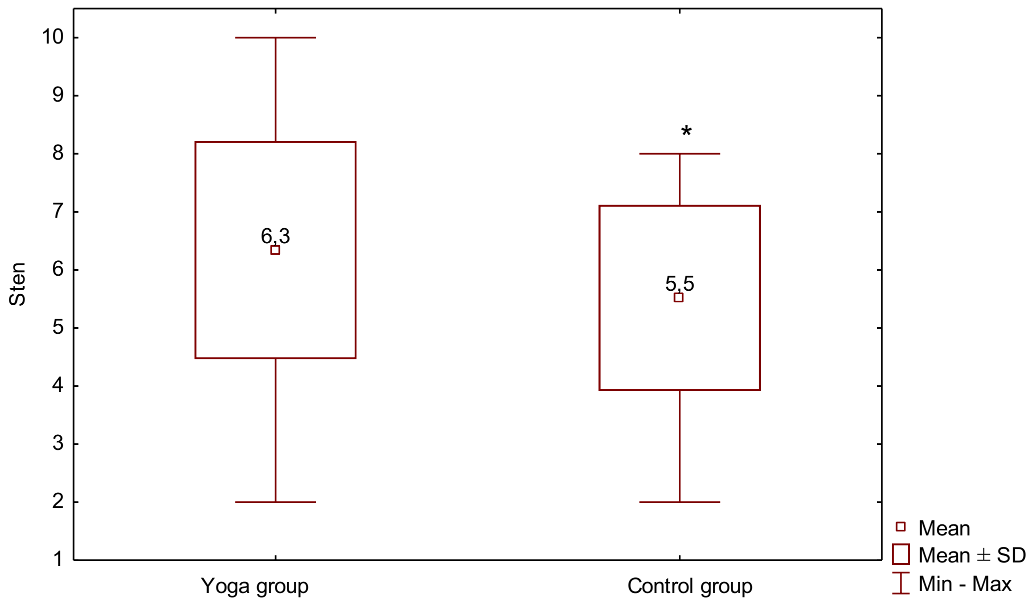

FIGURE 1
Comparative analysis of the average values of standard sten test in the studied groups. Data are presented as mean ± SD, minimum and maximum.

et al. (36), yoga exercises may be recommended to normalize BMI and WHR in overweight and obese people. They can also be used in the treatment of diabetes, hypertension and other metabolic diseases. This is also confirmed by the research of Swapna et al. (37), in which obese patients with type 2 diabetes participating in an intensive, weekly yoga course achieved a decrease in body weight by 2.15%, BMI by 2.1%, and WHR by 4.4%.

The results of our research are consistent with the study of Lim and Hyun (38). In their opinion, yoga helps shape healthy behaviors in yogis and induces positive beliefs about their subjective health, thus triggering a cycle of positive reinforcement. There are reports suggesting the implementation of low- and moderate-intensity yoga classes also among the elderly population to prevent physical and mental health (39). Also, research conducted in Bulgaria with the participation of 89 women practicing yoga showed that yoga practitioners eat healthily – the respondents consumed small amounts of pork and beef, and 60% did not eat meat at all. They consumed an average of 600 g of fruit and vegetables per day, corresponding to the 400 g recommended by the WHO. Practicing yoga helps maintain a proper body mass, which is one of the conditions for a healthy lifestyle. Assessment of the nutritional status of yoga participants was consistent with the WHO and American Cancer Society recommendations for a healthy diet (40).

According to Sreedevi et al. (41), a conscious sustained effort practiced through attitudinal changes implemented on good food habits and choices, exercise, yoga and meditation may have a cumulative impact on the continued beneficial effect on health and overall well-being.

Our results showed that women practicing yoga had a higher rate of proper eating habits. This is probably the result of obtaining higher scores on one of the four subscales regarding proper nutrition. Moreover, there were no significant differences in the nutritional status of women practicing yoga compared to women who did not. We suppose this is most likely due to the benefits of physical activity. Therefore, yoga seems to be a complex intervention that also covers issues related to achieving an ethical and healthy lifestyle, such as consciously making healthy and ethical food choices (42).

Yoga comes from religious and spiritual traditions, so in this case, particular emphasis is placed on a hygienic lifestyle consistent with health practices. In addition, some varieties of Yoga assume a vegetarian diet associated with nonviolence towards living beings. Yoga has connections with Hinduism, Buddhism, and Jainism based on a shared philosophical framework of oneness with all beings and a belief in ahimsa, or nonviolence. Therefore, changes in health behaviors among yoga practitioners seem to be more frequent and longer lasting than among other groups of physically active people practicing exercises unrelated to religious beliefs (43).

However, even recent investigations try to show the effects of Yoga as a recreational physical activity (44), and despite the findings obtained in this investigation, further research is needed.

5 Limitations of the study and future study suggestions

Even though the objectives of this research have been answered, the study has some limitations. On the one hand, based on the research conducted, it is difficult to claim whether this was due to yoga exercises or whether this group consisted of women who cared more about their health in general. On the other hand, a number of participants and a more significant sample would be needed to generalize the obtained results. Moreover, data were collected based on self-report, which may cause bias. In turn, if detailed information about participants' yoga and exercise habits is not collected, this may also pose a limitation in the interpretation of the results. Other than that, for future research, male yoga practitioners should be taken into account to show wider and more generalizable results and to see whether the benefits are the same gender-wise. The questionnaire used in our study is a Polish standardized tool for measuring the overall intensity of health practices. The reliability of the HBI, Cronbach's alpha is 0.85, and its four subscales range from 0.60 to 0.65, for which the values calculated for Cronbach's alpha are near or below the acceptable values. We suppose this is mainly due to the small number of items contributing to the subscales. Perhaps slightly increasing the number of items would lead to acceptable values for Cronbach's alpha.

6 Conclusion

To summarize the obtained research results, it could be suggested that the index of health behaviors and proper eating habits is significantly higher in the group of women who regularly participate in yoga classes. From these results, indicators of healthy habits in daily life could be associated with the regular practice of yoga activities. Therefore, yoga might be a good recreational physical activity to try to pursue health from a public health perspective.

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 study was reviewed and approved by Bioethics Committee at Poznan University of Medical Sciences in Poland (number 824/10). Written informed consent to participate in this study was provided by the participants.

Author contributions

AG: Data curation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. ŁP-S: Methodology, Project administration, Supervision, Writing – review & editing. NP-R: Formal analysis, Visualization, Writing – review & editing. PL-G: Software, Writing – review & editing. EM-M: Resources, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank dr hab. Ewa Śliwicka from Poznan University of Physical Education for her advice on statistical analyses and her valuable comments on the final version of this paper.

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.2024.1334428/full#supplementary-material

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TYPE Original Research
PUBLISHED 10 May 2024
DOI 10.3389/fnut.2024.1329720

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RECEIVED 29 October 2023
ACCEPTED 22 April 2024
PUBLISHED 10 May 2024

CITATION
Hong S, Jiang N, Lin G, Wang Q, Xu X, Shi X, Zhou Y, Wen X, Sun B, Wang H, Huang M, Wang J, Wang N, Chen Y and Jiang Q (2024) Association of maternal mineral status with the risk of preterm birth: a retrospective cohort study.
Front. Nutr. 11:1329720.
doi: 10.3389/fnut.2024.1329720

Association of maternal mineral status with the risk of preterm birth: a retrospective cohort study

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Background: There has been a gradual increase in the proportion of preterm birth in China during the past several decades. Maternal malnutrition is a significant determinant for preterm birth. Nevertheless, comprehensive studies investigating serum mineral levels during pregnancy associated with preterm birth remain scarce. This study aims to assess the associations between maternal serum mineral levels and the risk of preterm birth.

Methods: This retrospective cohort study of 18,048 pregnant women used data from a tertiary hospital in China from January 2016 to December 2022. Demographic data and serum mineral concentrations in the second and third trimesters of mothers were collected from the hospital information system. Analysis was performed using restricted cubic splines and logistic regression models.

Results: The proportion of preterm birth in this study was 6.01%. Phosphorus [P for overall = 0.005; P for nonlinear = 0.490; OR (95%CI) = 1.11 (1.04, 1.18)] and chlorine [P for overall = 0.002; P for nonlinear = 0.058; OR (95%CI) = 1.11 (1.03, 1.19)] showed a significant positive correlation with preterm birth in a linear fashion. Furthermore, serum levels of potassium (P for nonlinear <0.001), sodium (P for nonlinear = 0.004), and magnesium (P for nonlinear <0.001) exhibited non-linear relationships with the risk of preterm birth.

Conclusion: Serum levels of some minerals during pregnancy were associated with the risk of preterm birth among pregnant women. In addition to commonly recognized micronutrients such as folic acid, iron, and vitamin D, healthcare providers should also pay attention to the levels of these minerals during pregnancy.

KEYWORDS

mineral, preterm birth, micronutrients, gestational age, retrospective study

1 Introduction

In the past decades, the general health status of Chinese women and children has been significantly improved (1), and the neonatal mortality rate has substantially reduced (2). However, the proportion of preterm birth in China increased from 5.36% in 1990 to 7.04% in 2015 (3). Preterm birth, defined as baby born before 37 weeks of gestation, is associated with an increased risk of a range of short-and long-term comorbidities in the neonate (4). Preterm birth not only imposes an economic and psychological burden on families, but also associated with enormous costs to health systems (5, 6).

Preterm birth is influenced by a variety of maternal and fetal characteristics, including maternal demographic characteristics, psychological factors, pregnancy status, nutritional status, and genetic factors (7). During pregnancy, a series of continuous physiological changes lead to increased maternal energy and micronutrients requirements to support optimal fetal growth and maternal health (8, 9). Hence, Maternal malnutrition can have profound effects on fetal development and pregnancy outcomes, including the occurrence of preterm birth (10, 11). Minerals, as important nutrition elements, play a variety of roles in the body, such as construction of bones, cofactor for the enzyme activity, and regulation of blood sugar (8, 12). Deficiency in minerals may lead to several consequences, including increased risk of pregnancy complications and perinatal mortality, fetal growth retardation, preterm birth, low birth weight, and infants being small for gestational age (13–15). Currently, numerous studies focuses on investigating common nutrient deficiencies such as folate, iron, and vitamin D (16–19), while some recent studies paid attention to minerals (20). For example, the disturbances of calcium(Ca)-phosphorus(P)-magnesium(Mg) homeostasis in pregnant women may lead to gestational hypertension by enhancing smooth muscle reactivity (21). In addition, enhanced uterine smooth muscle tone and uterine contractility may lead to the occurrence of preterm birth (21, 22). Sodium(Na) retention during pregnancy can lead to alterations in maternal blood pressure and weight, thereby influencing fetal growth (23). Reduced potassium(K) levels may induce premature contraction of the uterus, leading to preterm birth (24). Mg supplementation in early pregnancy could play a role in preventing preterm birth (25, 26). However, another study found that Mg supplementation during pregnancy did not improve maternal and neonatal health outcomes (27). The impact of mineral intake and its level in maternal blood on the risk of preterm birth remains inconclusive. Specifically, whether deficiencies or excess of some minerals have different effects on preterm birth needs to be further explored.

However, most previous studies have only assessed the minerals individually in relation to preterm birth. To the best of our knowledge, there is only one cohort study that comprehensively investigated the relationships between various maternal mineral levels and the risk of preterm birth, but the sample size of the study was small, including only 780 mother-offspring pairs (28). Besides, maternal minerals are transferred to the fetus through the placenta, with this transfer process experiencing rapid growth starting from the second trimester and reaches its maximum in the third trimester (29, 30). Therefore, the effects of maternal mineral levels on fetal growth and delivery may be most significant in the second or third trimester. Hence, we conducted a large retrospective epidemiological study to investigate the relationships between maternal serum mineral levels in the second and third trimesters of pregnancy and the occurrence of preterm birth.

Abbreviations: Ca, calcium; K, potassium; P, phosphorus; Na, sodium; Cl, chlorine; Mg, magnesium; SD, standard deviation; IQR, interquartile range; OR, odds ratio; CI, confidence interval.

2 Materials and methods

2.1 Study population

This study was a retrospective cohort study of 18,048 pregnant women at the People's Hospital of Pingyang, Wenzhou City, Zhejiang Province, China between January 2016 and December 2022. The hospital serves as the primary provider of medical and healthcare services in Pingyang county, functioning as the sole tertiary hospital. A majority of expectant mothers in this region opt for this hospital for delivery. The hospital has an efficient information system that archives the demographic and clinical data of every patient. All participants in this study underwent pregnancy registration and examinations and had a singleton delivery. Pregnant women with missing information on mineral status or last menstrual period, age younger than 18 years, or intrauterine fetal death were excluded from this study. The study was approved by the Medical Research Ethics Committee of the School of Public Health, Fudan University (The international registry no. IRB00002408 and FWA00002399). The retrospective study used existing data and all the information on the personal identification was removed for the study. Informed consent was not sought, which was also approved by the Medical Research Ethics Committee of the School of Public Health, Fudan University.

2.2 Data collection and measurements

The demographic and clinical data were collected from the hospital information system. The primary outcome of this study was preterm birth, defined as birth before 37 weeks gestation. Gestational age was calculated by using the last menstrual period combined with ultrasound measurements. Mineral information was obtained from records of the latest antenatal examination prior to inpatient delivery, all in the second and third trimesters. Antecubital venous blood samples were collected from pregnant women who had fasted for more than 8 h using 5-mL BD vacutainer blood collection tube (Becton Dickinson, Franklin Lakes, NJ, United States). Fasting was required as the blood sample would also be utilized for a range of tests, including liver and renal function tests. After the blood samples were allowed to clot, it was centrifuged at 3500 rpm for 10 min. Following centrifugation, the serum samples were freed from the interference of hemolysis, jaundice and lipid turbidity. The levels of Na, K, and chlorine (Cl) were determined using the ion selective electrode method, Ca levels were determined using the arsenazo method, P levels were determined using the phosphomolybdate method, and Mg levels were determined using the enzymatic method. The corresponding data of minerals were obtained from the Architect c16000 clinical chemistry analyzer (Abbott Diagnostics, Abbott Park, United States).

2.3 Covariates

The covariates included age, parity (previous live births), amniotic fluid volume, hyperglycemia during pregnancy, hypertensive disorders of pregnancy, *in vitro* fertilization, and neonatal sex. Information on age and parity was recorded by the physician at the first pregnancy registration visit. Amniotic fluid volume was assessed using ultrasound

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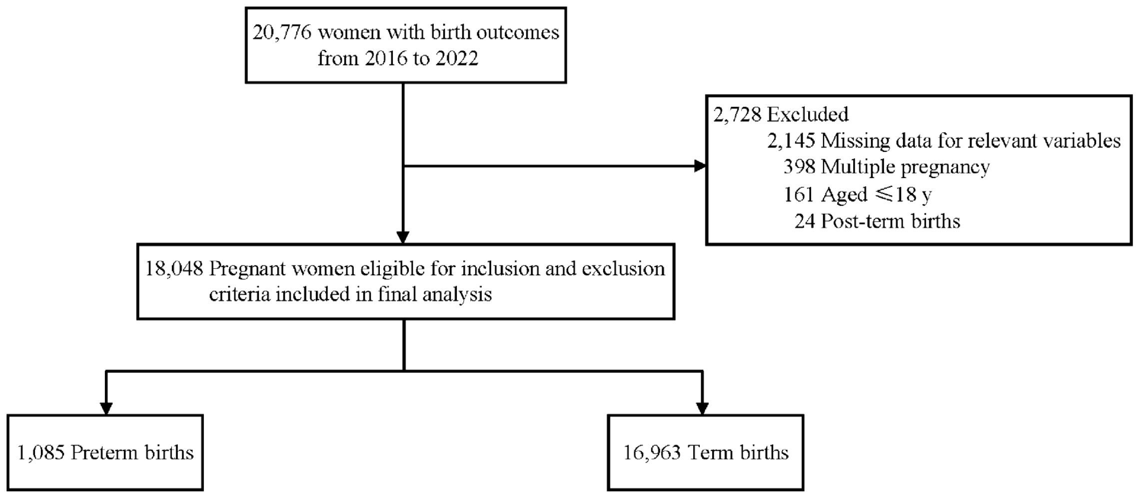

FIGURE 1
Flowchart of study participants.

measurements, including maximal vertical pocket and amniotic fluid index. Oligohydramnios was defined as maximal vertical pocket <2 cm or amniotic fluid index <5 cm. Polyhydramnios was defined as maximal vertical pocket >8 cm or amniotic fluid index >24 cm. Hyperglycemia during pregnancy including diabetes mellitus and gestational diabetes mellitus. Hypertensive disorders of pregnancy including chronic (preexisting) hypertension, gestational hypertension, preeclampsia, and eclampsia.

2.4 Statistical analysis

Statistical analysis was performed in R 4.2.3.[1] Continuous variables were presented as mean (standard deviation, SD) or median (interquartile range, IQR), where appropriate. Categorical variables were presented as numbers and percentages. We examined the dose–response relationship between maternal mineral levels and preterm birth risk using restricted cubic splines with 4 knots. The number of knots used in the restricted cubic spline analysis was selected corresponding to the minimum Akaike information criterion. Given the non-direct interpretability of regression parameters obtained from regression splines (31), we employed binary logistic regression models to derive meaningful parameters for linear relationship outcomes. For non-linear relationship outcomes, we constructed 2-piecewise logistic regression models to calculate inflection points and analyze threshold effects. In the logistic regression model, we calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for preterm birth in association with one standard deviation change of the mineral levels. Restricted cubic splines and logistic regression analyses were adjusted for age, parity (previous live births), amniotic fluid volume, hyperglycemia during pregnancy, hypertensive disorders of pregnancy, *in vitro* fertilization, and neonatal sex. A p value <0.05 was considered statistically significant.

1 http://www.R-project.org

3 Results

3.1 Characteristics of study participants

A total of 18,048 mother-singleton infant pairs were included in this retrospective cohort study (Figure 1), with the mean age at delivery of 30.05 ± 4.80 years, of which 16.52% were advanced maternal age (Table 1). Among the participants, 38.25% of pregnant women were primiparous, 13.99% were diagnosed with hyperglycemia during pregnancy, and 3.83% were diagnosed with hypertensive disorder of pregnancy. The average serum level for all the pregnant women in the second or third trimesters was 2.20 ± 0.16 mmol/L for Ca, 3.87 ± 0.28 mmol/L for K, 1.24 ± 0.21 mmol/L for P, 137.41 ± 1.85 mmol/L for Na, 103.74 ± 2.53 mmol/L for Cl, and 0.79 ± 0.12 mmol/L for Mg. The median gestational age of childbirth was 39.0 weeks (38.0–40.0 weeks), and 6.01% of mothers experienced preterm birth.

3.2 Association between mineral levels and preterm birth

No significant associations were observed between Ca and preterm birth (P for overall = 0.081; Figure 2A).

A significant linear positive correlation between P and preterm birth was demonstrated (P for overall = 0.005; P for nonlinear = 0.490; OR (95%CI) = 1.11 (1.04, 1.18); Table 2; Figure 2C). Also, there is a significant linear positive correlation between Cl and preterm birth [P for overall = 0.002; P for nonlinear = 0.058; OR (95%CI) = 1.11 (1.03, 1.19); Table 2; Figure 2E].

Restricted cubic spline regression analysis revealed that serum levels of K (P for overall <0.001; P for nonlinear <0.001; Figure 2B), Na (P for overall = 0.005; P for nonlinear = 0.004; Figure 2D), and Mg (P for overall <0.001; P for nonlinear <0.001; Figure 2F) exhibited nonlinear relationships with the risk of preterm birth. Specifically, the restricted cubic spline demonstrated a U-shaped association of both K and Na with preterm birth, as well as an L-shaped nonlinear relationship between Mg and preterm birth.

TABLE 1 Characteristics of participants.

Characteristics	All participants
Participants, *n*	18,048
Maternal age, mean (SD), y	30.05 (4.80)
Maternal age group, *n* (%), y	
<35	15,066 (83.48%)
≥35	2,982 (16.52%)
Parity group, *n* (%)	
None	6,904 (38.25%)
1–2	11,049 (61.22%)
3 or more	95 (0.53%)
Amniotic fluid volume, *n* (%)	
Oligohydramnios	1,919 (10.63%)
Normal	15,710 (87.05%)
Polyhydramnios	419 (2.32%)
Hyperglycemia during pregnancy, *n* (%)	2,525 (13.99%)
Hypertensive disorders of pregnancy, *n* (%)	691 (3.83%)
In vitro fertilization, *n* (%)	331 (1.83%)
Neonatal sex	
Male	9,805 (54.33%)
Female	8,243 (45.67%)
Calcium, mean (SD), mmol/L	2.20 (0.16)
Potassium, mean (SD), mmol/L	3.87 (0.28)
Phosphorus, mean (SD), mmol/L	1.24 (0.21)
Sodium, mean (SD), mmol/L	137.41 (1.85)
Chlorine, mean (SD), mmol/L	103.74 (2.53)
Magnesium, mean (SD), mmol/L	0.79 (0.12)
Gestational age at delivery, median (IQR), wk	39.0 (38.0–40.0)
Preterm birth, *n* (%)	1,085 (6.01%)

SD, standard deviation; IQR, interquartile range.

The inflection point of K was 4.10 mmol/L. On the left side of the inflection point, the risk of preterm birth decreased with increasing maternal serum K level (OR: 0.70; 95% CI: 0.65, 0.76) (Table 2). On the right side, the risk of preterm birth increased with increasing maternal serum K levels (OR: 1.20; 95% CI, 1.01, 1.42) (Table 2). The inflection point of Na was 135.90 mmol/L. Na was a protective factor for preterm birth on the left side of the inflection point (OR: 0.80; 95% CI: 0.68, 0.95) (Table 2), and a risk factor on the right side (OR:1.15; 95% CI: 1.04, 1.26) (Table 2). The inflection point of Mg was 0.99 mmol/L. On the right side of the inflection point, the risk of preterm birth increased with increasing maternal serum Mg levels (OR: 1.39; 95% CI: 1.19, 1.62), but not significant on the left side (OR: 0.93; 95% CI: 0.85, 1.02) (Table 2).

3.3 Subgroup analysis of preterm birth by maternal age, parity, and neonatal sex group

To further explore the association between maternal mineral levels and preterm birth, stratified analyses by maternal age, parity, and neonatal sex were performed (Figures 3–5). The restricted cubic spline plots illustrated that maternal serum Cl levels interacted with maternal age (P for interaction = 0.033; Figure 3E) and parity (P for interaction = 0.001; Figure 4E). Among women under age of 35, no significant association was observed between Cl and preterm birth (P for overall = 0.060; P for nonlinear = 0.157). Conversely, a linear positive correlation was observed between Cl and preterm birth among women of advanced maternal age (P for overall = 0.023; P for nonlinear = 0.471). Similarly, there was a linear positive correlation between Cl and preterm birth among multiparous women (P for overall <0.001; P for nonlinear = 0.340), whereas no association was observed among primiparous women (P for overall = 0.327; P for nonlinear = 0.274).

