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Maternal dietary and lifestyle patterns with pregnancy, birth, and child health outcomes

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Maternal dietary and lifestyle patterns with pregnancy, birth, and child health outcomes

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Table of contents

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Editorial: Maternal dietary and lifestyle patterns with pregnancy, birth, and child health outcomes

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Editorial on the Research Topic
Maternal dietary and lifestyle patterns with pregnancy, birth, and child health outcomes

Evidence from historical cohorts suggested that the children and grandchildren of women exposed to dietary alterations (e.g., famine) during pregnancy may experience increased risks of later health complications than their "control" counterparts (1). These findings drew attention to the importance of maternal pregnancy exposures and their implications on maternal/child health. Subsequently, mounting evidence revealed that maternal dietary, lifestyle (e.g., smoking, sedentary behaviors), and sociodemographic factors during the preconception, pregnancy and postpartum stages were associated with subsequent maternal and child outcomes (e.g., gestational diabetes, birth weight) among healthy, Caucasian women with access to health care (2, 3). However, there is insufficient evidence among non-Caucasian women and those of lower socioeconomic status (2) as well as paternal factors, despite their likely influence on both the mother and the child. The current literature highlighted the importance of micronutrients, adopting healthy diets, and optimizing various lifestyle behaviors to prevent adverse maternal and child health outcomes (4). Yet, few studies have examined the entirety of lifestyle behaviors. Addressing these research gaps will enable robust conclusions to be drawn and advance research in this field.

In this Research Topic, we collated nine articles featuring the latest research on maternal or paternal dietary, lifestyle and sociodemographic factors with subsequent maternal and child outcomes (5, 6). Notably, there is a good representation of study populations, with six studies from Asia- China (Chen et al., Li et al., Qin et al., Tao et al., Xie et al., Zhao et al.,), one study from Africa- Ethiopia (Ahmed et al.) and two studies from European countries- one involved a consortium of studies conducted in France, Ireland, and the Netherlands (Lecorguillé et al.) and one in Norway (Amberntsson et al.). Among these studies, one investigated preconception exposure (Li et al.), two investigated both preconception and pregnancy exposures (Lecorguillé et al., Xie et al.), four investigated maternal pregnancy exposures (Amberntsson et al., Chen et al., Qin et al., Tao et al.) and two investigated postpartum exposures (Ahmed et al., Zhao et al.).

Across preconception (Li et al.) and both preconception and pregnancy (Lecorguillé et al., Xie et al.) periods, maternal supplemental folate was associated with risk of gestational diabetes mellitus (Li et al.) and a combination of lifestyle factors (BMI, smoking, diet quality and sedentary behavior) was associated with higher risk of offspring overweight/obesity (Lecorguillé et al.). Additionally, maternal pre-pregnancy BMI and gestational weight gain were associated with sex-specific membership in BMI-z trajectories from birth to 5 years of age (Xie et al.). Future studies can consider investigating whether these trajectories would be associated with subsequent pubertal or disease-risk outcomes in children. Collectively, these three studies have certainly added to the limited literature on exposures during the preconception period, especially among non-Caucasian women (Li et al., Xie et al.). Notably, Lecorguillé et al. considered the synergistic effect of both maternal and paternal lifestyle factors that are valuable to support the initiation of family-based and multi-behavioral prevention strategies for childhood obesity.

Spanning the pregnancy period, Amberntsson et al., Chen et al., and Tao et al. demonstrated the associations between vitamin D intakes, serum levels of iron, magnesium, zinc, copper, and ferritin with maternal postpartum anemia and offspring birthweight outcomes. While these studies have identified several micronutrients associated with maternal and child health, results should be interpreted with caution as it is important to consider that nutrient bioavailability varies when interacting with other dietary constituents consumed in the diet (7). This limits our ability to directly translate the findings to dietary recommendations. As opposed to examining individual nutrients, the study by Qin et al. managed to circumvent these limitations by studying links between maternal dietary patterns and fetal intrauterine development. In particular, mothers who adhered to the "Snack and less eggs" low-protein pattern had increased risk of smaller head circumference for gestational age, which might implicate long-term health outcomes. This work by Qin et al. has the potential to inform the development of Chinese dietary guidelines for pregnant women to prevent adverse offspring health outcomes.

Spanning the postpartum period, Zhao et al. noted that Chinese women with a cesarean section birth tended to adhere less to the "Traditional" dietary pattern (characterized by high carbohydrates foods, fish and eggs) than those with vaginal delivery (Zhao et al.) among women with monthly household income of more than ¥9,000. The study also reported a positive correlation between cesarean section delivery and vegetable intakes only among those with tertiary education (Zhao et al.). Likewise, Ahmed et al. reported that lower maternal educational status and lower family income were correlated with stunting among 6–59 months old children to employed mothers in Ethiopia. While both of these studies are cross-sectional and causality cannot be inferred, they generated hypotheses for future studies and drew attention to the socio-demographic determinants for the health and wellbeing of maternal and child populations.

Finally, the studies included in this Research Topic have made valuable contributions to the evidence on