4 Discussion

We conducted a large-scale retrospective study to investigate the relationships between the serum concentrations of several minerals in pregnant women and the risk of preterm birth. We observed that maternal serum levels of K, P, Na, Cl, and Mg were shown distinct associations with preterm birth after adjusting for various confounding variables.

Among the minerals in this study, both low and high levels of K were found to be independent risk factors for preterm birth. K is an essential mineral for the body that maintains fluid balance, helps maintain blood pressure, and regulates muscle contraction, among other functions. K channels in the smooth muscle layer of the uterus play an important role in regulating myometrial tone and controlling uterine contractions during pregnancy. Studies have demonstrated that K^+ channel dysfunction or decreased expression would diminish the repolarization current of mesenchymal stem cells, thereby inducing premature uterine contractions and preterm birth (24). In addition, elevated K levels during pregnancy have been found to be associated with increased risks of gestational diabetes mellitus, preeclampsia, and cardiovascular disease, which may impair normal fetal growth and result in preterm birth (32–34). Currently, there is no defined threshold for normal levels of K during pregnancy (32). The findings of this study suggest that maintaining K levels at a moderate level of about 4.10 mmol/L is appropriate, which falls within the normal range of 3.5–5.5 mmol/L for adults (35). Nonetheless, further research is required to determine the optimal range of K levels for pregnant women.

In this study, it was found that elevated maternal serum P and Cl levels would increase the risk of preterm birth. P is crucial for numerous bodily functions such as blood clotting, nerve function, muscle movement, and bone strengthening (36). However, excess of P during pregnancy can be harmful to both mother and fetus. In excessive amounts, it inhibits the absorption of other essential minerals in the body, severely disrupts the hormonal regulation of phosphate, Ca, and vitamin D, leading to tissue hardening in the body, anemia, impaired kidney function, and bone loss (36, 37). Cl plays a vital role in electrolyte balance and the maintenance of kidney and muscle functions (38). Elevated serum Cl levels can lead to a range of health issues, including dehydration and metabolic acidosis (38). The subgroup analysis revealed interactions of Cl with maternal age and parity. The liner positive correlations between Cl and preterm birth only appeared in women of advanced maternal age and multiparous

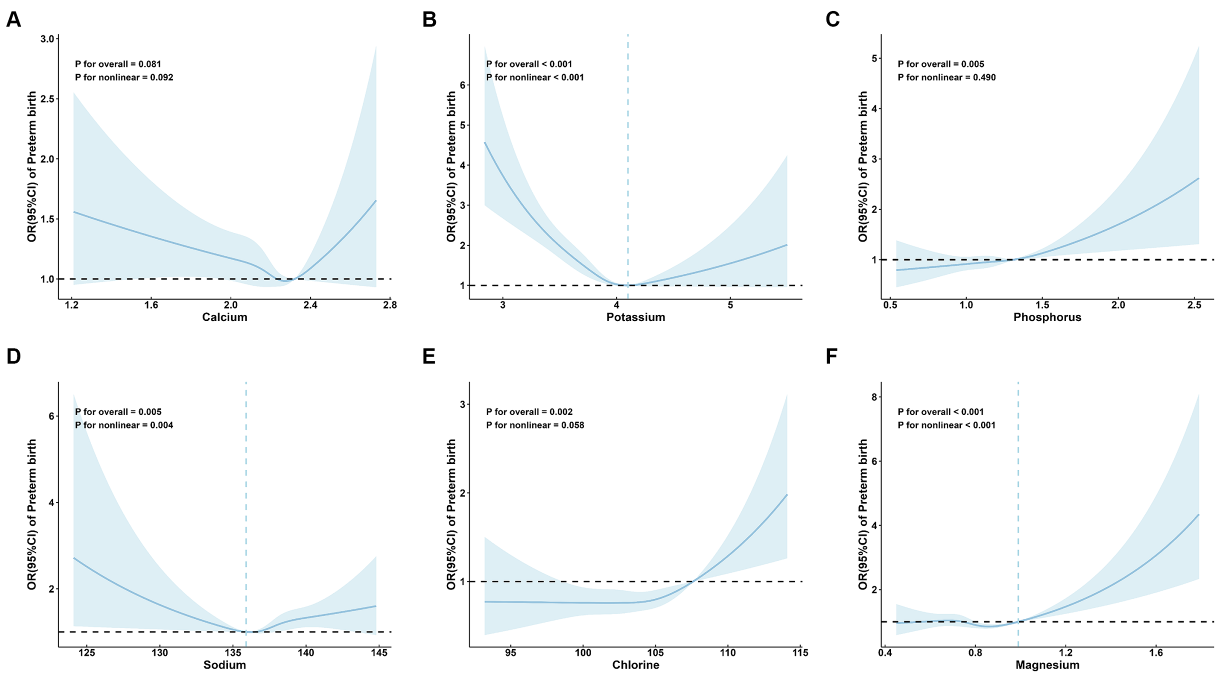

FIGURE 2
Adjusted* odds ratios and 95% confidence intervals for preterm birth in association with maternal serum mineral levels in restricted cubic spline regression. **(A)** calcium; **(B)** potassium; **(C)** phosphorus; **(D)** sodium; **(E)** chlorine; and **(F)** magnesium. * Adjusted for age (continuous), parity, amniotic fluid volume, hyperglycemia during pregnancy, hypertensive disorders of pregnancy, in vitro fertilization, and neonatal sex.

TABLE 2 Adjusted* odds ratios (ORs) and 95% confidence intervals (95% CIs) for preterm birth in association with maternal serum mineral levels in multivariable logistic regression.

Serum mineral level	Inflection point (mmol/L)	Group (mmol/L)	OR (95%CI)	*p* value
Potassium (per 1 SD)[a]	4.10	≤4.10	0.70 (0.65, 0.76)	<0.001
		>4.10	1.20 (1.01, 1.42)	0.042
Phosphorus (per 1 SD)	NA	NA	1.11 (1.04, 1.18)	0.001
Sodium (per 1 SD)[a]	135.90	≤135.90	0.80 (0.68, 0.95)	0.009
		>135.90	1.15 (1.04, 1.26)	0.004
Chlorine (per 1 SD)	NA	NA	1.11 (1.03, 1.19)	0.004
Magnesium (per 1 SD)[a]	0.99	≤0.99	0.93 (0.85, 1.02)	0.116
		>0.99	1.39 (1.19, 1.62)	<0.001

[a]Piecewise logistic regression.
*Adjusted for age (continuous), parity, amniotic fluid volume, hyperglycemia during pregnancy, hypertensive disorders of pregnancy, in vitro fertilization, and neonatal sex.

women. This suggests that women of advanced maternal age and multiparous women are more sensitive to the harm associated with elevated serum Cl levels. Therefore, it is crucial to pay more attention to preventing excessive serum Cl levels in these groups during pregnancy. However, the specific mechanisms by which P and Cl contribute to preterm birth in different populations require further exploration.

Our findings showed a U-shaped relationship between maternal serum Na levels and the risk of preterm birth. As the most important electrolyte in extracellular fluid, Na regulates the osmolality in the extracellular space and plays a crucial role during pregnancy (39). Decreased maternal Na levels during pregnancy may lead to an enhancement of the renin angiotensin system, which promotes cardiovascular and renal injury mechanisms (40, 41). Consequently, this could hinder the development of fetal cardiovascular or metabolic systems, contributing to impaired fetal growth and an increased risk of low birth weight and preterm birth (39, 40). Furthermore, studies have shown that elevated Na levels in the blood of pregnant women are related to an increased risk of developing high blood pressure and preeclampsia during pregnancy, which can lead to intrauterine growth retardation and preterm birth (42–44). Besides, researchers hypothesize that excessive Na intake during pregnancy may affect fetal nutrition supply by influencing placental blood flow, thereby impacting fetal growth and leading to preterm birth (42). Our study is consistent with previous studies showing the importance of keeping maternal Na levels within an appropriate range during pregnancy.

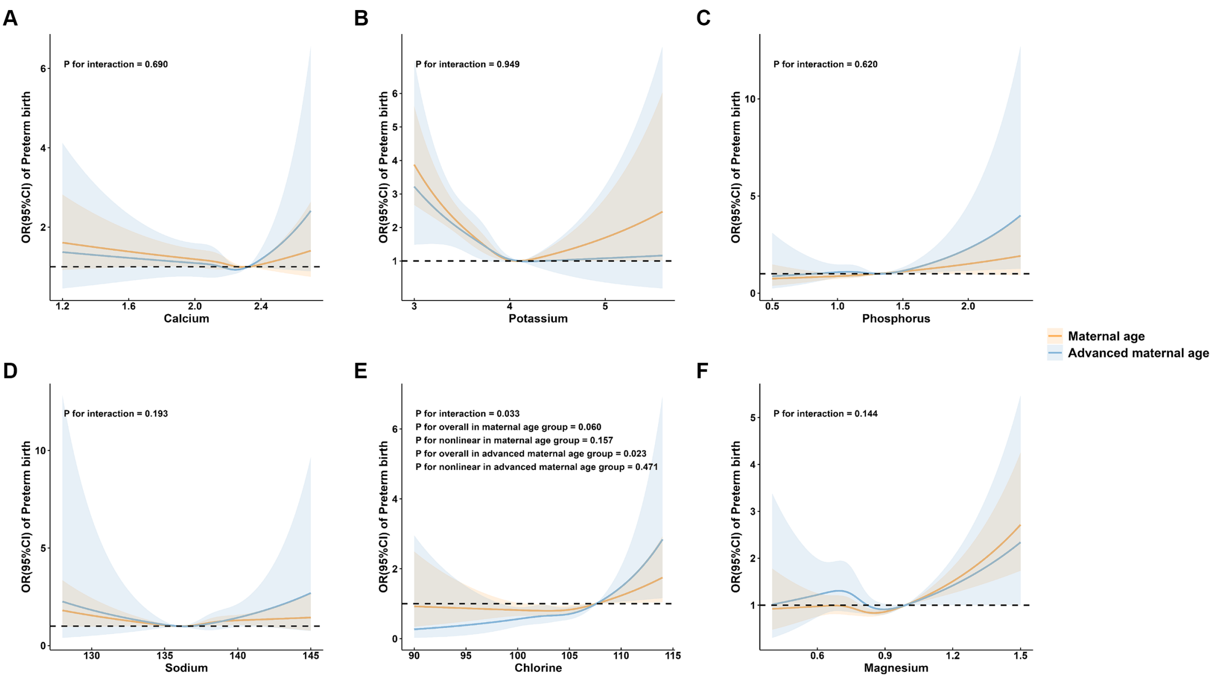

FIGURE 3
Subgroup analysis of preterm birth by maternal age group. **(A)** calcium; **(B)** potassium; **(C)** phosphorus; **(D)** sodium; **(E)** chlorine; and **(F)** magnesium.

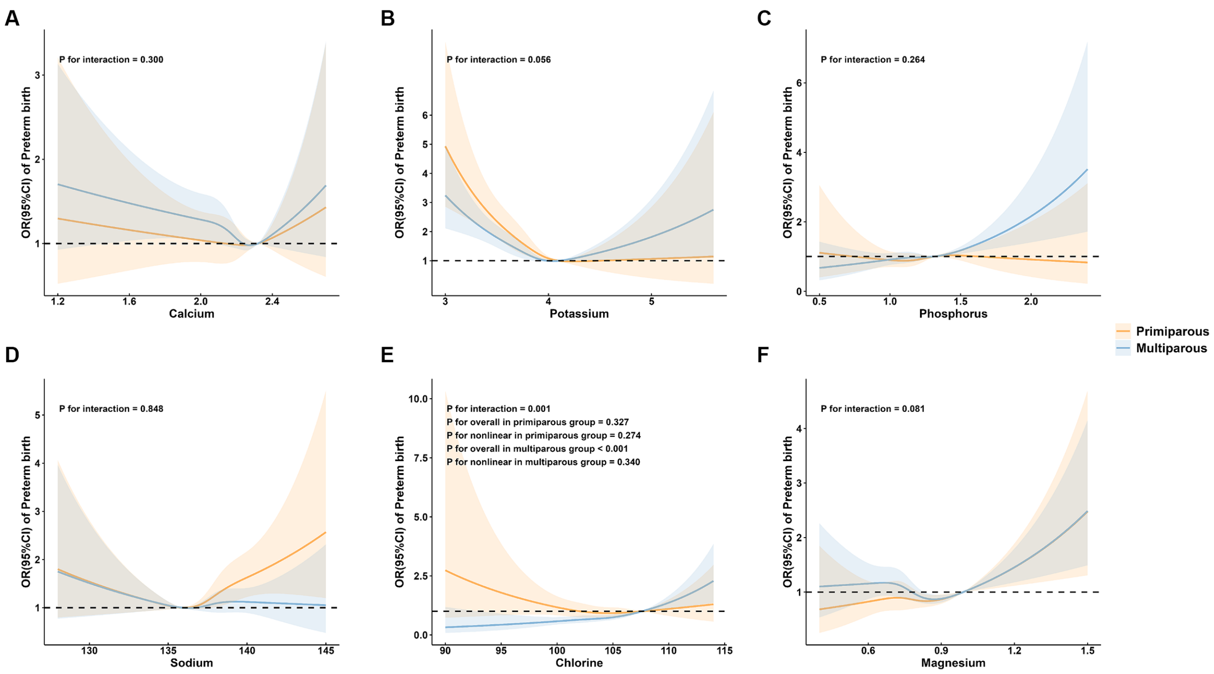

FIGURE 4
Subgroup analysis of preterm birth by maternal parity group. **(A)** calcium; **(B)** potassium; **(C)** phosphorus; **(D)** sodium; **(E)** chlorine; and **(F)** magnesium.

During pregnancy, on one hand, serum Na levels in pregnant women may mildly decrease due to increased circulatory volume (45). On the other hand, various conditions such as hemorrhage, overheating, hyperemesis, and diarrhea can lead to sodium deficiency and altered appetite for salt (46). Therefore, food, especially salt, as the main source of serum Na for pregnant women, should be strictly controlled during pregnancy to prevent harm from deficiency or excess.

Mg is a mineral that is beneficial for regulating almost every system in the body (27). Previous studies on Mg supplementation during pregnancy have yielded inconsistent results. Some studies

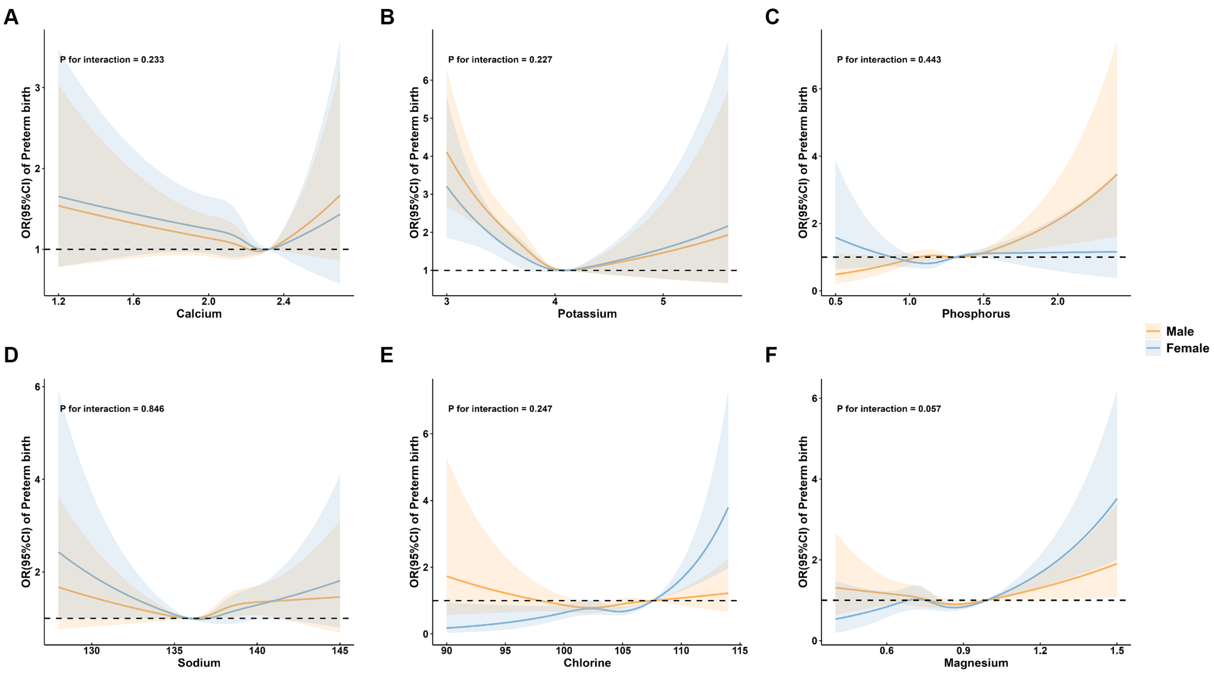

FIGURE 5
Subgroup analysis of preterm birth by neonatal sex group. **(A)** calcium; **(B)** potassium; **(C)** phosphorus; **(D)** sodium; **(E)** chlorine; and **(F)** magnesium.

suggested that supplementing Mg during pregnancy may reduce the incidence of various pregnancy complications, including fetal growth restriction and preeclampsia (47). However, a review incorporating ten studies indicates no evidence supporting the improvement of maternal and neonatal health outcomes through Mg supplementation during pregnancy (27). In this study, we found a plateau in the relationship between Mg and preterm birth at low levels, but as Mg levels continued to increase above a certain threshold, the risk of preterm birth also increased. Consistent with our results, the toxic effects of excess Mg on cardiovascular complications, apnea, and coma during pregnancy have been demonstrated in multiple studies (48, 49). Interestingly, our results suggest that below a certain threshold, changes in Mg concentration may not significantly impact the occurrence of preterm birth. Further high-quality evidence is still needed to confirm the optimal range of Mg levels during pregnancy and explore its impact on maternal and infant health in the future.

There are several limitations of our study. First, some potential risk factors were not incorporated due to the lack of corresponding data in the hospital information system, such as smoking status, maternal BMI, and usage of nutritional supplementation. Second, each mineral has different distributions in different organs and systems. This study only measured the concentrations of minerals in serum. Third, this study only included maternal serum mineral data collected in the second and third trimesters since only a small proportion of individuals had their mineral levels measured during early pregnancy. Moreover, we did not explore the associations of mineral levels in different trimesters with preterm birth, given that only 668 pregnant women had mineral data in the second trimester of pregnancy, which may result in insufficient statistical power due to the small sample size. The associations between mineral levels in different trimesters of pregnancy and the risk of preterm birth should be investigated in future prospective studies.

5 Conclusion

Our study demonstrated significant associations between some maternal mineral levels and the occurrence of preterm birth. There was a significant positive association of P and Cl with preterm birth, and a non-linear relationship between K, Na and Mg and preterm birth. Healthcare providers should pay a closer attention to the levels of these mineral elements during pregnancy, beyond the commonly recognized micronutrients such as folate, iron, and vitamin D. Monitoring mineral levels during antenatal care can help early identification of potential deficiencies or imbalances that may contribute to adverse pregnancy outcomes. In addition, further large-scale, high-quality prospective studies are needed to explore the underlying mechanisms and validate the best range of minerals for achieving the optimal maternal and fetal health.

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 Medical Research Ethics Committee of the School of Public Health, Fudan University (the international registry no. IRB00002408 and FWA00002399). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the retrospective study used existing data and all the information on the personal identification was removed for the study. Informed consent was not sought, which was also approved by the Medical Research Ethics Committee of the School of Public Health, Fudan University.

Author contributions

SH: Data curation, Formal analysis, Writing – original draft. NJ: Data curation, Formal analysis, Writing – original draft. GL: Resources, Supervision, Writing – review & editing. QW: Investigation, Methodology, Writing – review & editing. XX: Resources, Visualization, Writing – review & editing. XS: Investigation, Software, Writing – review & editing. YZ: Methodology, Resources, Writing – review & editing. XW: Data curation, Software, Writing – review & editing. BS: Resources, Writing – review & editing. HW: Software, Validation, Writing – review & editing. MH: Supervision, Writing – review & editing. NW: Project administration, Resources, Writing – review & editing. JW: Methodology, Project administration, Supervision, Writing – review & editing. YC: Methodology, Writing – review & editing. QJ: Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We are grateful to the staff of the People's Hospital of Pingyang for their assistance in data collection.

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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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 03 June 2024
DOI 10.3389/fnut.2024.1367767

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OPEN ACCESS

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RECEIVED 09 January 2024
ACCEPTED 23 May 2024
PUBLISHED 03 June 2024

CITATION
Rozmiarek M, Grajek M, Krupa-Kotara K and Malchrowicz-Mośko E (2024) Orthorectic behavior among students and motivation for physical activity, dietary habits, and restrictive eating.
Front. Nutr. 11:1367767.
doi: 10.3389/fnut.2024.1367767

Orthorectic behavior among students and motivation for physical activity, dietary habits, and restrictive eating

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Introduction: Orthorexia lacks official recognition as an eating disorder; however, orthorexic behaviors, associated with a stringent selection of food, may serve as a predisposing factor to the development of eating disorders. It is characterized by an obsessive preoccupation with healthy eating and strict dietary standards, often prevalent in high-risk groups such as athletes and individuals concerned with their physical appearance. The objective of this study was to evaluate the incidence of orthorexia among students exhibiting varying lifestyles (including dietary habits and levels of physical activity, along with their respective motivational factors). The research involved 600 participants equally distributed between health-related (HRF) and non-health-related (NRF) academic categories, with the majority of participants in the HRF category being women.

Methods: Assessments included BMI calculations, dietary evaluation based on Polish standards, categorization of physical activity levels, the EMI-2 questionnaire on motivation to exercise, the DOS test for orthorexia propensity, and the TFEQ-13 questionnaire for eating behavior.

Results and discussion: Results showed that primary motivators for physical activity included disease prevention, health maintenance, strength/endurance, and physical appearance. Orthorexia tendencies were prevalent, particularly in the HRF group, linked to lower BMI, better diet quality, higher physical activity levels, and a higher prevalence of restrictive eating. In conclusion, students in health-related fields, driven by a strong health consciousness, are at risk of orthorexia. This emphasizes the need for balanced health education and support.

Conclusion: Orthorexic tendencies are associated with distorted perceptions of food portions and calories, underscoring the importance of awareness and intervention.

KEYWORDS
orthorexia, dietary habits, restrictive eating, physical activity, students, motivation

1 Introduction

Recently, there has been a growing interest in physical activity and diet, as well as the pursuit of an ideal figure (1). In some cases, attention to health and image takes the form of obsession (2). This justifies the need to research the prevalence of eating disorders. People affected by them hold incorrect beliefs about nutrition, especially regarding energy provision and weight gain (3). Consequently, great emphasis should be placed precisely on assessing the risk of eating disorders in different population groups, with a particular focus on young and health-intensive individuals (4, 5). This is supported by the observation that the prevalence of eating behaviors that have features of eating disorders with atypical symptoms has increased in recent years (6). To distinguish this group, they are called nonspecific eating disorders (7, 8), which is also justified by the fact that they are searched for in vain in the official classifications of mental disorders (DSM-V), and in the Statistical Classification of Diseases (ICD-10) they have codes F50.8 and F50.9—other eating disorders; eating disorders, unspecified (in ICD-11 the entry is expanded to eating and eating disorders nowhere specified) (9–11).

One of the non-specific/unspecified eating disorders is orthorexia (12). The term was first used in 1997 by Bratman, indicating the possible emergence of a novel eating disorder, delineated as follows: "a pathological focus on healthy eating with features of rigorous attention to food quality and preparation and dietary norms" (13)—for this reason, orthorexia is sometimes classified as an obsessive-compulsive disorder (also known by the acronym OCD). According to Bratman et al. (6), this dietary pattern may be classified as a mental disorder on account of its physiological, psychological, and societal repercussions. Importantly, orthorexia can be multidimensional and encompass several neurobiologically-based variants (14, 15). The treatment of orthorexia in the category of an eating disorder is because the orthorexic loses objectivity about a healthy lifestyle, and how to eat and engage in physical activity. The given behaviors are performed schematically, and deviating from them triggers negative emotions. Symptoms of orthorexia involve making choices that are socially recognized as health-promoting, but in an exaggerated and radical way (16). It is estimated that orthorexia may occur in 1–7% of the general population (depending on the measurement methodology adopted) (12, 17–20), and in high-risk groups (athletes, dieters, and appearance-conscious individuals) this risk can increase to 60% and even 90% (7, 20). What is most interesting about orthorexia is that it is a kind of alternative to other eating disorders (6). From a psychopathological point of view, it is not clear whether orthorexia should be categorized as an eating disorder or as OCD. Considering the eating symptoms, it can be considered a non-specific eating disorder (21, 22). Given the cognitive-behavioral framework, it aligns more closely with obsessive-compulsive disorder (23, 24). The diagnostic criteria for orthorexia proposed in the literature define it as an independent pathological entity, not obligatorily including such features as body anxiety and general dissatisfaction with body weight (25), as well as a sense of detachment from one's own body (6, 26). In the course of the disorder, a person feels a sense of control over his or her own life due to maintaining a strict diet. The orthorexic's diet revolves around the quality of meals and the search for better and better food and the obvious inability to meet his or her demands leads the orthorexic to nutrient deficits (27, 28).

An individual diagnosed with orthorexia exhibits distinctions from someone diagnosed with a specific eating disorder (note: anorexia, bulimia, and BED) in that the former does not possess an obsessive drive to attain a slender physique. Instead, any deviation from the planned diet or the perception of a nutritional misstep is met with unwarranted health-related apprehension. Conversely, there is a fixation on meticulously monitoring the nutritional content of meals consumed, accompanied by a fear of ingesting anything deemed unhealthy, which leads to an avoidance of foods with un-disclosed composition or origin (7, 23, 24). Other consequences of orthorexia include the elimination of foods on the menu that do not meet the standards imposed by the orthorexic, as well as the avoidance of social contacts that would pose a risk of eating foods with unknown composition. As a result, the life of a person suffering from orthorexia revolves around searching for food, making food choices, and planning diet and physical activity (27, 28).

Commonly acknowledged predisposing factors implicated in susceptibility to the development and perpetuation of eating disorders, including orthorexia, encompass body image, perfectionism, attachment style, and self-esteem (29). These predictors were assessed in a study by Barnes and Caltabiano (30). The researchers discovered that elevated orthorectic tendencies exhibited a notable correlation with heightened scores on self-oriented perfectionism, appraisal orientation, and anxious and rejecting attachment style. Excessive fixation on weight, appearance orientation, and a history of eating disorder were identified as substantial predictors of orthorexia. Similar results were obtained by Bardone-Cone et al. (31) and Brown et al. (32).

In addition, researchers emphasize that in the case of orthorexia, an additional predisposing factor is a lifestyle and social role (e.g., occupation related to esthetic appearance) (28, 33, 34). The latter is confirmed by, among others, Asil and Sürücüoğlu (35), who found that about 50% of dieters are at risk for orthorexia, and 12.9% for other eating disorders. Another study involving health science students found orthorexic behavior in 68.2% of respondents (36). Similar results were found among those characterized by high physical activity and attention to body shape (26, 37). The results of the study showed that as many as 45.5% of medical students exhibited characteristics of orthorexia, while 88.2% of surveyed dietitians and 52% of surveyed physical therapists declared a change in their approach to food and nutrition after entering medical school (38).

Another study found a weak relationship between studying dietetics and the incidence of eating disorders (39). Arslantas et al. (40) demonstrated that nurses who prioritized sound nutrition and expressed apprehension regarding weight gain were at an elevated risk of developing orthorexia. Almeida et al. (41), on the other hand, showed an association between orthorexic tendencies and frequent exercise and dis-satisfaction with body image.

In light of the aforementioned relationships, it has been decided to conduct a study aimed at a thorough assessment of the prevalence of orthorexia among groups of students characterized by diverse lifestyles, encompassing both dietary habits and physical activity, including their motivation to engage in these behaviors. The research hypotheses were constructed: (1) The motivating factors for physical activity in the study sample are health issues; (2) The occurrence of orthorexia is associated with a normal BMI, high Physical Activity Levels (PAL), and a rational diet; (3) Individuals exhibiting orthorexic behavior tend to overestimate the portion sizes of products and foods on photo models; and (4) There is a correlation between orthorexic behavior and other eating behaviors.

2 Materials and methods

The study is a continuation of the original research project presented in the previous papers published in 2022 in *Nutrients* (42, 43). The present article, by demonstrating new relationships, complements the previously presented fragmented results, thereby expanding current scientific knowledge without raising any doubts regarding the reliability and research ethics (44). Moreover, the results were obtained during the implementation of a large research project, and their full presentation in a single manuscript was realistically impossible.

2.1 Sample group

The research encompassed 600 participants, evenly distributed between two academic domains: health-related fields (HRF) and non-health-related fields (NRF). The sample size was determined using the minimum sample size formula ($N_{\min} = [NP(\alpha 2 \cdot f(1 - f))]/[NP \cdot e2 + \alpha 2 \cdot f(1 - f)]$, where: $N_{\min}$—minimum sample size; NP—the size of the population from which the sample is taken; α—confidence level for the results; *f*—the size of the fraction; *e*—the assumed maximum error), taking into account the total number of students in a specific year at a particular university. This ensured a representative sample group. The survey questionnaire was administered to all students in a specific year and field of study, achieving a response rate of 83.1%. All participants were in the final year of their master's program, with the HRF group comprising dietetics and physical education students, while the NRF group consisted of management and computer science students. The main variable taken into account was the field of study, not the age of the students. The students came from the following universities: Medical University of Silesia, Academy of Physical Education in Katowice, University of Silesia and University of Economics in Katowice.

The surveyed group is representative of the Polish population, according to the Central Statistical Office; almost 1.2 million citizens are currently studying in Poland. Based on calculations, the minimum sample size for such a population is 384 cases, so the group of 600 people selected for the study meets the minimum research sample. The minimum sample size allows us to calculate how many elements (individuals, re-search units) we should survey so that our results with a certain confidence level and an assumed maximum error estimate the true results in the population.

2.2 Eligibility criteria

During the material collection phase, 689 correctly completed questionnaires were recorded, but 89 questionnaires had to be rejected due to restrictive inclusion criteria. The criteria are described below.

The HRF group included 300 students majoring in dietetics and physical education, selected for their specialized knowledge in rational nutrition and physical activity. In contrast, the NRF cohort consisted of 300 final-year students specializing in management and computer science, chosen for their absence of specialized knowledge in the aforementioned domains at the university level. Gender balance was taken into account in the selection of majors, considering the customary gender preferences for specific fields. Data were collected from January to March 2021. All final-year students were eligible. All students studied in Polish (Silesia region).

Exclusions from the NRF group involved individuals with prior or concurrent education in health-related fields, as well as those utilizing knowledge of rational nutrition and physical activity in their professional roles. Respondents with medical conditions affecting diet and physical activity, such as allergies, metabolic diseases, or tumors, were also excluded. Likewise, participants following specific dietary models (e.g., elimination diets) or experiencing pregnancy and puerperium were excluded.

The investigation targeted final-year students because of their anticipated in-depth understanding of health sciences and physical culture sciences, particularly among health science students. The inclusion of final-year students was also extended to the NRF group in order to uphold uniformity in inclusion criteria and guarantee a reasonably homogeneous student group.

In addition, people with a history of mental disorders, other eating disorders and substance abuse were excluded from the study. These data were subject to self-reporting in the survey questionnaire.

The study received approval from the Bioethics Committee of the Medical University of Silesia in Katowice (code: PCN/CBN/0052/KB/127/22, date: July 12, 2022), by the Act on Medical and Dental Professions of December 5, 1996, which defines medical experimentation. Additionally, participants in the study provided informed consent for their involvement.

2.3 Research tools

The body mass index (BMI) was calculated using the formula: BMI (kg/m^2) = body weight (kg)/height (m^2). The weight and height were self-reported by the surveyed students. The results were then evaluated using the following classifications (16): ≥30.00 kg/m^2, signifying obesity; 25.00–29.99 kg/m^2, indicating overweight; 18.50–24.99 kg/m^2, representing normal body weight; 17.00–18.49 kg/m^2, suggesting underweight; and ≤ 16.99 kg/m^2, denoting malnutrition.

The dietary assessment utilized a tool developed by the author based on Polish nutrition standards (45), comprising 20 dietary indices such as consumption frequency of specific food groups, meal count per day, meal regularity, snacking, and fluid intake. Respondents indicated ""yes" or "no" for each nutrition-related question and received one point for every correct answer based on established standards, with a maximum possible score of 20. The results were categorized using the following scale: 18–20 points for very good nutrition, 14–17 points for good nutrition, 10–13 points for moderate nutrition, and ≤ 9 points for poor nutrition. This questionnaire had been used in a prior study by the authors. The tool underwent validation through initial feedback from 10 specialists in the field, with revisions made based on their suggestions. Subsequently, the questionnaire was pilot-tested twice on a group of 30 adults, 2 weeks apart, and π Scott's coefficient was calculated to measure the questionnaire's consistency and relevance, yielding a relevance score of 0.93 (very good) for specific questions and 0.72 (good) for others (46).

Based on the physical activity score obtained from the survey, participants were classified into distinct PAL in accordance with established physical activity guidelines: 1.2 for sedentary behavior; 1.4 for low physical activity (approximately 140 min per week); 1.6 for moderate physical activity (around 280 min per week); 1.8 for high physical activity (about 420 min per week); and 2.0 for very high physical activity (around 560 min per week) (47).

The second version of the Exercise Motivations Inventory (EMI-2) questionnaire encompasses 56 variables distributed across 14 categories that delineate exercise motives. Within each category, participants could allocate five points, where 0 denoted the highest priority for the motivator and 5 signified the lowest priority. Consequently, lower scores for a particular motivator suggest a greater degree of motivation toward it (48).

The Düsseldorf Orthorexia Scale (DOS) test comprises 10 questions allowing respondents to choose between "agree' and "disagree." It offers a scoring range of 10–40 points. A score between 25 and 29 suggests the presence of orthorexic tendencies, while a score surpassing 30 indicates the presence of orthorexia (27).

The Three-Factor Eating Questionnaire (TFEQ-13) questionnaire facilitates the evaluation of three behaviors through a set of 13 questions distributed across three subscales: five questions pertain to eating restriction (RE) (questions 1, 9, 10, 12, and 13), five questions address a lack of control over eating (LCE) (questions 2, 5–7, and 11), and three questions directly inquire about eating influenced by emotions (EE) (questions 2, 4, and 8). Standardized responses are provided on a four-point scale, ranging from zero to three. Respondents select the most applicable statement for each question from options including "definitely yes," "rather yes," "rather no," and "definitely no." Scores are tabulated independently for each sub-scale, where a higher score indicates a more pronounced manifestation of the behavior. The overall scale exhibited a satisfactory internal consistency alpha Cronbach's coefficient of 0.78. For the individual subscales, it was 0.78 for eating restriction, 0.76 for lack of control over eating, and 0.72 for eating under the influence of emotions. Significantly, all subscales displayed positive and statistically significant correlations with one another ($p = 0.001$) (49).

2.4 Study procedure

The study involved a survey questionnaire and an album showcasing sample foods and dishes. Ethical guidelines, anonymity principles, and the RODO clause (Polish Law on Respect for Classified Information) were strictly followed during the study. The survey was administered through an online form, an accepted method in psychological research. Participants were sent the questionnaire link via dedicated email accounts. To prevent fake or bot responses, measures were taken during data collection, including checking login and completion times. The questionnaire was further secured with a CAPTCHA key.

In the second phase of the study, participants were presented with an album featuring sample foods and dishes. This album aimed to evaluate their ability to estimate portion size and calorie content. It comprised 12 photographs, each representing one of the 12 food groups (50). Before each study, participants' visual perception (image interpretation) was assessed using select Ishihara and optical illusion boards. These tools are commonly used to evaluate visual color perception and object perception in images (e.g., size, shape, and length). To link questionnaire results with the album, each participant was assigned a unique number while completing the questionnaire, which was then used to identify their responses in the album.

2.5 Statistical analysis

Data obtained from the survey questionnaire were organized into tables for descriptive examination, involving the calculation of percentages (%), counts (*N*; *n*), mean (*X*), and standard deviations (SD). Extensive statistical analyses were conducted to evaluate discrepancies between the exhibited behaviors (pro-health or anti-health) and the occurrence of EE within the sample cohort. The statistical analysis involved the utilization of chi-square (χ^2), U Mann–Whitney, and Kruskal-Wallis ANOVA tests. Kruskal-Wallis ANOVA test (Kruskal-Wallis H test), is used to compare three or more independent groups in terms of median or other central position. It is a non-parametric alternative to the one-way ANOVA and is used when the normality of the data distribution cannot be assumed. The odds ratio was calculated based on pooled calculations. The numbers of successes were divided by the number of failures in each group, and then the score of one group was divided by the score of the other group. The study adopted a pre-established significance level of $p = 0.05$.

3 Results

In the HRF group, women accounted for 55%, men 45%. In the NRF group, women accounted for 58%, men 42%. The statistical test showed no differences between the subjects in terms of the gender trait ($p < 0.05$). The social diversity of the subjects was present, but it was not significant and did not affected the final results of the study ($p < 0.05$). All respondents were students in the final year of their Master's degree. Nearly 90% of the respondents lived in cities with a population of more than 100,000. More than 80% of the respondents did not work permanently in any place. The mode of study and education of the respondents' parents were not reportable.

Considering the most significant motivating factors for physical activity, it was demonstrated that within the examined group, important motivators included (Table 1).

The intensity of specific motivations significantly varied between the HRF and NRF groups. The mean rank in the "maintaining health" subscale for HRF was (2.34 ± 1.75); significantly lower than the mean rank for NRF, which was (1.80 ± 1.74). This indicates that maintaining health is the strongest incentive for physical activity among HRF. In the 'weight control' subscale, the mean rank for HRF was (1.77 ± 1.76), higher than the mean rank for NRF (1.81 ± 1.82). Therefore, weight control is the most significant motivator for exercise in the NRF group. Both noted relationships were statistically significant ($p = 0.001$). Additionally, a statistically significant relationship was observed among individuals with low BMI values (98.2% of the underweight group and 65.7% of the normal weight group), and the motivator 'disease prevention' was revealed to be significant ($p = 0.001$). In this case, no differences were found between the study groups.

None of the participants examined were identified as malnourished. Approximately 15.5% of the participants were underweight. The majority of participants, about 61.6%, had a normal weight. Overweight and obesity were predominantly found in the NRF group, making up 23.7%. Statistically significant differences were observed concerning the prevalence of overweight and obesity in the NRF group ($p = 0.001$). In terms of dietary assessment, the HRF group demonstrated the most favorable dietary pattern, with 97.5% of students displaying a very good or good dietary pattern (84.0 and 13.5%, respectively). Conversely, the NRF group predominantly exhibited a moderate dietary pattern, constituting 64.7% of all cases

TABLE 1 The most significant motivating factors for physical activity.

Motivating factors for physical activity	Mean and SD (points)*	HRF	NRF	*T*	*f*	*p*
Disease prevention	2.08 ± 1.75	2.08 ± 1.71	2.08 ± 1.74	-	-	-
Maintaining health	2.06 ± 1.85	2.34 ± 1.75	1.80 ± 1.74	15.381	0.582	0.001
Strength/endurance	2.03 ± 1.84	2.02 ± 1.75	2.04 ± 1.79	-	-	-
Physical appearance	1.83 ± 1.86	182 ± 1.72	184 ± 1.80	-	-	-
Mental rejuvenation	1.85 ± 1.77	186 ± 1.78	184 ± 1.71	-	-	-
Weight control	1.77 ± 1.91	1.77 ± 1.76	1.81 ± 1.82	17.002	0.489	0.001
Exercise enjoyment	1.79 ± 1.84	178 ± 1.81	180 ± 1.84	-	-	-

*0—highest priority; 5—lowest priority.

in this group. A less common dietary pattern classified as "good" was identified in only 24.9% of cases within the NRF group. It is worth noting that an inadequate dietary pattern was predominantly observed in individuals from the NRF group (3.6% of the total participants).

Analyzing the data on physical activity and the motivations connected to it, it was noted that the majority of the HRF group (98.9%) and a significant portion of the NRF group (83.3%) demonstrated varying degrees of physical activity. Nearly half of the participants (46.5%) exhibited a low level of physical activity, with a notable prevalence among the NRF group (79.2%). In terms of moderate physical activity, approximately a quarter of the participants (25.4%) fell into this category, distributed across both the HRF group (33.5%) and the NRF group (16.7%). On the other hand, high to very high levels of physical activity were reported by over a quarter of the students (28.4%), with a substantial proportion coming from the HRF group (48.1%).

During the evaluation of portion sizes, it was noted that 32.7% of participants overestimated the sizes of products and dishes depicted in the images. The majority of this demographic belonged to the HRF group, accounting for 57.9%, whereas a smaller proportion came from other fields of study, totaling 7.2%. Conversely, in the case of underestimation (34.1%), primarily individuals from the NRF group underestimated the sizes of the products and dishes, comprising 56.5%. In contrast, within the HRF group, the percentage of underestimations was notably lower (10.8%). The remaining participants accurately assessed the portion sizes, accounting for 34.1%. After a slight adjustment of 0.3%, the overestimation increased to 33%, while the underestimation decreased to 34.5%. Upon analyzing the outcomes of the test regarding the capacity to estimate the caloric content of portions based on images, it was observed that 36.1% of participants overestimated the caloric content of the products and dishes presented in the images. Predominantly, individuals affiliated with health disciplines constituted this group (58.6%), whereas those without such affiliations were less prevalent (13.3%). On the contrary, in the case of underestimating the caloric content of the dishes (35.5%), individuals from the NRF group most frequently underestimated the energy value of the products and dishes featured in the album (55.8%); within the HRF group, such instances were considerably less common (15.6%). The remaining participants accurately indicated the caloric content of the portions, accounting for 29%. Following a minor adjustment of 0.3%, the percentage of overestimation rose to 36.4%, while underestimation decreased to 35.2%.

The analysis of the DOS questionnaire outcomes revealed that 52.7% of all participants exhibited inclinations toward orthorexia, with 12.3% displaying pathological (full-scale) orthorexia (totaling 390 individuals with orthorexia—65.0% from HRF and NRF group together). Orthorexic tendencies were more prominent in the HRF group compared to the NRF group (Table 2). Based on odds ratio calculations, it was approximated that orthorexia occurs 4.5 times more frequently in the HRF group than in the NRF group. When comparing BMI risk groups for orthorexia, it was observed that individuals with orthorexic tendencies from the HRF group had lower BMI values ($p = 0.002$). Similarly, in terms of diet, individuals with good and very good nutritional habits were more likely to be associated with the group at higher risk of orthorexia. In this instance, a statistically significant correlation with HRF group membership was also established ($p = 0.001$). Through the conducted statistical inference, it was deter-mined that high PAL values were prevalent in the HRF group exhibiting orthorexic tendencies, indicating a statistically significant association between the variables ($p = 0.002$). Regarding motivations, it was revealed that the primary driver for engaging in physical activity among the group displaying orthorexic tendencies was health concern. These motivations were selected three times more frequently by individuals from the HRF group than from the NRF group ($p = 0.001$). Furthermore, a statistically significant relationship was demonstrated in both the estimation of portion sizes and caloric content of meals; individuals from the HRF group with orthorexic behaviors tended to overestimate portion sizes and caloric content in the photographic model test ($p = 0.002$).

Based on TFEQ-13 scores, 33.4% exhibited dietary restriction (RE) behaviors (HRF: 62.6%; NRF: 10.1%), while lack of control over food intake (LCE) was exhibited by: HRF—11.7%; NRF—15.2%. Emotional eating (EE) was present in 57.7%, with the NRF group being the main demographic group (73.5%). There was no correlation between LCE and EE and the incidence of orthorexia in the study group ($p > 0.05$). However, a correlation was observed between the incidence of orthorexia and RE ($p = 0.001$). In this group, 85.5% of orthorexia cases also exhibited RE, and the condition was 2.5 times more common in the ON group (Table 3).

4 Discussion

The research conducted within the framework of the study on orthorexic behavior and emotional eating among young people related to the issue of taking care of health and fitness allowed us to learn about

TABLE 2 Identified risk factors for orthorexia in HRF I NRF groups (*n* = 390).*

Variable	Orthorectic HRF	Orthorectic NRF	*T*	*f*	*p*
BMI < 25 kg/m^2	59.7% (233)	40.3% (157)	13.644	0.562	0.002
Good diet quality	54.4% (212)	45.6% (178)	11.443	0.633	0.001
PAL > 1.6	55.2% (215)	44.8% (175)	14.002	0.459	0.002
Health-related physical activity motivation	51.2% (200)	48.8% (190)	10.982	0.458	0.001
Overestimated portion size	55.9% (218)	44.1% (172)	11.323	0.781	0.001
Overestimated caloric size	58.7 (229)	41.3% (161)	12.034	0.433	0.002

N, Sample size; HRF, Health-related fields; NRF, Non-health-related fields. *The results presented are only for the percentage of the risk factor in the subgroup studied.

TABLE 3 Relationship between prevalence of orthorexia and selected eating behaviors (*n* = 390).

TFEQ-13	HRF	NRF	*T*	*f*	*p*
	n = 390	*n* = 210			
Restrictive eating (RE)	62.6% (244)	10.1% (39)	10.091	0.289	0.001
Lack of control over eating (LCE)	11.7% (46)	15.2% (59)	–	–	–
Emotional eating (EE)	25.7% (100)	73.5% (286)	–	–	–

n, Orthorectic sample size; HRF, Health-related fields; NRF, Non-health-related fields.

the determinants of the occurrence of the indicated phenomena. Primarily, it has been confirmed that individuals exhibiting behaviors deemed health-promoting are characterized by a greater risk of developing orthorexia. These same individuals tend to overestimate the size and caloric content of foods and dishes on photo models presented to them. In addition, no links have been found between orthorexic behavior and emotional eating. However, orthorectic tendencies are associated with a behavior referred to in the literature as restrictive eating. In instances of emotional eating, it was observed to be more prevalent among individuals characterized by insalubrious and sedentary lifestyles, manifested through diminished levels of physical activity and erratic eating patterns. The same people in the study on estimating portion sizes and calories based on photographs showed a tendency to underestimate the portions and food items visible in them.

Learning about the motivators for physical activity in groups at potential risk for non-specific eating disorders seems reasonable, as they can provide an early diagnostic signal (51, 52). In the study provided by López-Gil et al. (53), data concerning the prevalence of orthorexia nervosa symptoms across 18 countries were presented, involving a total sample of over 30,000 participants. This meta-analysis reveals that the overall proportion of orthorexia nervosa symptoms stands at 27.5%, with marginal differences observed between genders. The highest prevalence of orthorexia nervosa symptoms was observed among individuals focused on sports performance or body composition. Furthermore, the analysis indicates a rising trend in the prevalence of these symptoms over the years, highlighting a significant public health concern and underscoring the necessity for the development of psychometric tools to support clinical diagnosis and treatment efficacy. In Poland, the situation regarding orthorexia is also noteworthy. Emerging research suggests a growing awareness of orthorexia nervosa within the country's population, however, with an increasing number of cases reported in recent years (42, 43). This underscores the importance of further investigation and intervention strategies tailored to the Polish context.

Several studies cited earlier noted that groups of individuals at risk for orthorexia have an above-average interest in the topic of maintaining a healthy life-style (13, 54–57). Such a group is very likely to include health science students (16, 28, 37). It is noted that in orthorexics, the motivation may or may not be weight loss, and the main driving force behind the disorder is the need to maintain health. It is emphasized that the primary motivator in undertaking activities aimed at improving and maintaining health in orthorexics will be reasons related to physical health, its regulation and maintenance (51). This includes motives for engaging in physical activity, which is a direct factor in maintaining health (52).

There are scientific reasons to suspect that behaviors indicative of orthorexia are more common in groups of people concerned with health and proper body shape (33, 36, 37). Several research studies emphasize the link between orthorexia and physical activity. For example, Herranz et al. (58) observed a higher prevalence of orthorexia in a group of yoga practitioners. Segura-García et al. (59) showed that in a group of athletes studied, 60% showed orthorexic tendencies. Similar relationships have been shown in groups of dancers, runners, swimmers, cyclists, and gym-goers (13, 55–57). This is accompanied by the creation of certain beliefs and patterns of compulsive repetition of certain activities. Such schematic behavior is often associated with the occurrence of anankastic personality (a.k.a. obsessive-compulsive personality) (OCPD) (60), a personality disorder during which a person feels an internal compulsion to act according to strictly defined procedures—the is not flexible and acts ac-cording to a scheme: "black or white"; "all or nothing" (61, 62).

Exercise is not only associated with improving fitness and functioning of the body but also with regulating emotions, which may be an important aspect of orthorexics (63, 64). Because orthorectic behavior can be a response to inappropriate emotion regulation, which in turn may contribute to the development of faulty eating patterns. Such as emotional overeating or restricting food intake, as well as misperception of food size and caloric content (65, 66). In their study, Strahler et al. highlighted that individuals with orthorexia exhibit markedly elevated levels of stress, depression, and anxiety, along with diminished life satisfaction when compared to their healthy counterparts (67). In other studies, orthorexia tendencies have been linked to other eating behaviors such as restricting food intake or emotional eating (68–70). In the aforementioned study (68), female students with orthorexia claimed that negative emotions lead them to increase cravings or restrict food intake. Similar emotional-motivational relationships were found in studies by Koven and Senbonmatsu (71) and Tan and Chow (69).

The scientific literature distinguishes between two emotion-based phenomena that project into the realm of eating behavior: emotional eating and food restriction (69). Both phenomena can be linked to stress and the occurrence of strong emotions in life. In the case of emotional eating, the main problem is that affected individuals con-fuse psychological signals with physiological ones, in effect consuming food at a time when real hunger is not present (70). Eating restriction can also be based on situations associated with elevated levels of stress, and the effect of this phenomenon is restraint in food intake or restriction of certain foods (72). Research to date emphasizes that normal-weight individuals may exhibit behaviors typical of emotional eating, but it is more of a problem for overweight individuals (73–75). More than half (57.3%) of overweight or obese adults report high levels of emotional eating (76). Emotional eating alone increases the risk of being overweight 14-fold (77, 78). Additionally, a study by Kowalkowska and Poinhos (79) noted that emotional eating tended to be more prevalent among women, whereas restrictive eating was more frequently observed in men. Another study, which involved 529 adult participants and 358 adolescents, discovered that girls exhibiting higher scores in restrained eating consumed fewer calories than their counterparts, while those characterized as emotional eaters had a greater intake of snack foods (80). According to results, emotional eating and uncontrolled eating are positively correlated in both genders, with the relationship being stronger in females (79, 81). The literature further emphasizes that orthorexia itself may be a response to negative emotions experienced by creating a way of coping (82–85). Hence, the connections between these phenomena may be legitimate.

5 Strengths and limitations

At this point, it is worth emphasizing that an important strength of the conducted research is that, in light of current scientific reports, the material developed appears to be a novel approach to non-specific eating disorders. Few studies in the scientific literature approach the topic from a psychodietetic angle—this approach allows a comprehensive assessment of the phenomenon and the setting of further research goals. The main goal of the conducted research was to identify the phenomenon of non-specific eating disorders among a group of people working in the field of health (dietetics and physical education). Of course, it was not assumed that it is the field of study that defines the type of unfavorable eating behavior, but rather certain personality conditions of the individual who chooses a particular field of study. It is worth emphasizing here that this aspect should be expanded with further research.

It should be noted that the research methods used have some limitations, but also development potential. Thus, in the future, it would be advisable to expand the scope of the research to include other social groups, and a larger number of research tools and deepen the existing conclusions. The main limitation of the research was that it was conducted using a diagnostic survey method with the help of online forms. The adoption of such a procedure was justified by the fact that the research part fell in 2020–2023 when the COVID-19 pandemic prevailed in the world. In order to mitigate potential response biases and minimize the risk of distortions, various precautions were implemented, including the use of access keys (CAPTCHA) and monitoring login times. In addition, the safeguards used completely reduced the risk of a fake/bot responder. An additional limitation was that the identification of respondents' behavior was based only on psychometric tools, so to minimize possible error the tools used were validated. Additionally, a limitation of the study can be considered the use of self-reported data regarding height and weight, which could be subjective and thus occasionally inaccurate. Another limitation of the study is that no other tools were used to study eating disorders, which will be expanded upon in future studies. Furthermore, due to the homogeneity of the population, the study did not examine the effect of gender and demographic characteristics on the prevalence of orthorexia. These will be undertaken in future research projects.

6 Practical implications

This study is important due to the lack of official recognition of orthorexia as an eating disorder and the associated behaviors, which may constitute predisposing factors to the development of eating disorders. By assessing the frequency of orthorexia among students with different lifestyles, including dietary habits and levels of physical activity, as well as their motivations, this study provides significant information. It identifies high-risk groups, especially students in health-related fields, who due to their strong health awareness may be more susceptible to orthorexic behaviors. Analyzing the motivations behind dietary habits and physical activity helps understand factors influencing orthorexic tendencies. The results indicate that these tendencies may be associated with lower BMI, better diet quality, and higher levels of physical activity, suggesting significant health consequences.

Simultaneously, while the studies conducted as part of this project are epidemiological in nature and contribute significantly to theories regarding eating disorders, it is important to emphasize their contribution to practice and potential future actions in the field of health promotion. Primarily, these studies managed to identify phenomena related to unfavorable dietary behaviors among young people. Therefore, further actions should focus on promotional and educational activities in identified high-risk groups. Given that the goals of national health promotion strategies include actions aimed at reducing the effects of mental disorders, including eating disorders, in society, as well as psychoeducation for high-risk groups. The conclusions drawn from the study provide an important lesson in further planning and implementing health policy programs and building support groups for individuals with problematic eating behaviors. Additionally, given the nature of the studied groups, it is worth considering incorporating into research programs sessions on methods and techniques for coping with stress and emotional regulation, as well as promoting basic psychological self-help skills.

7 Conclusion

For young individuals pursuing studies in health-related fields, their motivation to engage in regular exercise is primarily driven by a keen awareness of health issues. This heightened consciousness of health, however, can sometimes lead to a concerning phenomenon known as orthorexia. Orthorexia is an obsessive focus on consuming a "perfect" or excessively healthy diet, which can have detrimental effects on one's over-all well-being. Interestingly, those involved in health care topics or professions, who already adhere to what is commonly considered a healthy lifestyle—comprising regular physical activity and a nutritious diet—are at an increased risk of developing orthorexic tendencies. This underscores how the pursuit of health and knowledge in health-related domains can inadvertently foster a harmful fixation on dietary habits and body image. Individuals with orthorexic tendencies often exhibit a distorted perception of food portions and calorie content, perceiving them as larger than they truly are. This skewed perception reflects the rigidity and obsession associated with orthorexia, further emphasizing the need for awareness and intervention. Moreover, research has revealed a correlation between orthorexic behavior and food restriction. Those who engage in food restriction practices, whether due to dietary beliefs or body image concerns, are more susceptible to developing orthorexic tendencies. This inter-connection underscores the complex and multifaceted nature of disordered eating patterns and the importance of addressing both physical and psychological aspects of health in the education and support provided to young individuals in health-related fields.

In conclusion, it is worth emphasizing that orthorexic behavior *per se* is very often indicative of leading a pro-health lifestyle, which at first glance is not so bad, but as a consequence, worsening orthorexia can lead to many pathologies, such as the development of other eating disorders, such as anorexia or bulimia. In view of this, the results of the cited study may be a contribution to deepening expertise related to the prevalence of orthorexia in the general population and the study of its relationship with other eating disorders.

7.1 Implementation

Research findings on orthorexia among young individuals provide valuable insights for practitioners and clinicians to undertake effective actions in both mental and physical health domains. Based on these studies, specific strategies can be devised to aid in the identification, prevention, and treatment of this disorder. Firstly, community education about orthorexia is crucial. By organizing workshops, lectures, and seminars, awareness about this disorder can be raised among both young individuals and their caregivers. Secondly, routine screening in clinical practice can help swiftly identify individuals at risk of orthorexia. Diagnostic tools based on research findings can assist doctors and therapists in diagnosing this disorder. Thirdly, therapeutic interventions based on research data, such as cognitive-behavioral therapy, can be effective in treating orthorexia. Developing therapeutic programs tailored to the specific needs of young individuals is paramount. Fourthly, promoting healthy eating habits without falling into obsessive behaviors is essential. Practitioners and clinicians can use research findings to develop dietary guidelines emphasizing moderation, a balanced approach to eating, and enjoyment of meals. Fifthly, collaboration among specialists such as dietitians, psychiatrists, and family physicians is crucial in providing comprehensive care for individuals affected by orthorexia. Collaborative teamwork can offer more effective support for patients. Finally, further research on orthorexia is imperative. Such research could focus on identifying risk factors, the effectiveness of various therapeutic interventions, and the influence of social media and culture on the development of this disorder. In summary, research findings on orthorexia among young individuals serve as a foundation for practical actions for practitioners and clinicians. These findings enable effective responses to this disorder through identification, prevention, and treatment, contributing to the improvement of mental and physical health among the younger generation.

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 Bioethics Committee of the Medical University of Silesia in Katowice. 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. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MR: Formal analysis, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. MG: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. KK-K: Investigation, Methodology, Writing – review & editing, Writing – original draft. EM-M: Formal analysis, Resources, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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

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Frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 20 June 2024
DOI 10.3389/fnut.2024.1371077

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OPEN ACCESS

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RECEIVED 17 January 2024
ACCEPTED 13 June 2024
PUBLISHED 20 June 2024

CITATION
Chen H, Wang J, Guo H, Zhao Q, Lin G, Hocher B, Kalk P, Wang Z and Gong F (2024) Mediterranean diet improves blastocyst formation in women previously infected COVID-19: a prospective cohort study. *Front. Nutr.* 11:1371077.
doi: 10.3389/fnut.2024.1371077

Mediterranean diet improves blastocyst formation in women previously infected COVID-19: a prospective cohort study

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Objectives: Our study tries to investigate the effect of the Mediterranean diet (MeDiet) on assisted reproductive treatment outcomes in women after COVID-19 infection.

Design: A prospective observational cohort study in the Reproductive and Genetic Hospital of CITIC-Xiangya from February 2023 to August 2023.

Subjects: A total of 605 participants previously infected with COVID-19 were enrolled.

Exposure: None.

Main outcome measurement: The primary outcomes are oocyte and embryo quality. The secondary outcomes are pregnancy outcomes.

Results: A majority of participants ($n = 517$) followed low to moderate MeDiet, and only a small group of them ($n = 88$) followed high MeDiet. The blastocyst formation rate is significantly higher in MeDiet scored 8–14 points women (46.08%), compared to the other two groups (which is 41.75% in the low adherence population and 40.07% in the moderate adherence population respectively) ($p = 0.044$). However, the follicle number on hCG day, yield oocytes, normal fertilized zygotes, fertilization rate, day three embryos (cleavage embryos), and embryo quality are comparable among the three groups. For those who received embryo transfer, we noticed an obvious trend that with the higher MeDiet score, the higher clinical pregnancy rate (62.37% vs. 76.09% vs. 81.25%, $p = 0.197$), implantation rate (55.84% vs. 66.44% vs. 69.23%, $p = 0.240$) and ongoing pregnancy rate (61.22% vs. 75.00% vs. 81.25%, $p = 0.152$) even though the p values are not significant. An enlarging sample size study, especially in a high adherence population should be designed to further verify the effects of MeDiet's role in improving IVF performance.

Conclusion: High adherence to MeDiet is associated with improved blastocyst formation in women after COVID-19 infection. There is also a trend that high adherence to MeDiet might be beneficial to clinical pregnancy, embryo implantation as well as ongoing pregnancy in these women.

KEYWORDS

mediterranean diet, post COVID-19, IVF outcomes, embryo, pregnancy

1 Introduction

The Mediterranean diet (MeDiet) is a dietary pattern inspired by the traditional eating habits of countries bordering the Mediterranean Sea, such as Greece, Italy, and Spain (1). This dietary pattern was first coined by Ancel Keys back in 1960 (2). It is characterized by an abundance of fruits, vegetables, whole grains, legumes, and nuts, with olive oil as a primary source of fat. Fish and poultry are consumed in moderate amounts, while red meat is limited (1, 3, 4). The diet is known for its potential health benefits, including reducing the risk of cardiovascular disease (5, 6), diabetes (7, 8), cancers (9, 10), and overall mortality (11), promoting weight management and lowering the risk of metabolic syndrome (12, 13), and providing essential nutrients.

The Mediterranean diet is also said to offer a promising and relatively straightforward approach to mitigating the severity of COVID-19 infection (14). R. Perez-Araluce et al. revealed that individuals demonstrating moderate to high adherence to the Mediterranean diet experienced a significantly reduced likelihood of contracting COVID-19 (15). Notably, observational studies have emphasized a correlation between adherence to the Mediterranean diet and improved outcomes in individuals with COVID-19 (such as mortality and recovery rate), as well as a reduced risk of COVID-19 infection across various populations (16, 17). It is also recommended as a useful nutritional approach for patients with post-COVID-19 syndrome (18).

Moreover, MeDiet is associated with the improvement of female infertility, decreasing the risk of developing pregnancy-associated complications (19). Published evidence also revealed MeDiet's role in assisted reproduction. A previous cohort study investigated the Mediterranean diet's effect on *in vitro* fertilization (IVF) outcomes and it turned out that the higher MeDiet adherence group showed more embryos available (8.40 ± 5.26 vs. 7.40 ± 4.71, $p = 0.028$) while the pregnancy rate and implantation rate was similar (20). However, another study showed that women with higher Mediet scores had significantly higher clinical pregnancy rates (50.0% vs. 29.1%, $p = 0.01$) and live birth rates (48.8% vs. 26.6%, $p = 0.01$) (21). Conversely, an Italian study finds that the Mediterranean diet score was not significantly associated with IVF outcomes (22). A recent meta-analysis including 11 studies also concludes that insufficient current evidence exists to support the clinical application of high adherence to the Mediterranean diet and fertility markers (23). More evidence of well-designed clinical studies is needed to prove the comprehensive role of Mediet in IVF outcomes.

Current evidence demonstrates that COVID-19 infection impairs reproductive function and leads to infertility as well as unsuccess in IVF treatment (24). In a small-sample observational study, a reduction in the proportion of top-quality embryos was observed in women post-COVID-19 infection (25). Additionally, a slight decrease in the blastocyst (day 5 or later embryo) formation rate was recorded in the case group (26). Based on these findings MeDiet is helpful in many pathological situations of COVID-19 infection and is still controversial in IVF outcomes. Thus, our study tries to investigate the effect of MeDiet on IVF outcomes in women after COVID-19 infection.

2 Materials and methods

2.1 Study design and setting

We performed a prospective observational cohort study in women undergoing assisted reproductive technology (ART) treatment from February 2023 to August 2023.

2.2 Ethical approval

The current study was approved by the Ethics Committee of the Reproductive and Genetic Hospital of CITIC-Xiangya (approval number: LL-SC-2023-012) and written consent was obtained from all participating patients.

2.3 Participants

Women who were infected with COVID-19 before IVF treatment would be eligible for enrollment. Inclusion criteria: (1) age between 18 and 45 years and willingness to participate in the study, (2) women received ovarian stimulation, (3) the maximal time from COVID-19 infection to IVF treatment was defined as half a year, (4) only the first cycle following COVID-19 recovery was included. Exclusion criteria were as follows: (1) oocyte donation, (2) intrauterine insemination, (3) oocyte cryopreservation, (4) never being affected with COVID-19, (5) ART contraindications according to the guideline, such as either the man or the woman suffering from severe mental disorders, acute infections of the genitourinary system, or sexually transmitted diseases.

2.4 Sample size calculation

In this study, we considered a clinical pregnancy rate difference of 5% to detect a statistically significant difference, with a test power of 90% and a set α of 0.05. The calculated sample size required for the study was 594 participants. Accounting for a dropout rate of 5%, the final sample size for the study is 624.

2.5 Questionnaire and MeDiet score

The questionnaire, which consists of 14 questions, was published in a lot of journals and widely used to evaluate adherence to the

Mediterranean diet (27). The questionnaire focused on the category and consumption of food and drinks in daily life such as olive oil, fresh vegetables and fruits, seafood, and grains and nuts. Each question can be scored 1 point, with a total of 14 points. A higher score indicates higher adherence to the Mediterranean diet (Table 1).

Infertile couples were informed about the importance of lifestyle and dietary habits for preparing for pregnancy on their first visit to the hospital. Advise was given to them to adopt a healthy lifestyle and dietary habits for at least 1 month. Which includes a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation, consumed with meals (28). Most commonly, the recommended numbers of servings for these food groups are represented as a diet pyramid. A diet pyramid is considered a useful way to display the general principles of a diet including approximate recommendations for quantities of food groups (i.e., those consumed in the greatest quantities appear in the largest section of the pyramid) (29). Study participants were required to complete the Mediterranean diet questionnaire at the onset of ovulation stimulation treatment, providing information based on their actual dietary habits. The data was collected afterward and analyzed.

2.6 Outcome measurement

The clinical pregnancy was identified as the presence of gestational sac(s) exhibiting fetal heart activity through ultrasound in the fourth week following embryo transfer. The implantation rate was calculated by dividing the total number of embryos transferred by the number of sacs. Subsequently, miscarriage was characterized as the loss of intrauterine pregnancy after the confirmation of gestational sacs by ultrasound (30).

2.7 Data analysis

In the data processing procedure, all the missing data will be excluded from the final analysis. Data analyses were conducted using Statistical Package for Social Sciences for Windows, version 25.0 (SPSS Inc., Chicago, IL, United States). The homogeneity of variance and normality of data were assessed using the Levene and Kolmogorov–Smirnov tests, respectively. Results were presented as medians (interquartile ranges), means ± standard deviation, or frequency (%). Group comparisons for quantitative variables employed the Kruskal-Wallis test or ANOVA based on normality, while qualitative variables were compared using the Chi-square test or Fisher's exact test. Statistical significance was defined as a two-sided p-value <0.05.

3 Results

A total of 635 participants were recruited for the study, while 10 of them refused to fulfill the questionnaire and 10 of them did not meet the inclusive criteria, and the remaining 615 were enrolled in our study. However, 5 of them accepted oocyte cryopreserve due to personal reasons. 3 participants conceived spontaneously and 2 participants did not start the IVF treatment at the end of the study, leaving 605 participants to finish the ART procedure and their data was analyzed (Figure 1). Table 1 shows the 14 questions of the questionnaire and the answer distribution. The MeDiet score

TABLE 1 Mediterranean diet questionnaire and answer distribution.

Questions	Score		Frequency	
	1	0	1	0
1.Do you use olive oil as the principal source of fat for cooking?	Yes	No	27	578
2.How much olive oil do you consume per day, including that used in frying, salads, meals eaten away from home, etc.?	≥54 g	<54 g	74	531
3.How many servings of vegetables do you consume per day? (count garnish and side servings as ½ point; a full serving is 200 g)	≥2	<2	362	243
4.How many servings of fruit do you eat per day (including fresh fruit juice)?	≥3	<2	123	482
5.How many servings of red meat/burgers/sausages do you consume per day (a full serving is 100-150 g)?	<1	≥1	309	296
6.How many servings of (artificial) cream/butter/cheese do you consume per day (a full serving is 12 g)?	<1	≥1	551	54
7.How many carbonated and/or sugar-sweetened beverages do you consume per day?	<1	≥1	535	70
8.What is your weekly alcohol consumption?	≥700 mL	<700 mL	48	557
9.How many servings of legumes do you consume per week (a full serving is 150 g)?	≥3	<3	179	426
10.How many servings of fish/seafood do you consume per week? (100-150 g of fish, 4-5pieces or 200 g of seafood)	≥3	<3	128	477
11.How often do you consume (non-homemade) pastries/cookies/cakes per week?	<2	≥2	462	143
12.How many servings of nuts do you eat per week (a full serving is 30 g)?	≥3	<3	126	479
13.Do you prefer chicken/turkey/rabbit over beef/pork/burgers/sausages?	Yes	No	159	446
14.How often do you consume boiled vegetables/pasta/rice or tomatoes/garlic/onions/chives sautéed in olive oil per week?	≥2	<2	240	365

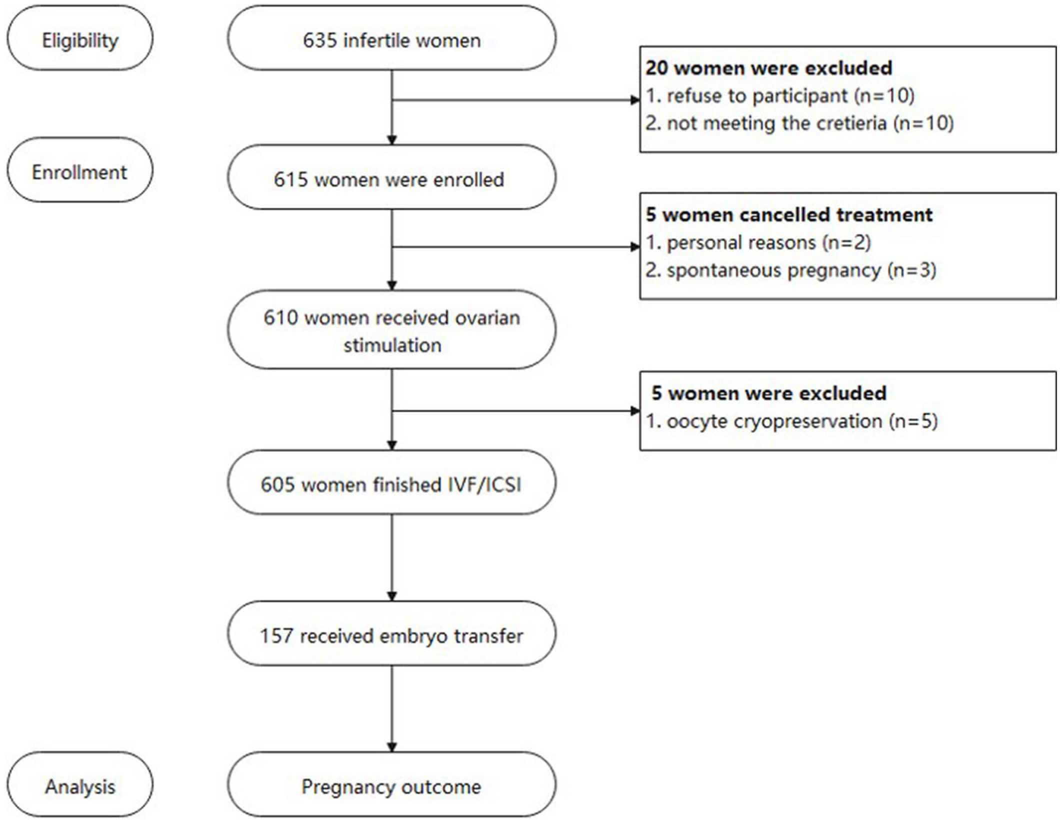

FIGURE 1
Flow chart of the study.

distribution is shown in Figure 2A. We divided our participants into three groups according to the MeDiet score: low adherence [MeDiet score 0–4 ($n = 191$)], medium adherence [MeDiet score 5–7 ($n = 326$)] and high adherence [MeDiet score 8–14 ($n = 88$)]. A majority of participants followed low to moderate MeDiet, and only a small group of them followed high MeDiet. There is no difference in demographic information such as age, infertility type and reason, body mass index, waist-to-hip ratio, blood pressure, etc. among these groups. Besides, we also evaluated some serological markers to evaluate the metabolic status of our participants. No difference was found in fasting glucose, insulin level, HOMA-IR (homeostatic model assessment of insulin resistance) as well as thyroid function among groups. Similarly, no differences were found in blood cells and coagulation indicators in our participants (Table 2).

Ovarian stimulation protocol differs among the groups with less gonadotropin-releasing hormone agonist (GnRH-a) protocol while more uncommon protocols (such as mild stimulation, letrozole protocol, etc.) are administrated in the higher MeDiet score group ($p = 0.019$). Nevertheless, there is no difference in sex hormones such as estradiol (E2), progesterone (P), and luteinizing hormone (LH) on human chorionic gonadotropin (hCG) day. The follicle number on hCG day, yield oocytes (including metaphase II (MII), metaphase I (MI), germinal vesicle (GV), degenerated oocytes), 2 pronucleus (2PN) zygotes, fertilization rate, day three embryos (cleavage embryos) and embryo quality are comparable among the three groups. Interestingly, there is an obvious difference in that the blastocyst formation rate is significantly higher in MeDiet scored 8–14 points women (46.08%), compared to the other two groups (which is 41.75 and 40.07% respectively) ($p = 0.044$). Further multivariate regression analysis also shows the positive relationship between MeDiet and blastocyst formation [adjusted β:0.077, 95% confidential interval: (0.028, 0.313), $p = 0.019$]. Moreover, age is negatively related to blastocyst formation [adjusted β: −0.099, 95% confidential interval: (−0.098, −0.018), $p = 0.005$] (Supplementary Table S1). However, there is no difference in blastocyst quality (Table 3).

There were only 157 women out of 605 participants received fresh embryo transfer. The reasons for other participants' embryo transfer cancellation are as follows: 1. Ovarian hyperstimulation syndrome ($n = 15$), 2. No oocytes retrieved ($n = 5$), 3. No transferrable embryo ($n = 35$), 4. Desynchronization between the endometrium and the embryo ($n = 165$), 5. Peri-implantation genetic test ($n = 169$), 6. Personal reasons ($n = 59$). The follow-up in this study ends 3 months after the embryo transfer. For those who received embryo transfer, we noticed an obvious trend that with the higher MeDiet score, the higher clinical pregnancy rate (62.37% vs. 76.09% vs. 81.25%, $p = 0.197$), implantation rate (55.84% vs. 66.44% vs. 69.23%, $p = 0.240$) and ongoing pregnancy rate (61.22% vs. 75.00% vs. 81.25%, $p = 0.152$) even though the p values are not significant (Table 4; Figure 2B). Only two miscarriage cases and no ectopic pregnancy cases were observed in the study population.

To further validate the age risk for blastocyst formation, we divided our participants into two age groups: women with age less than 35 years old and those beyond 35 years old. Surprisingly,

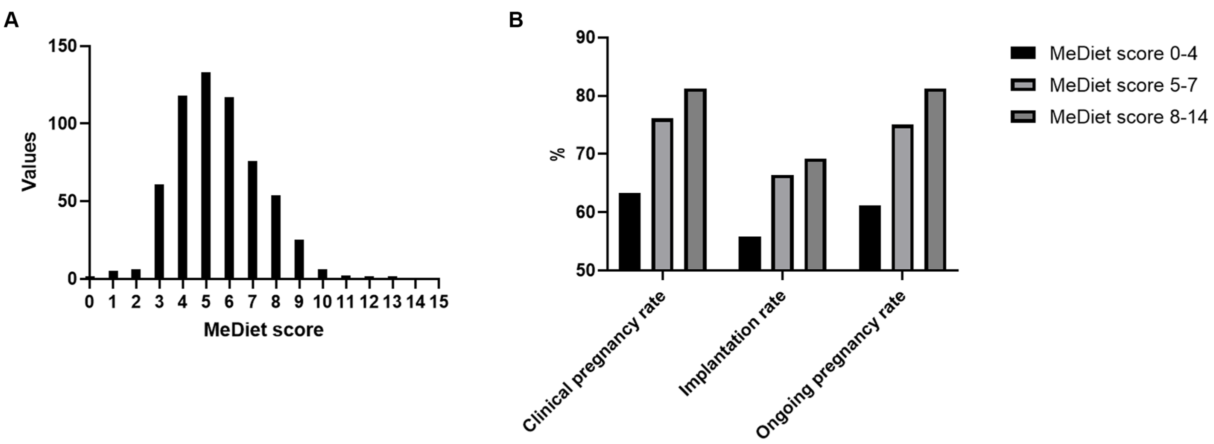

FIGURE 2
MeDiet score distribution and pregnancy outcomes.

we observed a similar result in women under 35 that the blastocyst formation rate is higher in the highest MeDiet appliance women(47.03%), compared to low (40.23%) and moderate (39.74%) appliance women ($p = 0.033$). No difference is observed in pregnancy outcomes (Supplementary Table S2). However, there is no difference in oocyte and embryo quality as well as pregnancy outcomes in women with age above 35 years old (Supplementary Table S3).

4 Discussion

In the present study, we noticed that women after COVID-19 infection with high adherence to MeDiet obtained a higher blastocyst formation rate. Meanwhile, MeDiet might play a favorable role in pregnancy outcomes such as clinical pregnancy, implantation as well as ongoing pregnancy. However, there is no relationship between MeDiet and the quantity and grade of oocyte and embryo.

MeDiet is characterized by the incorporation of predominantly plant-based nutritional elements, including fruits, vegetables, legumes, nuts, and olive oil. These items serve as notable reservoirs of bioactive polyphenols. Polyphenols, specifically flavonoids and their derivatives, exhibit diverse health-promoting effects, particularly in cardiovascular and metabolic conditions, owing to their antioxidant, anti-inflammatory, anti-thrombotic attributes, and immunomodulatory effects (31, 32). Accumulating evidence from prospective cohort observational studies suggests that the nutritional status of both the father and mother during the periconceptional period influences early fetal development and the perinatal and long-term health of the offspring (33). Recent studies gradually focus on dietary habits and early embryo development and pregnancy. In an observational study, it was shown that embryos from women reporting higher consumption of fruit and fish had an elevated likelihood of forming a blastocyst. Conversely, there was a decreased probability of blastocyst formation in those who consumed more red meat or were on a weight loss diet (34). Similarly, we found that women with high adherence to Mediet obtained more blastocyst formation in the present study, which is in accordance with the previous results. It is reported that a short MeDiet dietary supplementation alters the rate of embryo cleavage, indicating improved embryo quality (35). However, this study was limited to the cleavage embryos with no data on blastocyst formation.

Mediterranean diet showed a positive correlation with elevated levels of red blood cell folate and vitamin B6 in both blood and follicular fluid. Additionally, following this diet was associated with a reported 40% increase in the likelihood of achieving pregnancy (36). Vitamin B6 serves as a versatile coenzyme engaged in numerous biochemical pathways. Studies indicate that administering vitamin B6 to women experiencing subfertility enhances reproductive performance (37). Additionally, earlier research findings have indicated that the consumption of fruits and vegetables is linked to reduced oxidative stress and enhanced antioxidant status (38), while oxidative stress has been shown to cause defective embryo development *in vitro* (39). Optimal concentrations of antioxidants in oocytes are essential for regular fertilization and subsequent embryonic development during the preimplantation stage (40). It was demonstrated that women with a high intake of alpha-linolenic acid exhibited elevated baseline oestradiol levels, suggesting that increased intake of alpha-linolenic acid and docosahexaenoic acid may enhance embryo morphology (41). This results in accordance with another study which shows the relationship between fish consumption and the likelihood of blastocyst formation (34).

COVID-19 infection could cause a series of body defensive responses, which damages the reproductive process. One of the important mechanisms is associated with exaggerated immune responses like "cytokine storm" and intense inflammation. Excessive production of proinflammatory cytokines can modulate the cellular microenvironment in a way that impairs reproductive physiology (24). Another mechanism is oxidative stress and disturbed reproductive health. Massive reactive oxygen species (ROS) are produced at the subcellular level during the COVID-19 infection period, which is involved in the etiology of errant embryo implantation and development, ovulatory failure, and hyperandrogenism (42, 43). In patients with past COVID-19 infection, decreased pregnancy rates were observed after embryo transfer (44). In another study, a reduced proportion of top-quality embryos was observed (25). Based on those findings, we designed this study to evaluate whether MeDiet improves IVF outcomes in women with past COVID-19 infection. Unfortunately, we did not observe a significant difference in

TABLE 2 The demographic and baseline information of participants.

	MeDiet score 0–4 (n = 191)	MeDiet score 5–7 (n = 326)	MeDiet score 8–14 (n = 88)	p value
Age (year)	32.00 (29.00, 36.00)	32.00 (29.00, 35.25)	33.00 (31.00, 36.75)	0.104
Infertility type (%)				
Primary	36.65 (70/191)	30.67 (100/326)	35.23 (31/88)	0.570
Secondary	55.50 (106/191)	58.28 (190/326)	54.55 (48/88)	
Others	7.85 (15/191)	11.04 (36/326)	10.23 (9/88)	
Infertility reason (%)*				
PCOS	19.37 (37/191)	19.94 (65/326)	2045 (18/88)	0.976
Endometriosis	32.98 (63/191)	38.96 (127/326)	29.55 (26/88)	0.168
Oviduct malfunction	64.92 (124/191)	66.26 (216/326)	63.64 (56/88)	0.884
Infertility duration (year)	3.00 (1.00, 4.00)	3.00 (1.00, 4.00)	3.00 (1.25, 5.00)	0.382
BMI (kg/m2)	22.43 (20.24, 24.03)	22.37 (20.28, 24.22)	21.57 (20.34, 23.83)	0.713
Waist-to-hip ratio	0.81 (0.77, 0.85)	0.80 (0.77, 0.85)	0.81 (0.77, 0.85)	0.932
AMH (ng/ml)	3.14 (1.57, 4.91)	2.79 (1.60, 4.84)	2.66 (1.45, 4.47)	0.410
AFC	21.00 (10.00, 33.00)	22.00 (13.00, 33.00)	18.50 (9.00, 30.00)	0.228
Basal FSH (mIU/ml)	6.37 (5.32, 7.88)	6.24 (5.14, 7.83)	6.55 (5.40, 8.59)	0.275
Basal LH (mIU/ml)	4.44 (2.77, 6.77)	4.25 (2.66, 6.22)	4.23 (2.66, 6.47)	0.642
Basal E2 (pg/ml)	38.60 (29.78, 97.00)	42.05 (30.98, 91.35)	40.10 (29.60, 130.00)	0.571
Basal P (ng/ml)	0.32 (0.18, 1.08)	0.38 (0.19, 1.23)	0.39 (0.22, 1.57)	0.441
Fasting glucose (mmol/L)	5.15 (4.91, 5.44)	5.20 (4.97, 5.42)	5.15 (4.86, 5.44)	0.534
Fasting insulin (μIU/mL)	8.00 (5.70, 10.60)	7.60 (5.40, 10.91)	7.10 (5.03, 9.90)	0.299
HOMA-IR	1.69 (1.19, 2.43)	1.75 (1.23, 2.43)	1.62 (1.03, 2.40)	0.294
Free T3 (pg/ml)	2.86 (2.64, 3.09)	2.82 (2.60, 3.07)	2.73 (2.50, 3.03)	0.073
Free T4 (ng/ml)	1.00 (0.92, 1.09)	0.99 (0.92, 1.09)	0.99 (0.89, 1.07)	0.416
TSH (μIU/ml)	1.90 (1.37, 2.57)	1.76 (1.23, 2.55)	1.61 (1.13, 2.37)	0.100
Systolic blood pressure (mmHg)	114.00 (106.00, 122.00)	115.00 (105.00, 122.00)	111.00 (102.00, 121.00)	0.184
Diastolic blood pressure (mmHg)	73.00 (67.00, 81.00)	74.00 (68.00, 80.00)	72.00 (65.00, 79.00)	0.524
WBC (x10^9/L)	5.90 (5.10, 7.40)	5.90 (5.01, 7.20)	6.20 (5.00, 7.38)	0.781
RBC (x10^12/L)	4.49 (4.22, 4.71)	4.43 (4.23, 4.66)	4.39 (4.21, 4.69)	0.347
HGB (g/L)	135.00 (128.00, 140.00)	133.00 (127.00, 139.00)	135.00 (127.25, 139.00)	0.403
MCV (fl)	90.10 (87.70, 92.80)	90.60 (87.68, 93.20)	90.80 (88.33, 93.28)	0.568
PLT (x10^9/L)	240.00 (201.00, 282.00)	239.00 (202.00, 281.50)	245.00 (212.00, 294.50)	0.713
D-Dimer (mg/L)	0.23 (0.16, 0.40)	0.24 (0.15, 0.35)	0.25 (0.15, 0.32)	0.873
APTT (s)	33.40 (31.50, 35.60)	33.05 (31.00, 35.20)	32.30 (30.20, 35.28)	0.104
PT (s)	11.00 (10.70, 11.40)	11.10 (10.70, 11.50)	11.00 (10.50, 11.50)	0.336
FIB (g/L)	2.76 (2.50, 3.15)	2.82 (2.47, 3.11)	2.90 (2.62, 3.24)	0.194
TT (s)	14.00 (13.30, 14.80)	14.00 (13.20, 14.90)	13.90 (13.20, 14.90)	0.949

PCOS, polycystic ovary syndrome; BMI, body mass index; AMH, anti-Müllerian hormone; AFC, antral follicle count; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2: estradiol; P, progesterone; HOMA-IR, homeostatic model assessment of insulin resistance; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; MCV, mean corpuscular volume; PLT, platelet; APTT, activated partial thromboplastin time; PT, prothrombin time; FIB, fibrinogen; TT, thrombin time. *Some participants have more than one infertility reason.

improvement in pregnancy outcomes, which is attributed to the small sample size of women who received embryo transfer. However, there is a trend that the clinical pregnancy rate, implantation rate, and ongoing pregnancy rate are higher along with higher adherence to MeDiet.

Participants in our study adhered to MeDiet at least 1 month before they started IVF treatment. However, it's a short period. Whether a longer dietary history could prevent adverse effects of infections and/or promote a healthy pregnancy in general should be verified in further research. Moreover, it is a Western dietary

TABLE 3 Ovarian stimulation outcomes.

	MeDiet score 0–4 (n = 191)	MeDiet score 5–7 (n = 326)	MeDiet score 8–14 (n = 88)	p value
Protocol (%)				
GnRH-agonist protocol	37.70 (72/191)	41.41 (135/326)	27.27 (24/88)	**0.019**
GnRH-antagonist protocol	37.17 (71/191)	41.72 (136/326)	39.77 (35/88)	
PPOS	17.28 (33/191)	11.35 (37/326)	19.32 (17/88)	
Others*	7.85 (15/191)	5.52 (18/326)	13.64 (12/88)	
Gn dosage/[IU]	2250.00 (1537.50, 2975.00)	2306.25 (1612.50, 3000.00)	2193.75 (1650.00, 2971.88)	0.806
Gn duration/[day]	10.00 (9.00, 12.00)	10.00 (9.00, 12.00)	10.00 (9.00, 11.25)	0.428
E2 on hCG day/[pg/ml]	2931.50 (1819.00, 4437.75)	2983.50 (1577.75, 4285.00)	2540.00 (1531.00, 3874.00)	0.271
P on hCG day/[ng/ml]	0.72 (0.49, 1.11)	0.71 (0.47, 1.04)	0.67 (0.46, 1.03)	0.451
LH on hCG day/[mIU/ml]	2.23 (1.53, 3.67)	2.30 (1.58, 3.79)	2.59 (1.51, 4.54)	0.423
hCG dosage for triggering (IU)	5000.00 (5000.00, 6000.00)	5000.00 (2000.00, 6000.00)	5000.00 (2000.00, 6000.00)	0.226
Follicles on hCG day	11.00 (7.00, 14.00)	11.00 (7.00, 14.00)	10.00 (5.00, 13.00)	0.226
No. of oocytes retrieved	11.00 (6.00, 14.00)	10.50 (6.00, 14.00)	10.00 (4.25, 12.75)	0.149
MII oocytes	9.00 (5.00, 12.00)	9.00 (5.00, 13.00)	8.00 (3.25, 11.75)	0.161
MI oocytes	0.72 ± 1.59	0.79 ± 1.28	0.53 ± 1.13	0.092
GV oocytes	0.85 ± 1.54	0.69 ± 1.24	0.76 ± 1.70	0.701
Degenerated oocytes	0.14 ± 0.36	0.17 ± 0.41	0.16 ± 0.37	0.831
No. of 2PN zygotes	6.00 (3.00, 9.00)	6.00 (3.00, 9.00)	6.00 (3.00, 8.00)	0.259
Fertilization methods (%)				
IVF	49.74 (95/191)	46.63 (152/326)	45.45 (40/88)	0.942
ICSI	43.98 (84/191)	46.93 (153/326)	48.86 (43/88)	
IVF + ICSI	6.28 (12/191)	6.44 (21/326)	5.68 (5/88)	
Fertilization rate (%)	61.54 (50.00, 76.44)	62.50 (50.00, 76.92)	66.67 (42.86, 82.58)	0.560
Cleavage embryos	8.00 (5.00, 11.00)	7.00 (4.00, 11.00)	6.50 (3.00, 10.75)	0.268
The number of day 3 good quality embryo	4.00 (1.00, 6.00)	3.00 (1.00, 5.00)	2.50 (1.00, 5.00)	0.413
Blastocyst formation rate (%)	41.75 (516/1236)	40.07 (864/2156)	46.08 (235/510)	**0.044**
The number of good-quality blastocysts	0.29 ± 0.88	0.32 ± 0.89	0.31 ± 0.98	0.820

GnRH, gonadotropin-releasing hormone; PPOS, progestin-primed ovarian stimulation; Gn, gonadotropin; LH, luteinizing hormone; E2, estradiol; P, progesterone; hCG, human chorionic gonadotropin; MII, metaphase II (reflects oocytes quality, only MII oocytes can be fertilized); MI, metaphase I; GV, germinal vesicle; 2PN, pronucleus; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; Good quality embryo is defined as D3 embryo ≥ 7C-II and blastocyst ≥ 4BB while fair embryo is defined as D3 embryo <7C-II and blastocyst <4BB; Data are given as medians (interquartile ranges), means ± standard deviation, or number (percentage). *Others include mild stimulation, Gn stimulation, letrozole protocol, and natural cycle.
Bold values present p<0.05, means significantly different.

TABLE 4 Pregnancy outcomes.

	MeDiet score 0–4 (n = 49)	MeDiet score 5–7 (n = 92)	MeDiet score 8–14 (n = 16)	p value
Endometrium thickness (mm)	12.50 (11.05, 14.00)	12.40 (11.00, 13.80)	13.20 (11.80, 14.55)	0.306
The number of embryos transferred	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.931
Good-quality embryo transferred	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.50 (0.00, 2.00)	0.988
Clinical pregnancy rate (%)	63.27 (31/49)	76.09 (70/92)	81.25 (13/16)	0.197
Implantation rate (%)	55.84 (43/77)	66.44 (97/146)	69.23 (18/26)	0.240
Early miscarriage rate (%)	2.04 (1/49)	1.09 (1/92)	0	0.729
Ectopic pregnancy rate (%)	0	0	0	–
Ongoing pregnancy rate (%)	61.22 (30/49)	75.00 (69/92)	81.25 (13/16)	0.152

pattern, indicating that it is possible that other healthy dietary patterns that suit Asia people could also be beneficial factors in this regard and needs to be determined.

To the best of our knowledge, the present study is the first to propose the influence of the Mediterranean diet on the IVF outcomes of post-COVID-19 females. However, limitations also exist in our study. On one hand, the sample size for women who received embryo transfer is relatively small, especially in women with high MeDiet adherence, which limited the efficacy of the results. On the other hand, a majority of participants in our study with low to moderate adherence to the MeDiet, leaving a minority of them with high adherence. The sample size difference might restrict the effectiveness of the test to some extent. However, the main reason underlying is that the dietary habits differ substantially from Asian to European, thus, only a small group of people could follow the MeDiet. More importantly, we cannot avoid the potential biases associated with self-reported dietary habits. Lastly, we did not follow up on the long-term outcomes such as live birth, or gestational complications. Further studies should give full consideration to sample size and long-term outcomes such as live birth rates and gestational complications.

5 Conclusion

High adherence to MeDiet is associated with improved blastocyst formation in women after COVID-19 infection. There is also a trend that high adherence to MeDiet might be beneficial to clinical pregnancy, embryo implantation as well as ongoing pregnancy in these women.

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 Ethics Committee of the Reproductive and Genetic Hospital of CITIC-Xiangya. 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

HC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. JW: Methodology, Formal analysis, Validation, Software, Writing – review & editing. HG: Data curation, Project administration, Writing – review & editing. QZ: Data curation, Project administration, Writing – review & editing. GL: Supervision, Writing – review & editing. BH: Writing – review & editing. PK: Writing – review & editing. ZW: Validation, Writing – review & editing. FG: Methodology, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research was supported by Hunan Provincial Grant for Innovative Province Construction (2019SK4012). Internal Grant of Reproductive and Genetic Hospital of CITIC-Xiangya (YNXM-202304, YNXM-202217). China Scholarship Council supported Huijun Chen (202108430016). Xiangyang City Science and Technology Program in Health Care (2022YL19B).

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.2024.1371077/full#supplementary-material

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frontiers | Frontiers in Nutrition

TYPE Brief Research Report
PUBLISHED 12 September 2024
DOI 10.3389/fnut.2024.1395977

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Ketogenic diet improves fertility in patients with polycystic ovary syndrome: a brief report

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RECEIVED 04 March 2024
ACCEPTED 15 August 2024
PUBLISHED 12 September 2024

CITATION
Tsushima Y, Nachawi N, Pantalone KM, Griebeler ML and Alwahab UA (2024) Ketogenic diet improves fertility in patients with polycystic ovary syndrome: a brief report.
Front. Nutr. 11:1395977.
doi: 10.3389/fnut.2024.1395977

Introduction: Polycystic ovary syndrome (PCOS) affects up to 20 % of reproductive-age individuals and is strongly linked to obesity. The impacts of ketogenic diet on fertility in people with PCOS are unknown. This study aims to determine the effect of a ketogenic diet on restoration of regular menstrual cycles and fertility.

Methods: After approval from the Institutional Review Boards of Cleveland Clinic, a retrospective analysis was conducted using the electronic health record system. We analyzed data from thirty patients (n = 30) with polycystic ovary syndrome who followed a ketogenic diet for at least 3 months at the Cleveland Clinic, Cleveland, Ohio, USA. Main outcomes were percentage of women with restoration of regular menstrual cycles and pregnancy rate.

Results: All women (n = 30) had restoration of regular menstrual cycles. The overall pregnancy rate of women desiring pregnancy (n = 18) was 55.6% (n = 10). Pregnancy rate was 38.5% for women on metformin and 100% for those who were not (P = 0.036). Pregnancy rate was 62.5% for women using ovulation induction agents and 50.0% for those who did not (P = 0.66). Percent weight change between the pregnant and non-pregnant groups did not significantly differ [-8.1 ± 6.2, vs -6.4 ± 8.4, P = 0.64, respectively].

Conclusion: This study reports a higher rate of pregnancy with the ketogenic diet in women with PCOS compared to existing literature.

KEYWORDS

ketogenic diet, fertility, polycystic ovary syndrome, obesity, ovulation, pregnancy

Highlights:

- Obesity plays a key role in the mechanism of infertility affecting up to 60% of women with PCOS.
- Keto Diet (KD) improves characteristics of PCOS such as insulin levels, free testosterone, and LH/FSH ratio.
- The effect of Keto Diet on fertility in patients with PCOS is unknown.
- The KD may improve ovulation and fertility rates in women with PCOS regardless of metformin or ovulation induction use.

- Further prospective studies evaluating the impact of a KD on fertility appear warranted, as well as mechanistic studies to further elucidate the mechanism by which a KD may improve fertility, with or without weight loss.

1 Introduction

Polycystic ovary syndrome (PCOS) affects 6–20 % of reproductive-age women depending on the population studied and the diagnostic criteria used (1). It is one of the most common causes of anovulatory infertility in this population. PCOS is strongly associated with obesity and its prevalence in the PCOS population may be as high as 75% (2). Obesity, along with insulin resistance, plays a key role in the mechanism of infertility in these women, whereby an elevation in luteinizing hormone leads to increased circulating androgens which inhibits ovulation (3).

Diet-induced weight loss and insulin-sensitizing agents are shown to improve ovulation (2, 4). The ketogenic diet (KD) has garnered increasing attention for its ability to cause significant weight loss and improve metabolic syndrome, both of which are characteristics of PCOS. Currently, the term KD is used broadly because of its many variants. The original KD was designed to treat pediatric epilepsy and is composed of a 4:1 ratio of fat to protein plus carbohydrates (in grams) (5). Modified versions of this have been adapted for weight loss and diabetes. Feinman et al. have suggested that a very low carbohydrate ketogenic diet consists of 20–50 g of carbohydrates per day or carbohydrates < 10 % of a 2000 kcal per day (6).

Investigations regrading the effects of KD on patients with PCOs are limited to small and short-term studies. In a small study, patients with obesity and PCOs who underwent KD for 24 weeks, had significant reductions in body weight (−12%), fasting insulin (−54%), percent free testosterone (−22%), and LH/FSH ratio (−36%). Insulin, glucose, testosterone, HgbA1c, triglyceride, and perceived body hair didn't differ from baseline. Two patients conceived despite previous infertility problems (7). Same changes were demonstrated in another study involving 12 patients with PCOs and overweight who underwent KD for 12 weeks had significant reductions in body weight, BMI, fat body mass and visceral adipose tissue with slight reduction in lean body mass. Significant reductions in insulin, glucose, HOMA-IR, total cholesterol, triglycerides, LDL, LH/FSH ratio, LH, total and free testosterone, and DHEAS levels were observed. HDL, estradiol, progesterone and SHBG levels increased. The study didn't show any difference in Ferriman Gallwey Score (8).

However, the effect of a KD on fertility in patients with PCOS has not been previously reported. In a small case series, our group previously reported that the KD restored regular menses in all patients and achieved pregnancy in 50% of the cohort (9). The objective of this report is to build upon this previous report and provide additional evidence for the use of KD to restore regular menstruation and achieve pregnancies in women with PCOS.

2 Materials and methods

After approval from the Institutional Review Boards of Cleveland Clinic, a retrospective analysis was conducted using the enterprise-wide electronic health record system at Cleveland Clinic, Cleveland, Ohio.

Patients with PCOS who were referred to the Endocrinology and Metabolism Institute's Integrated Weight Management Program for management of PCOS and obesity were identified. The Integrated Weight Management Program is comprised of monthly shared medical appointments (SMAs) of up to 10 patients who are evaluated using a multidisciplinary approach consisting of encounters with a registered dietitian who provides education and structured guidance on the KD plan, exercise physiologists for individualized exercise programs, and endocrinology and obesity specialists who lead the program.

The KD plan implemented in our SMA consists of up to 20 g of net carbohydrates, protein intake of 1.6 x weight in Kg = grams/day, Fat intake up to 40 grams/day. At least 64 oz of water intake is required. The use of ketogenic supplements was discouraged. However, potassium chloride supplement of 10 meq per day were prescribed. Calorie count was not required however, the above plan would reach 1000–1200 Kcal/day for all patients.

2.1 Study population

The electronic health record system at the Cleveland Clinic was queried for women who were enrolled in the SMA program for PCOS management from September 2017 to September 2019. The SMA program enrolls 50 to 60 patients per year and involves unlimited number of monthly visits. Of patients enrolled in the SMA program, women who were diagnosed with PCOS, had clear documentation of KD initiation, remained on the KD for at least 3 months, or were on a KD for less than 3 months but achieved pregnancy, were included. We excluded women who discontinued the KD prior to 3 months duration (for reasons other than achieving pregnancy), changed to a non-KD before 3 months or initiation date of the KD was not clearly documented, and those actively using contraception or were post-menopausal. Women receiving metformin and ovulation induction agents were also included. Thirty women who met the above outlined criteria were identified.

2.2 Intervention

Participants were enrolled in SMA program that included monthly visit. Exercise counseling was provided in the first visit without further monitoring. Participants had an initial visit with the physician and dietician at the start of the KD. Monthly visits were conducted to document changes in weight and menstruation and to address any dietary and medical concerns. Patients were given the option to start metformin if there was no prior history of intolerance. Ovulation induction agents were also offered to women seeking pregnancy. Patients were asked to notify the provider if they became pregnant or stopped the KD plan. Women who because pregnant were advised to switch to a healthy pregnancy diet plan provided to them on their initial visit with the dietician.

2.3 Outcome measures

The primary outcomes were (1) percentage of women with return to regular menstrual cycles and (2) pregnancy rates. Additional outcomes included time to return of regular menstrual cycles, time to conception, change in weight at return of regular menstrual cycles, and change in weight at conception. The primary outcomes were compared between women receiving metformin and not receiving metformin and between those receiving fertility induction and those who were not. Regularity of menstrual cycles was documented based on self-report of monthly cycles.

2.4 Statistical analysis

The study used a convenience sample of 30 women with PCOS that followed the KD for at least 3 months. A formal sample size calculation prior to starting the study was not performed. However, the chosen sample size of 30 allows for 80% power to detect moderate effect sizes of more than 0.5 standard deviations for continuous changes based on a paired t-test with 0.05 significance level. Categorical variables were described using frequencies and percentages, and comparisons between groups were assessed using Pearson's chi square or Fisher's exact tests. Continuous variables were described using means and standard deviations, or medians and quartile, based upon results of a Shapiro-Wilk test for normality and normality q-q plots. Comparisons between normally-distributed continuous variables were assessed using two sample t-tests with equal or unequal variance assumptions, as appropriate. Paired t-tests were performed to assess weight change within groups with regular period return and pregnancy. Kaplan- Meier estimates were calculated for time to return to regular periods and pregnancy, and Kaplan-Meier plots were used to show time to these events by Metformin and Fertility Induction use. Hazard ratios from Cox proportional hazards models were used to compare Metformin and fertility induction agent use on these outcomes. Analyses were performed SAS Software (version 9.4; Cary, NC).

3 Results

3.1 Patient characteristics

A total of 30 women met the inclusion criteria. Baseline patient characteristics are summarized in Table 1. The mean age of the cohort was 31.1 ± 4.9 years and mean BMI was 43.4 ± 9.1 kg/m^2. Sixty percent of patients were receiving metformin. Sixty percent of the women reported desire for pregnancy.

3.2 Menstruation and weight

Approximately 92% of women who had irregular menstrual cycles had return of regular menstruation at 6 months and it was 100% at 15 months. Mean weight change was −7.12 ± 6.63 kg at return of regularity of menstrual cycles compared to initial weight ($P < 0.001$).

TABLE 1 Patient characteristics.

	Total(N = 30)	
Factor	N	Statistics
Patient Characteristics		
Age*	30	31.1 ± 4.9
Race, n (%)	30	
Caucasian		24 (80.0)
African American		4 (13.3)
Other		2 (6.7)
Presence of acne, n (%)	29	12 (41.4)
Presence of hirsutism, n (%)	29	22 (75.9)
Testosterone (ng/dL)*	24	40.9 ± 28.3
Serum Anti-Mullerian Hormone (ng/mL)ǂ	12	3.7 [2.5, 9.0]
Regularity of periods, n (%)	30	
Regular		6 (20.0)
Irregular		24 (80.0)
Desire for pregnancy, n (%)	30	18 (60.0)
Initial BMI*	30	43.4 ± 9.1
Metformin use, n (%)	30	18 (60.0)
HDL (mg/dL)*	13	45.8 ± 14.2
LDL 9mg/dL)*	13	116.1 ± 12.8
Triglycerideǂ	13	105.0 [80.0, 130.0]
Induction Agent Use		
None, n (%)	30	22 (73.3)
Clomiphene, n (%)	30	4 (13.3)
Letrazole, n (%)	30	5 (16.7)
FSH, n (%)	30	1 (3.3)
hCG, n (%)	30	0 (0.00)
Other, n (%)	30	0 (0.00)

*mean ± SD, ǂ median [Q1, Q3].

3.3 Pregnancy and weight

Eighteen of the 30 women desired pregnancy. In this sub-cohort, 10 women (55.6%) achieved pregnancy. Approximately 63% of those who successfully achieved pregnancy did so within 12 months. Women who became pregnant vs. those that did not, lost a similar amount of weight (−7.05 kg vs. −6.85 kg, respectively). The pregnant group achieved resumption of regular menstruation in an average of 81.4 ± 39.0 days compared to 143.6 ± 172.5 days in the non-pregnant group. The overall weight change is summarized in Table 2.

TABLE 2 Weight Change By Pregnancy Status.

Status	N	Initial Weight (kg)	Post Weight (kg)	Weight Change (kg)	Weight Change (%)	*P*-value
Pregnant	10	108.5 ± 22.9	99.4 ± 20.5	−9.1 ± 7.8	−8.1 ± 6.2	0.64[a1]
Not Pregnant	8	135.5 ± 29.0	126.4 ± 27.7	−9.1 ± 12.2	−6.4 ± 8.4	

Statistics presented as mean ± SD. *p*-values: a1 = *t*-test.

TABLE 3 Weight change by metformin use.

Factor	Not on Metformin(*N* = 12)		On Metformin(*N* = 18)		*P*-value
	N	Statistics	N	Statistics	
Patient Characteristics					
Initial BMI*	12	41.7 ± 10.8	18	44.6 ± 8.0	0.41[a1]
HbA1c*	9	5.7 ± 0.57	13	5.6 ± 0.33	0.49[a1]
Return Of Regular Period					
Return of regular menstruation, n (%)	10	10 (100.0)	18	14 (100.0)	N/A
Initial weight (kg)*	10	110.9 ± 33.7	14	122.3 ± 24.9	0.35[a1]
Weight at resumption of regular menstruation (kg)*	10	104.7 ± 29.9	14	114.5 ± 25.6	0.40[a1]
Initial weight to weight at return of regular menstruation *	10	−6.2 ± 6.9	14	−7.8 ± 6.6	0.58[a1]
Time to return of regular menstruationƚ	10	75.0 [47.0, 105.0]	14	71.5 [31.0, 88.0]	0.98[b]
Pregnancy					
Pregnancy, n (%)	5	5 (100.0)	13	5 (38.5)	*0.036*[d]
Initial weight (kg)*	5	107.7 ± 26.2	5	109.3 ± 22.2	0.92[a1]
Weight at conception (kg)*	5	100.8 ± 21.7	5	98.0 ± 21.6	0.84[a1]
Initial weight to weight at conception*	5	−6.9 ± 5.9	5	−11.3 ± 9.6	0.40[a1]
Time to Pregnancyƚ	5	328.0 [223.0, 385.0]	5	223.0 [175.0, 232.0]	0.76[b]

P-values: a1 = *t*-test, b = Wilcoxon Rank Sum test, d = Fisher's Exact test. *mean ± SD, ƚ median [Q1, Q3].

3.4 Effect of metformin

Eighteen out of the 30 women were receiving metformin (60%). All women who had irregular menstruation at the start of the KD achieved regularity regardless of metformin use. Mean weight change at return of regular menstruation was −7.8 ± 6.6 kg in the metformin group and −6.2 ± 6.9 kg in the no metformin group (P = 0.58). Mean time to return of regular menstruation was 71.5 [310, 88.0] days in the metformin group and 75.0 [47.0, 105.0] days in the no metformin group (P = 0.98).

In terms of pregnancy outcomes, 5 out of 13 (38.5%) patients in the metformin group achieved pregnancy and 5 out of 5 (100%) in the non-metformin group achieved pregnancy (P = 0.036). Mean change in weight at conception was −11.3 ± 9.6 kg in the metformin group and −6.9 ± 5.9 kg in the no metformin group (P = 0.40). Time to pregnancy was 223.0 [175.0, 232.0] days for the metformin group and 328.0 [223.0, 385.0] days in the no metformin group (P = 0.76) Table 3.

3.5 Effect of ovulation induction agents

In the 18 women who desired pregnancy, 8 utilized ovulation induction agents. In the ovulation induction group, 5 out of 8 (62.5%) achieved pregnancy, and among those that did not utilize ovulation induction agents, 5 out of 10 (50%) achieved pregnancy (P = 0.66). Time to pregnancy was 223.0 [175.0, 232.0] days in the ovulation induction group and 385.0 [223.0, 453.0] days in the no ovulation induction group (P = 0.37). There was no statistically significant difference in pregnancy rates at 9 months whether metformin or ovulation induction agents were used.

3.6 Anti-mullerian hormone

Out of the 18 women who desired pregnancy, 10 had anti-mullerian hormone (AMH) values available for review. Out of the 4 women who became pregnant, only 1 woman used an ovulation induction agent. The lowest AMH value in the pregnant groups was 3.4 ng/mL and 0.1 ng/mL in the non-pregnant group. Two women with the lowest AMH values (0.1 and 2.1 ng/mL) were unable to become pregnant despite fertility induction Table 4.

4 Discussion

This study examined the effect of a KD on menstruation and pregnancy rates in women with PCOS. All women who had

TABLE 4 AMH by Pregnancy Outcome and Fertility Induction.

Patient	Fertility Induction	BMI	HbA1c (%)	AMH (ng/mL)
Pregnant				
1	N	40.8	6.6	3.4
2	N	46.8	5.2	3.6
3	Y	33.1	5.4	8.6
4	N	25.6	5.3	10.8
Not Pregnant				
5	Y	47.5	5.3	0.1
6	Y	54.0	6.3	2.1
7	N	40.8	5.1	5.1
8	N	65.6	5.7	9.4
9	N	25.6	5.3	10.8
10	N	40.8	5.3	23.7

N: no, Y: yes.

irregular menstrual cycles achieved regularity and 58.8% of those who desired pregnancy became pregnant. The pregnancy rate of women who used ovulation induction agents (62.5%) was higher in our study compared to data from existing literature (10–12). The percentage of women who became pregnant without the use of ovulation induction agents (50.0%) was also higher than previously reported (10–12).

The prevalence of obesity in women with PCOS is high with some studies reporting up to 75% (2), and a pooled estimated prevalence of 49% according to a meta-analysis performed by Lim et al. (13). Obesity further worsens insulin resistance (14) which correlates with ovulatory dysfunction (15). In small studies, a KD was found to improve weight along with metabolic and endocrine parameters such as serum testosterone, serum insulin, and luteinizing hormone/follicle stimulating hormone ratio (7, 8). Physiology suggests that improvements in these parameters would also improve ovulation and fertility. However, studies evaluating the effect of weight loss on ovulation and pregnancy rates are lacking. To the best of our knowledge, our study is one of the first studies to address the effects of a KD on fertility in women with PCOS.

Legro et al. performed a post-hoc analysis of two randomized studies examining women with overweight or obesity and PCOS and the effect of lifestyle intervention before ovulation induction versus immediate ovulation induction on infertility (16). The authors found that preconception weight loss with lifestyle interventions significantly improved ovulation and live birth rates compared to immediate ovulation induction (62.0% vs. 44.7%, RR 1.4 (1.1–1.7), $P = 0.003$; 25.0% vs. 10.2%, RR 2.5 (1.3–4.7), $P = 0.01$, respectively) (16). Lifestyle intervention consisted of caloric restriction, meal replacements, anti-obesity medication, behavioral modification, and increased physical activity leading to approximately a 5.4 kg weight-loss from the intervention prior to receiving ovulation induction (16).

Current literature supports weight loss as a tool to improve fertility in women with obesity and PCOS. In a study of 24 women with PCOS and obesity or overweight, a low-calorie, low-fat diet was implemented for 6–7 months. Of the 13 women who lost > 5% of their initial weight, 11 had menstrual dysfunction in which 9 showed improvement in regards to menstrual function and 5 conceived. In women who lost < 5% of their weight, only 1 out of 8 women showed improvement in menstrual function (4).

The exact mechanism by which a KD improves fertility is unknown and large clinical trials evaluating this have yet to be performed. Possible mechanisms are hypothesized to be associated with improvements in reproductive hormones and insulin resistance which are known to play a key role in the pathogenesis of PCOS and impaired ovulation.

Insulin and other inflammatory factors play a negative role in enhancing the production of Androgens especially Testosterone by the ovary. Reducing insulin levels are well as other inflammatory factors would slow that enzymatic reaction and improve ovarian function (17).

A meta-analysis including 170 women with PCOS on a KD for 45 days or more demonstrated reduced luteinizing hormone/follicle stimulating hormone ratio, reduced serum free testosterone, and increased sex hormone binding globulin (18). In another meta-analysis that compared insulin resistance markers in women with recurrent pregnancy losses with healthy women, women with recurrent pregnancy losses had significantly higher fasting plasma insulin, higher HOMA-IR, and lower glucose to insulin ratio (19). Furthermore, in a small study in which women with PCOS who previously failed an in vitro fertilization cycle were placed on a KD, markers of insulin resistance and fertility rates were evaluated pre and post intervention. KD resulted in significant improvements in fasting insulin, HOMA-IR, implantation (83.3% vs. 8.3%) and clinical pregnancy (66.7% vs. 0%) (20).

Diets other than KD are reported to have benefits in patients with PCOs. Low-carbohydrate diet (carbohydrates accounts for less than 45% of the three major nutrients) demonstrated significant reductions in BMI, HOMA-IR, total cholesterol, LDL and T levels while increasing FSH and SHBG levels (21). The question of whether a specific type of diet improves fertility in women with PCOS more than others is unknown. In a randomized trail, Mediterranean/low carbohydrate diet (maximum carbohydrate intake of less than 20%, a maximum carbohydrate intake of 100 g throughout the day and an increased intake of protein and fat) showed similar metabolic benefits when compared to low fat diet (less than 30% of total dietary calories from fat, less than 40 g of fat intake throughout the day and up to 10% saturated fat). However, no significant different in restoration in regular menses between both diets (22).

Head-to-head studies comparing KD to other diets in patients with PCOs are scarce. In a recent study that randomized 27 patients with PCOs to mediterranean diet versus very low-calorie keto diet (VLCKD) for 16 weeks, reductions in BMI, waist circumference, fat mass, and blood pressure were significantly higher in the VLCKD arm. No differences in fasting insulin, HOMA-IR, total cholesterol, HDL, Triglycerides, AST or hirsutism between the two arms. However, VLCKD resulted in significant increase in sex hormone binding globulins (SHBG) and free testosterone. Psychological stress and well-being were similar between both groups. Ovulation improved significantly in the VLCKD group, however, changes in pregnancy rates were not examined (23).

In a similar study to ours, 17 women with PCOS underwent mixed ketogenic diet for 45 days. The study diet protocol allowed a maximum daily carbohydrate intake of 30 grams and daily lipid intake of 30 grams, but restricted daily calorie intake to 600 kcal. The study resulted in a dramatic average weight loss of 9.4%. Twelve participants had restoration of regular cycles with 5 of them achieving pregnancy. However, the correlation between the degree of weight loss and the restoration of regular menstruation and pregnancy was not explored. Furthermore, the role of metformin and ovulation induction use was not studied (24). In our study, women on a KD for at least 3 months achieved > 5% weight loss at the time regular menses resumed and at conception. The rate of improvement in menstruation (100%) and pregnancy (55.6%) is considerably higher in our study compared to prior studies even when metformin and ovulation induction were used concomitantly. Furthermore, there were 5 women who achieved pregnancy without the use of ovulation induction agents (only one was on metformin). Two of them lost < 5% of their body weight at the time of conception and two other women had BMIs > 40. Based on current literature, these factors generally impede ovulation and pregnancy. Thus, we hypothesize that a physiologic change besides weight loss that the KD induces, such as improvement in insulin resistance, is the key to improving fertility in this population.

The gold standard technique for measuring insulin resistance, euglycemic insulin clamp studies, have not been conducted in women with PCOS who are placed on a KD. Surrogate markers of insulin resistance such as HOMA-IR, fasting insulin, HDL, and triglycerides have been evaluated in small studies. Paoli et al. conducted a twelve week, single-arm, prospective study evaluating the metabolic effects of a KD on overweight women with PCOS. The study found that the mean weight reduction was 12%, HOMA-IR decreased significantly before and after the intervention (2.85 ± 0.15 vs. 2.32 ± 0.13; $P < 0.0001$) as well as serum triglycerides (2.31 ± 0.40 vs. 1.87 ± 0.27 mmol/L; $P < 0.0008$), HDL (1.79 ± 0.41 vs. 2.02 ± 0.43 mmol/L; $P = 0.0146$), and insulin (12.62 ± 0.48 vs. 11.31 ± 0.60 μU/mL; $P < 0.0001$) (8). Another study in which women with BMI ≥ 27 kg/m2 and PCOS were placed on a KD for 24 weeks, demonstrated significant reductions in weight (12.1%) and fasting insulin (−54%) while maintaining normal fasting glucose levels (7). Serum triglycerides and HDL did not significantly differ. In a recent study by Magaganini et al. (25), 25 patients with obesity and PCOS underwent VLCKD for 12 weeks. At the end of the study, 76% of patients switched from obesity to overweight, 96% of participants had normalization HOMA-IR, serum AMH levels significantly decreased, and progesterone and SHBG significantly increased after VLCKD. The rates of ovulation or pregnancy were not examined (25). All of these studies are small (n = 14, 5, and 25 respectively) and do not address fertility outcomes, but the KD has a profound effect on weight loss and improving metabolic parameters of insulin resistance.

Although euglycemic insulin clamp studies (clamp study) have not been performed in the PCOS population, a short-term, small, clamp study involving 10 patients with type 2 diabetes (T2DM) and obesity showed that insulin resistance improved on a KD. Patients had weight and metabolic parameters including serum insulin checked at the end of the 7-day control period (usual diet) and at the end of the 14-day KD period. Mean 24-hour serum insulin level was statistically significantly lower after the end of the KD period compared to the usual diet period demonstrating the insulin sensitizing effect of KD (26). Furthermore, an open-labeled, non-randomized, controlled study of 359 patients with T2DM who were started on a KD and followed for 1 year, demonstrated an earlier decrease in insulin resistance markers compared to weight loss. The significance of change during the first 70 days of the intervention and the next 295 days was compared. The percentage of effect that the first 70 days on the KD had on weight was 62% compared to 73% for serum insulin and 87% for HOMA-IR suggesting that a KD improves insulin resistance before weight loss becomes apparent (27). This earlier response in insulin resistance reduction may be the reason for improved fertility despite minimal weight loss seen in some of the patients in our study.

KD is reported to have positive impact on inflammation and comorbidities and health outcomes related to PCOs. Ketone bodies, specifically, β-hydroxybutyrate, are found to have anti-inflammatory effects through inhibiting interleukins and anti-oxidative effects (28). This anti-inflammatory role alongside lipids, body weight and blood pressure reduction are thought to contribute significantly to the KD role in cardiovascular protection (28). KD is shown to have a beneficial effect in patients with type 2 diabetes by reducing oral intake along with concordant reductions in insulin requirements and the amount of other anti-diabetes therapies (29). Beyond anthropometric, metabolic and endocrine parameters, KD have promising effects on health related quality of life, social behavior (30) and mental health disorders including schizophrenia and bipolar disorders (30, 31). Improvements in other health outcomes associated with PCOS may also have influenced the observed fertility.

Studies examining the long-term effects of a KD on fertility are lacking and its effects on metabolic/reproductive markers are scarce. In a meta-analysis comparing KDs with a low-fat diet in patients with obesity over a period of 12 months or more, participants assigned to a KD had statistically lower body weight [weighted mean difference −0.91 (95% IC −1.65, −0.17) kg], lower triglyceride levels [weighted mean difference −0.18 (95% CI −0.27, −0.08) mmol/l], lower diastolic blood pressure [weighted mean difference −1.43 (95% CI −2.49, −0.37) mmHg], higher LDL-C [weighted mean difference 0.12 (95% CI 0.04, 0.2) mmol/l], and higher HDL-C [weighted mean difference 0.09 (95% CI 0.06, 0.12) mmol/l] (32). Although statistical significance was shown for these parameters, the clinical significance of, for example, a weight reduction of 0.91 kg is questionable.

Because of the general lack of long-term studies on KD, its adverse effects of the KD over the long-term are not well known. Difficulty with adherence to a KD due to its strict dietary restrictions may play a role in this (33). In rodents, long-term maintenance KD precipitates the development of non-alcoholic fatty liver disease as well as glucose intolerance (34).

In a randomized trial of 100 women with PCOS but no obesity, the ovulation rate at 6 months was 100% in the metformin group and 37% in the placebo group (35). The number of menstrual cycles over a 6-month period per patient was 4.6 in the metformin group compared to 2.4 in the placebo group (P < 0.001) (35). Overall, past trials have been consistent with these findings where metformin monotherapy increases ovulation rate in women with PCOS (36).

In terms of pregnancy rates, existing studies in which a metformin group was compared to a placebo group were underpowered and did not provide meaningful results. However, a meta-analysis performed by Tang et al. suggested mild improvement in pregnancy rates in the metformin group compared to placebo (OR 2.31; 95% CI 1.52–3.51) (37).

Our study demonstrated return of regular menstrual cycles in all patients regardless of metformin use and resulted in 100% pregnancy rate in the non-metformin group compared to 41.7% in the metformin group (P = 0.036). Four out of the 5 patients in the non-metformin group were not using any ovulation induction agents as opposed to the metformin group in which 4 out of 5 patients were using an ovulation induction agent. The difference in pregnancy rate may be explained by the slightly heavier initial weight of the metformin group leading to potentially more severe insulin resistance and resistant anovulation. Furthermore, the ability to achieve regular menstruation and pregnancies without the aid of metformin can likely be attributed to weight loss and improvements in insulin resistance.

In our study, 7 of the 8 patients receiving ovulation induction agents who desired pregnancy were also on metformin, and 62.5% of them achieved pregnancy. Four patients used clomiphene, 5 used letrozole, and 1 used both clomiphene and letrozole. The one patient who was not on metformin used letrozole alone. Combination therapy of metformin and clomiphene citrate resulted in a higher rate of conception compared to metformin alone (38.3% vs 12.0%, $P < 0.001$) and to clomiphene citrate alone (38.3% vs 29.7%, P = 0.003) (11).

There is no data regarding the combination use of metformin and letrozole, but letrozole monotherapy has been shown to improve pregnancy rates more than clomiphene citrate monotherapy (31.3% vs 21.5%, P = 0.003) (12). Compared to previous studies using combination therapy, our pregnancy rate of 62.5% appears to demonstrate a higher rate of success. Again, weight loss and improved insulin resistance, in addition to pharmacotherapy, are the likely drivers to achieving a higher successful pregnancy rate.

In women, AMH is produced by the granulosa cells of the pre-antral and small antral follicles (38). Based on animal studies, AMH seems to inhibit both follicle recruitment and growth, thereby regulating the pool size of follicles (39). Because AMH is essentially secreted by follicles that are in the stage immediately after recruitment from the primordial pool and just before selection, it has become a biomarker for ovarian reserve (39). AMH level usually declines with age and becomes undetectable at menopause (40).

In PCOS, AMH levels are elevated compared to those without (41). This is likely due to the increased number of AMH-producing pre-antral and small antral follicles in PCOS ovaries as well as increased production of AMH by individual granulosa cells (42). In women with PCOS, lower AMH levels are associated with better response to ovulation induction. A meta-analysis reported that BMI is negatively correlated with AMH in patients with obesity who had or didn't have PCOS (43).

Mahran et al. studied women with PCOS and BMI $\leq$ 35 kg/m2 (mean 28.8) and found that serum concentrations above 3.4 ng/mL markedly reduced ovulation rates from 97% to 48% and pregnancy rates from 46% to 19% with use of clomiphene citrate (44). In a similar study, El Halawaty et al. reported that an AMH value above 1.2 ng/mL predicted lower ovulation rates with clomiphene citrate with a sensitivity of 71% and specificity of 65.7% in women with PCOS and BMI > 30 kg/m2 (mean 36.7) (41).

In our small sample of women with recorded AMH values, AMH ranged widely both within the pregnant group (3.4 to 10.8 ng/ml) and the non-pregnant group (0.1 to 23.7 ng/mL). Contrary to previous literature by Mahran et al. and El Halawaty et al., all of the women in this sub-cohort who became pregnant had AMH values greater than 1.2 ng/ml and 3 out of 4 had AMH values greater than 3.4 ng/ml (lowest AMH value was 3.4 ng/mL). Three out of 4 women did not require fertility induction agents to become pregnant.

The small sample size prohibits statistical comparison, but the non-pregnant group had a higher overall BMI compared to the pregnant group but HbA1c did not differ between the groups. The two women who were unable to become pregnant despite AMH values < 3.4 ng/mL and the use of ovulation induction agents, had BMIs of 47.5 and 54.0. As higher BMI is associated with lower AMH values, it is prudent to consider the effect of severely elevated BMIs when interpreting AMH values in women with PCOS.

The small sample size and retrospective nature of the study design may limit interpretation of our results. A more diverse population of women including varieties of ethnicities, different severities of PCOS, and different metabolic comorbidities would improve the generalizability of our findings. Adherence to the KD was also difficult to assess given the retrospective nature of the study. However, this is one of the first studies to report the effect of a KD on fertility outcomes in women with obesity and PCOS and the results are encouraging. A large prospective trial of a diverse population of women with obesity and PCOS comparing a control group (KD followed by ovulation induction) versus immediate ovulation induction group, with ovulation and pregnancy as primary outcomes, would provide critical insight into the effects of a KD on fertility. Improved health associated with PCOS may indirectly lead to better fertility rates. Assessment of improved overall health associated with PCOS were not assessed in the present study, and the study didn't assess the effect of Ketogenic Diets on clinical outcomes associated with PCOS. Further studies to evaluate the association between improved health and fertility rates are necessary, as are studies that assess other clinical outcomes related to PCOS. An additional limitation of this report is the potential for residual confounding, a limitation that is inherent to all retrospective analyses. Only data that was documented and available to the investigators could be recorded and included in the analyses. The duration and intensity of exercise performed by the subjects was not recorded. Additionally, patients may have participated in other activities (mind-body practices) and/or consumed supplements outside of the nutrition recommendations they were provided. At present, the KD should be considered as an option to improve fertility in women with PCOS and obesity. However, future studies are needed to build a standardized KD protocol for this population to maximize efficacy and safety.

5 Conclusion

The KD may improve ovulation and fertility rates in women with PCOS regardless of metformin or ovulation induction use. This may be, in part, due to the weight loss and improvement in insulin resistance which may occur after initiation of a KD. Further prospective studies evaluating the impact of a KD on fertility appear warranted, as well as mechanistic studies to further elucidate the mechanism by which a KD may improve fertility, with or without weight loss.

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 the Institutional Review Boards of Cleveland Clinic. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this was a minimal risk research using secondary research for which consent is not required and the research involves only information collection and analysis regulated by HIPAA for the purposes of health care operations, research or public health activities.

Author contributions

YT: Writing – review and editing, Writing – original draft. NN: Writing – review and editing, Writing – original draft. KP: Writing – review and editing, Writing – original draft. MG: Writing – review and editing, Writing – original draft. UA: Writing – review and editing, Writing – original draft.

Funding

The author(s) declare no financial support was received for the research, authorship, and/or publication of the article.

Conflict of interest

KP reported receiving consulting honoraria from AstraZeneca, Bayer, Corcept Therapeutics, Diasome, Eli Lilly, Merck, Novo Nordisk, and Sanofi; speaker honoraria from AstraZeneca, Merck, and Novo Nordisk; and research support from Bayer, Merck, Novo Nordisk, and Twin Health.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 19 September 2024
DOI 10.3389/fnut.2024.1391983

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RECEIVED 26 February 2024
ACCEPTED 28 August 2024
PUBLISHED 19 September 2024

CITATION
Wang W, Dong Y, Wang K, Sun H, Yu H and Ling B (2024) Dietary Inflammatory Index and female infertility: findings from NHANES survey. *Front. Nutr.* 11:1391983.
doi: 10.3389/fnut.2024.1391983

Dietary Inflammatory Index and female infertility: findings from NHANES survey

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Background and objectives: Infertility is a pressing public health concern on a national scale and has been linked to inflammatory conditions. However, limited research has been conducted on the impact of the Dietary Inflammatory Index (DII) on female infertility. This study sought to investigate the association between DII and infertility utilizing data from the National Health and Nutrition Examination Survey (NHANES).

Methods: This cross-sectional study included a cohort of 3,071 women aged 20–44 years from three NHANES cycles (2013–2018). Dietary information was collected to calculate the Dietary Inflammatory Index (DII), while infertility status was determined through positive responses to specific questions in a questionnaire. The association between DII scores and infertility was assessed using adjusted multivariate logistic regression analyses. Subgroup analysis and restricted cubic spline (RCS) was conducted for further investigation.

Results: Among the participants, 354 women (11.53%) were identified as experiencing infertility. Upon adjusting for all covariates, a positive correlation was observed (OR = 1.61, 95% CI: 1.12–2.31). Individuals with DII scores in the highest quartile exhibited significantly greater odds of infertility compared to those in the lowest quartile (OR = 1.71, 95% CI = 1.17–2.51). The relationship between DII and infertility in the RCS models demonstrated an S-shaped curve. When using the median DII as a reference point, a higher DII was associated with an increased prevalence of infertility. Additionally, obesity was found to be a significant factor.

Conclusions: Our research indicated that the DII was positively correlated with an increased likelihood of infertility in American women among the ages of 20 and 44. These results contribute to the existing literature and underscore the need for further validation through larger prospective cohort studies.

KEYWORDS

infertility, Dietary Inflammatory Index, diet, inflammation, NHANES

Introduction

Infertility is a medical condition characterized by the inability to achieve a clinical pregnancy following 1 year of unprotected sexual intercourse (1). It impacts ∼15% of couples of reproductive age worldwide, resulting in significant economic and psychological consequences for society (2). The U.S. Centers for Disease Control (CDC) have identified the diagnosis and treatment of infertility as a priority in public health (3). Research suggests that inflammatory conditions like polycystic ovary syndrome (PCOS) and endometriosis may be connected to infertility, and anti-inflammatory treatments have been shown to improve pregnancy outcomes in affected women (4–6).

Evidence suggests that adopting healthy dietary patterns such as the Healthy Nordic Diet, the Okinawan diet, and the Mediterranean Diet, which are known to reduce inflammation, can have positive effects on fertility outcomes. Conversely, Western dietary patterns characterized by high intake of saturated fat, refined carbohydrates, and animal proteins are associated with increased inflammation and adverse pregnancy outcomes (7). Various nutrients like vitamins, minerals, fatty acids, phytochemicals, and non-nutritive compounds like carotenoids and flavonoids can modulate inflammatory processes. Recent research indicates that diet can impact inflammation and infertility by influencing the gene function, gut microbiome composition, BMI, and other factors (7).

The impact of diet on inflammatory potential can be assessed using the Dietary Inflammatory Index (DII), a validated dietary index derived from literature to measure inflammatory potential (8). The DII has been shown to correlate with systemic inflammation levels and is closely linked to the expression of various blood inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor (TNF)-a, interleukin (IL)-1β, IL-6, and IL-10 (9). It is widely utilized to investigate the relationship between diet-induced inflammation and the development of conditions like metabolic syndrome, cardiovascular disease, and cancer (10).

However, the relationship between the DII and infertility remains inadequately understood, and there is limited knowledge regarding its potential as an assessment tool for infertility. We hypothesized that DII serves as a predictor for infertility risk. This study aims to explore the association between DII and infertility, offering insights for the treatment and management of infertility. We conducted a national population-based survey utilizing data from three cycles of the National Health and Nutrition Examination Survey (NHANES) conducted between 2013 and 2018, which included representative samples of American civilian women.

Methods

Data source and study population

A cross-sectional study was conducted using data from the NHANES cycles between 2013 and 2018 to evaluate the health and nutritional status of adults and children in the United States. NHANES employs complex stratified sampling methods in a multistage study to gather a representative sample of the U.S. population every 2 years. Approval for all protocols was obtained from the National Center for Health Statistics institutional review board, and participants were required to provide informed consent.

This study specifically targeted female respondents aged 20–44 years, as this age range already has available data on reproductive health. Women who did not provide dietary information were excluded from the study. Additionally, those who had undergone hysterectomy or bilateral oophorectomy were also excluded, as they may not have had the experience of trying to conceive. A total of 3,071 participants were included in the complete case analysis. The process of sample selection is detailed in Figure 1.

The definition of DII

Dietary Inflammatory Index (DII) serves as a valuable tool for assessing the inflammatory potential of an individual's diet (10). By conducting a 24-hour dietary recall interview at a mobile examination center, data on 27 components of each participant's daily food intake were collected. The DII score, reflecting the inflammatory properties of the diet, was calculated using a built-in function in the "nhanesR" package. The Nutrition Methodology Working Group of the NHANES conducted comprehensive dietary recall interviews to gather detailed dietary information. Initially, face-to-face interviews were conducted in the Mobile Examination Center (MEC), followed by a second review via telephone. For this study, we opted to utilize the average of two dietary interviews as a representation of an individual's daily dietary intake for calculating the Dietary Inflammatory Index (DII). All food components available in the NHANES database were considered in the DII calculation, with each component being assigned a specific DII score based on its impact on six major inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP. Utilizing this scoring system, the DII for each food component was computed. To evaluate the overall impact of all dietary intakes on inflammation for a participant within a day, individual DII scores for all food components were summed to derive the participant's overall DII. This involved standardizing each food parameter, converting it to a *Z*-score, and adjusting for centered proportions based on the inflammatory effect index. The resulting DII score provided insight into the inflammatory nature of each participant's diet (11). Higher DII scores signify a more pro-inflammatory diet, while lower scores indicate a more anti-inflammatory diet. In our analysis, we treated the DII score as a continuous variable and divided the total sample into quartiles (Q1, Q2, Q3, and Q4) for further examination.

The definition of infertility

According to the definition of infertility (24), women who answered "yes" to either of the following questions were considered ever infertile: "Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant?" or "Have you ever been to a doctor or other medical provider because you have been unable to become pregnant?"

Covariates

The selection of covariates in this study was based on professional judgment and informed by previous research (12, 24). The included covariates encompassed factors such as age, race/ethnicity, education, BMI, marital status, family income, menstrual periods, pelvic infection, as well as history of female hormone use, birth control pill use, smoking, and alcohol consumption. These covariates were sourced from the demographic, examination, reproductive health questionnaire, and smoking questionnaire sections of the NHANES database.

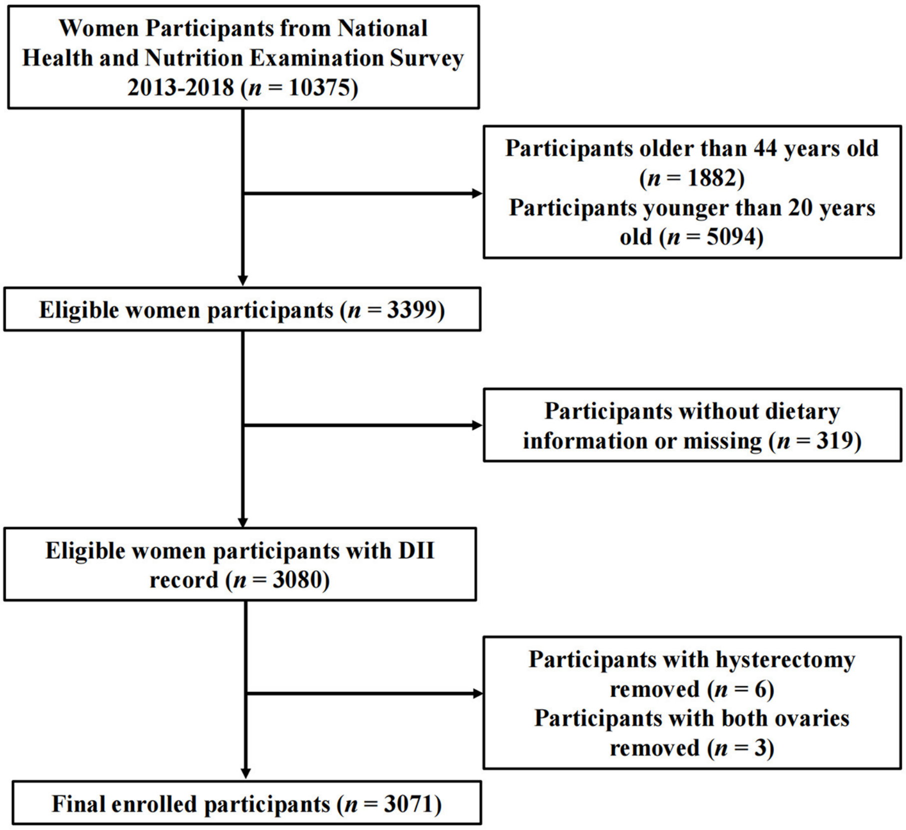

FIGURE 1
Participants flow chart.

Statistical analysis

All statistical analyses were performed following the NHANES analytic guidelines. A descriptive analysis was carried out on the demographic and measurement indicators of the study population, categorized into two groups based on infertility status. Continuous variables were presented as mean ± standard deviation for normal distributions, median with interquartile range for skewed distributions, or percentages for categorical variables. χ^2-tests were used for categorical variables, two independent sample t-tests for normally distributed variables, and Wilcoxon rank sum test for variables not following a normal distribution to assess differences among the groups.

The association between DII and infertility was evaluated through two logistic regression models: a crude model with no covariate adjustment and an adjusted model including all covariates. To account for the impact of age on infertility, a subgroup analysis stratified by age (35 years) was conducted. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to measure the strength of the association. Additionally, a restricted cubic spline (RCS) regression model was used to further explore the relationship between DII and infertility. This model included four knots at the 5th, 35th, 65th, and 95th percentiles of DII, with the median DII serving as the reference point. Single-factor logistic regression analysis was initially performed in a crude model, followed by a multi-factor logistic regression analysis in model 1 and model 2. Two models were used in the analysis: Model I adjusted for age, marital status, and race/ethnicity, while Model II further adjusted for education levels, family income, BMI, regular menstrual periods, pelvic infection, female hormones taken, birth control pills taken, drinking history, and smoking history. Additionally, the subgroup analysis was conducted based on age, race/ethnicity, and BMI. Statistical analyses were carried out using SAS software version 9.4, with a significant level set at $p < 0.05$.

Results

Population characteristics of participants

A total of 3,071 women were included in this study, consisting of 354 infertile women and 2,717 control women. The basic characteristics of the study population are presented in Table 1. Infertile women exhibited significantly higher age and BMI compared to control women ($P < 0.05$). Detailed baseline clinical characteristics categorized by DII score quartiles are provided in Supplementary Table 1.

TABLE 1 Baseline characteristics.

	Overall (n = 3,071)	DII-Q1	DII-Q2	DII-Q3	DII-Q4	P-value
Age, years	31.18 [30.80, 31.57]	31.65 [31.04, 32.26]	30.80 [29.92, 31.68]	31.33 [30.69, 31.98]	30.91 [30.45, 31.38]	0.21
Race/ethnicity						<0.001***
White	56.38 [48.75, 64.00]	57.93 [52.95, 62.91]	55.87 [50.00, 61.75]	57.27 [50.16, 64.37]	54.16 [48.41, 59.92]	
Black	13.26 [10.81, 15.71]	9.27 [6.58, 11.95]	11.40 [8.51, 14.30]	14.10 [10.98, 17.23]	18.86 [14.53, 23.20]	
Mexican	11.79 [8.88, 14.71]	13.06 [9.56, 16.57]	14.93 [10.74, 19.12]	9.86 [6.79, 12.93]	9.09 [6.27, 11.90]	
Other Hispanic	8.05 [6.33, 9.77]	8.44 [6.67, 10.20]	7.39 [5.30, 9.49]	8.01 [5.00, 11.02]	8.39 [5.81, 10.96]	
Others	10.52 [8.98, 12.06]	11.30 [8.51, 14.09]	10.40 [8.49, 12.32]	10.76 [7.38, 14.13]	9.50 [7.39, 11.61]	
Education levels						<0.001***
Less than high school	3.26 [2.37, 4.16]	3.04 [1.74, 4.35]	3.22 [1.99, 4.45]	4.14 [2.62, 5.67]	2.56 [1.38, 3.73]	
High school or equivalent	28.03 [24.70, 31.36]	18.35 [14.81, 21.89]	27.62 [23.86, 31.38]	27.14 [22.33, 31.95]	40.47 [34.76, 46.18]	
College or above	68.68 [61.84, 75.52]	78.61 [74.37, 82.84]	69.16 [64.82, 73.50]	68.72 [63.40, 74.03]	56.97 [51.27, 62.68]	
Marital status, n (%)						0.02*
Divorced	6.09 [4.91, 7.27]	5.85 [3.49, 8.21]	5.48 [3.54, 7.43]	5.68 [3.37, 7.99]	7.49 [5.47, 9.51]	
Living with partner	14.69 [12.68, 16.69]	12.14 [8.67, 15.61]	14.72 [11.90, 17.53]	15.13 [11.55, 18.72]	17.02 [13.91, 20.12]	
Married	44.16 [39.56, 48.76]	50.96 [46.35, 55.57]	44.15 [38.84, 49.46]	43.65 [38.89, 48.41]	37.08 [32.31, 41.85]	
Never married	31.62 [28.52, 34.72]	28.69 [24.52, 32.87]	33.18 [28.57, 37.79]	31.32 [27.45, 35.19]	33.54 [29.04, 38.04]	
Separated	3.18 [2.48, 3.87]	2.11 [1.05, 3.18]	2.12 [1.25, 2.99]	3.93 [2.44, 5.42]	4.69 [3.03, 6.35]	
Widowed	0.27 [0.07, 0.47]	0.24 [0.04, 0.52]	0.36 [0.04, 0.67]	0.28 [0.11, 0.68]	0.19 [0.08, 0.46]	
Family income						0.002**
<2,000$	17.44 [15.42, 19.46]	13.66 [10.84, 16.49]	16.79 [13.53, 20.04]	20.14 [16.91, 23.38]	22.32 [18.21, 26.42]	
≥2,000$	78.76 [72.28, 85.23]	86.34 [83.51, 89.16]	83.21 [79.96, 86.47]	79.86 [76.62, 83.09]	77.68 [73.58, 81.79]	
BMI, kg/m^2	29.38 [28.92, 29.84]	28.02 [27.30, 28.74]	29.21 [28.28, 30.13]	29.70 [29.03, 30.38]	30.73 [29.92, 31.54]	<0.001***
Regular menstrual periods, (%)	90.12 [83.59, 96.64]	93.21 [90.47, 95.94]	90.58 [87.23, 93.92]	90.89 [88.16, 93.62]	85.24 [82.86, 87.62]	0.01*
Pelvic infection, (%)	4.47 [3.46, 5.48]	2.74 [1.28, 4.21]	4.65 [3.10, 6.21]	4.67 [2.79, 6.54]	6.10 [4.24, 7.97]	0.06
Female hormones taken, %	4.46 [3.11, 5.81]	3.96 [1.91, 6.01]	4.65 [2.29, 7.02]	5.08 [2.48, 7.68]	4.16 [2.08, 6.23]	0.86
Birth control pills taken, %	72.92 [66.43, 79.41]	75.76 [72.21, 79.31]	72.90 [69.15, 76.65]	73.84 [70.47, 77.21]	69.01 [64.80, 73.21]	0.05*
Smoking, %	19.75 [17.29, 22.22]	12.00 [9.27, 14.72]	14.36 [11.16, 17.56]	23.10 [18.63, 27.57]	30.69 [26.61, 34.77]	<0.001***
Drinking, %	83.64 [77.24, 90.04]	87.35 [83.52, 91.18]	86.77 [83.49, 90.05]	86.38 [82.34, 90.41]	85.44 [82.41, 88.47]	0.84

Continuous variables are presented as the mean and 95% confidence interval, category variables are presented as the proportion and 95% confidence interval.
BMI, body mass index.
***P-value < 0.001.
**P-value < 0.01.
*P-value < 0.05.

Association of DII with infertility

Table 2 illustrates the comparison of DII components between the non-infertility group and the infertility group. The Wilcoxon rank sum test revealed that the average DII in infertile women was significantly higher than in the control group [2.01 (1.80, 2.21) vs. 1.73 (1.59, 1.87), P = 0.03]. Multivariate regression analysis indicated a positive correlation between DII score and infertility (OR = 1.09; 95% CI = 1.01–1.18; Table 3). Q4 showed a significantly higher risk of infertility compared to Q1 in various models, with a 71% increased likelihood of infertility observed when comparing Q4 to Q1 (OR = 1.71; 95% CI = 1.17–2.51).

The relationship between predicted infertility risk and DII was effectively modeled and visualized using RCS, as illustrated in Figure 2. In this study, we found that when DII is <2.4, the increase in infertility rates is relatively slow with the elevation of DII. However, when it exceeds

TABLE 2 Comparison of DII components between non-infertility group and infertility group.

Variables	Overall (n = 3,071)	Non-infertility (n = 2,717)	Infertility (n = 354)	P-value
DII	−0.03 [−0.04, −0.03]	1.73 [1.59, 1.87]	2.01 [1.80, 2.21]	0.03*
Vitamin A	0.35 [0.33, 0.37]	0.20 [0.19, 0.21]	0.22 [0.20, 0.24]	0.05*
Vitamin B1	0.00 [0.00, 0.00]	0.03 [0.03, 0.03]	0.03 [0.02, 0.04]	0.53
Vitamin B2	0.05 [0.05, 0.06]	0.00 [−0.01, 0.00]	0.00 [−0.01, 0.00]	0.43
Vitamin B6	0.13 [0.12, 0.13]	−0.06 [−0.07, −0.04]	−0.03 [−0.06, −0.01]	0.14
Vitamin B12	0.23 [0.21, 0.24]	−0.03 [−0.04, −0.03]	−0.03 [−0.04, −0.03]	0.93
Vitamin C	0.25 [0.24, 0.27]	0.22 [0.20, 0.24]	0.26 [0.23, 0.29]	0.04*
Vitamin D	0.09 [0.08, 0.11]	0.25 [0.24, 0.27]	0.26 [0.23, 0.29]	0.51
Vitamin E	0.10 [0.09, 0.12]	0.09 [0.07, 0.11]	0.11 [0.07, 0.16]	0.37
Iron	0.05 [0.03, 0.06]	−0.01 [−0.01, −0.01]	−0.01 [−0.01, 0.00]	0.85
Magnesium	−0.01 [−0.01, −0.01]	0.10 [0.08, 0.11]	0.13 [0.10, 0.16]	0.1
Zinc	−0.09 [−0.09, −0.08]	0.04 [0.03, 0.06]	0.06 [0.02, 0.09]	0.46
Selenium	0.08 [0.08, 0.08]	−0.08 [−0.09, −0.08]	−0.09 [−0.10, −0.07]	0.88
Total fatty acid	−0.09 [−0.10, −0.08]	0.01 [0.00, 0.02]	0.02 [0.00, 0.05]	0.28
Total saturated fatty acid	0.00 [0.00, 0.00]	−0.10 [−0.11, −0.09]	−0.07 [−0.10, −0.03]	0.08
MUFA	−0.07 [−0.08, −0.06]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.14
PUFA	−0.03 [−0.03, −0.02]	−0.07 [−0.08, −0.06]	−0.08 [−0.11, −0.05]	0.6
n3 Polyunsaturated fatty acid	0.28 [0.27, 0.28]	0.28 [0.27, 0.28]	0.27 [0.27, 0.28]	0.4
n6 Polyunsaturated fatty acid	−0.06 [−0.07, −0.06]	−0.06 [−0.07, −0.06]	−0.06 [−0.07, −0.05]	0.58
Cholesterol	0.21 [0.19, 0.22]	−0.03 [−0.03, −0.03]	−0.02 [−0.03, −0.01]	0.29
Folate	−0.03 [−0.04, −0.03]	0.13 [0.12, 0.13]	0.13 [0.11, 0.14]	0.92
β-Carotene	0.03 [0.03, 0.03]	0.35 [0.32, 0.37]	0.38 [0.33, 0.43]	0.18
Niacin	−0.05 [−0.07, −0.04]	0.05 [0.05, 0.06]	0.05 [0.03, 0.06]	0.76
Energy	0.00 [−0.01, 0.00]	−0.03 [−0.04, −0.03]	−0.02 [−0.04, −0.01]	0.37
Protein	−0.04 [−0.04, −0.03]	0.00 [−0.01, 0.00]	0.00 [−0.01, 0.00]	0.9
Carbohydrate	0.24 [0.21, 0.27]	−0.04 [−0.04, −0.03]	−0.04 [−0.04, −0.03]	0.94
Dietary fiber	0.01 [0.00, 0.02]	0.24 [0.21, 0.27]	0.28 [0.22, 0.34]	0.18
Caffeine	0.18 [0.16, 0.19]	0.08 [0.08, 0.08]	0.08 [0.08, 0.08]	0.8
Alcohol	0.28 [0.27, 0.28]	0.18 [0.16, 0.19]	0.17 [0.14, 0.20]	0.67

Data are presented as the mean and 95% confidence interval.
DII, dietary inflammatory index; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.
*P value < 0.05.

2.4, the infertility rate increases more significantly with the rise of DII. Therefore, proper control of DII is crucial for preventing infertility.

Subgroup analysis

Subgroup analysis was conducted using stratified logistic regression, categorizing participants by age, race/ethnicity, and BMI. The forest plot (Figure 3) revealed that obese patients had a higher risk of infertility (OR = 1.16, 95% CI = 1.01–1.33). Despite this finding, likelihood ratio tests showed that there were no significant interactions between age, race/ethnicity, and the association between DII and infertility.

Discussion

This cross-sectional study aimed to explore the relationship between Dietary Inflammatory Index (DII) and infertility. After accounting for potential confounding factors, the results indicated that individuals consuming a diet with higher inflammatory properties, as measured by DII, had a significantly higher prevalence of infertility. The study demonstrated that with

TABLE 3 Logistic regression on the association between DII and infertility.

	Non-adjusted model		Model I		Model II	
	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value
Continuous DII	1.09 [1.01, 1.17]	0.04*	1.09 [1.01, 1.18]	0.03*	1.09 [1.01, 1.18]	0.04*
DII-Q1	Reference	-	Reference	-	Reference	-
DII-Q2	1.37 [0.94, 1.98]	0.1	1.42 [0.98, 2.08]	0.07	1.51 [1.00, 2.28]	0.05*
DII-Q3	1.09 [0.78, 1.53]	0.6	1.09 [0.76, 1.57]	0.62	1.07 [0.73, 1.57]	0.74
DII-Q4	1.61 [1.12, 2.31]	0.01*	1.66 [1.14, 2.40]	0.01*	1.71 [1.17, 2.51]	<0.001***

Data are presented as OR [95% confidence interval]. Model I adjusted for age, marital status and race/ethnicity. Model II adjusted for age, marital status and race/ethnicity, education levels, family income, BMI, regular menstrual periods, pelvic infection, female hormones taken, birth control pills taken, drinking history and smoking history.
BMI, body mass index; DII, dietary inflammation index.
***P-value < 0.001.
*P-value < 0.05.

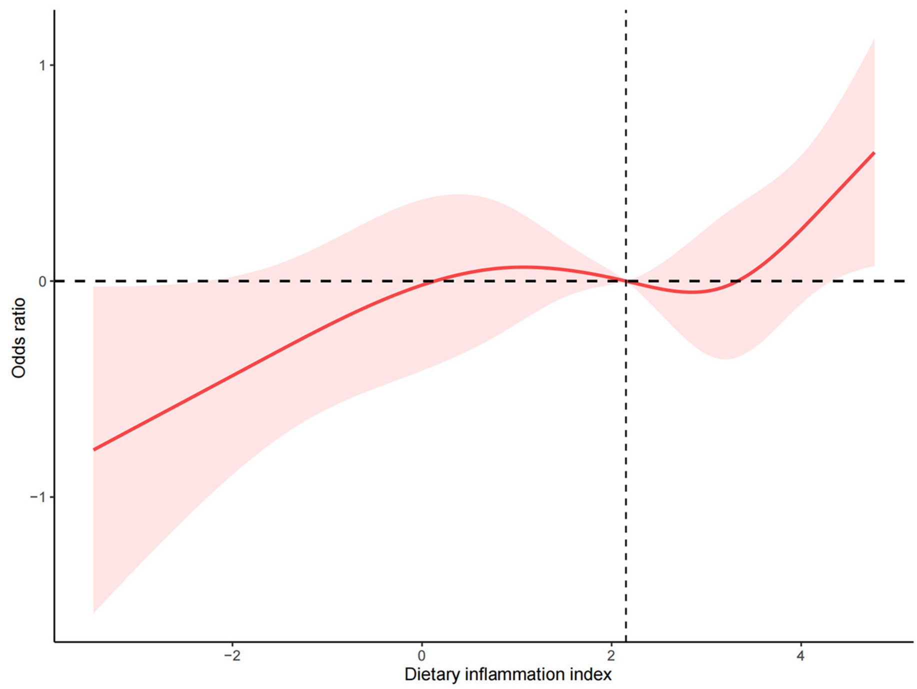

FIGURE 2
Association of Dietary Inflammatory Index and infertility.

each increase in DII score, the likelihood of experiencing infertility increased.

In recent years, there has been a rising trend in the incidence of infertility, which has been significantly impacting individuals of childbearing age and imposing a burden on society (13). Inflammation has emerged as a key factor contributing to poor reproductive outcomes, commonly referred to as "inflammatory infertility" (7). Numerous studies have established a link between inflammatory conditions and an elevated risk of infertility, such as pelvic inflammatory disease, endometriosis, and polycystic ovary syndrome (14). Systemic inflammation can adversely affect the uterus, cervix, and placenta, thereby decreasing fertility (15).

Decades ago, researchers observed that women following a "fertility diet" may have a higher likelihood of becoming pregnant and ovulating (16). Recent studies have indicated that infertile women undergoing *in vitro* fertilization (IVF) and adhering to a Mediterranean diet may experience improved pregnancy outcomes (17, 18). Western dietary patterns, known for their high fat and calorie content, have been associated with elevated levels of CRP and IL-6, leading to heightened systemic inflammation (19). A cross-sectional study demonstrated that consuming a pro-inflammatory diet is associated with an 86% higher likelihood of infertility in women, a relationship that remained statistically significant even after adjusting for confounding variables with odds ratio of 76% (20). While the exact ways in which anti-inflammatory components impact fertility outcomes are not completely understood, it is suggested that diet, as a modifiable

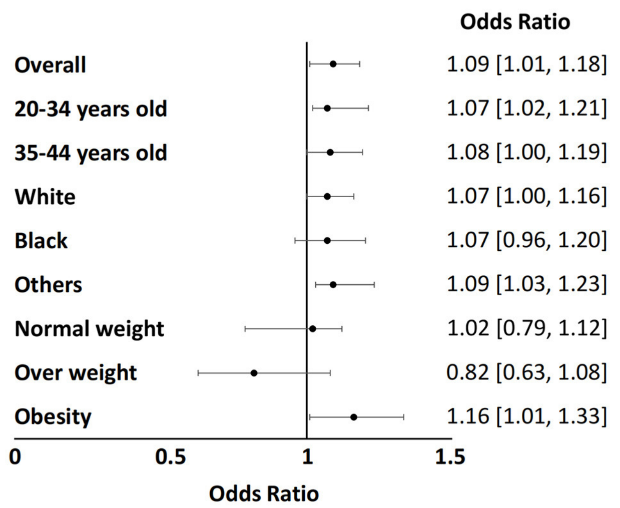

FIGURE 3
Subgroup analysis of the correlation between Dietary Inflammatory Index and infertility.

lifestyle factor, could play a crucial role in the treatment of inflammation-related diseases.

DII plays a significant role in influencing the female reproductive system by impacting the body's inflammatory status. Studies have shown that a diet high in DII can result in elevated levels of inflammatory markers like CRP and interleukins. These increased levels have the potential to disturb the secretion of ovarian hormones, hinder the maturation and release of eggs, and affect endometrial angiogenesis and cell proliferation. As a result, this reduced endometrial receptivity may hinder the successful implantation of embryos (9). Moreover, a high DII diet can affect female fertility through metabolic pathways, such as insulin resistance and obesity triggered by excessive consumption of red and processed meats. These factors can compromise ovarian function and disrupt the hormonal balance, thereby escalating the risk of infertility (25). On the other hand, a low DII diet is characterized by the consumption of anti-inflammatory foods and nutrients that help reduce inflammation in the body. These antioxidant-rich foods help support reproductive system health by reducing oxidative stress and combating free radicals. Reducing inflammation with a low-DII diet could improve ovarian function, boost endometrial receptivity, and decrease the risk of fallopian tube blockage (21).

Despite the existing literature, there is limited research exploring the relationship between DII and infertility. A recent cross-sectional study encompassing 4,437 participants indicated that adherence to a pro-inflammatory diet, as indicated by a higher DII, was associated with a 76% increased risk of infertility in women (20). Conversely, a prospective observational study conducted by Diba-Baghtash et al. reported no significant association between DII and pregnancy outcomes in infertile women undergoing IVF (22). However, given the relatively small sample size of this study ($n = 144$), the findings should be interpreted with caution. Therefore, further research, including clinical trials with human participants, is essential to achieve a more comprehensive understanding of this relationship.

In addition to the physiological effects, the relationship between DII and female infertility could also involve psychological and social aspects (23). Infertility often causes significant psychological stress in women, leading to problems such as anxiety and depression. Poor mental health can further impact the endocrine system and worsen infertility symptoms. In such situations, dietary modifications to reduce DII levels may help alleviate psychological distress in women, indirectly benefiting fertility.

Reducing the intake of pro-inflammatory foods and increasing the consumption of anti-inflammatory foods can enhance the body's inflammatory environment, thus benefiting the reproductive system's health. This dietary shift not only aids in preventing infertility but also effectively boosts women's fertility. Therefore, incorporating dietary interventions as a critical element in strategies for preventing and treating infertility is of paramount importance for safeguarding women's reproductive health. By making sensible dietary modifications, we can offer substantial backing for women's reproductive health and achieve a more holistic approach to health management.

This study also has some limitations. Firstly, the infertility assessments were based on self-reported data, which while a valid method, may be influenced by factors such as the male partner's infertility and memory recall issues regarding the timing of conception, potentially leading to biased results. Additionally, some participants may have altered their dietary habits after being diagnosed with infertility. Thirdly, due to the cross-sectional nature of the NHANES study, establishing a causal relationship between DII and infertility risk is challenging. In conclusion, further validation of the findings is necessary through additional prospective studies.

Conclusion

This study, which encompassed a nationally representative sample, identified a positive association between increased consumption of a pro-inflammatory diet, as measured by a higher DII score, and the risk of infertility in American adults. The findings of the study imply that lowering DII levels through dietary interventions could potentially mitigate inflammation, enhance reproductive health, improve female fertility, and yield positive outcomes on various socio-demographic variables. However, infertility is a complex issue influenced by multiple factors, requiring a holistic approach and individualized treatment strategies. Additional research is warranted to establish a robust evidence base regarding the specific correlation between DII and female infertility.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Author contributions

WW: Conceptualization, Writing – original draft, Writing – review & editing. YD: Conceptualization, Writing – original draft, Writing – review & editing. KW: Data curation, Investigation, Writing – original draft, Writing – review & editing. HS: Methodology, Writing – original draft, Writing – review & editing. HY: Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. BL: Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Capital's Funds for Health Improvement and Research (No. 2022-2-406), the National High Level Hospital Clinical Research Funding (No. 2022-NHLHCRF-PY-02), and the Funds of the China-Japan Friendship Hospital (No. 2017-RC-4).

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.2024.1391983/full#supplementary-material

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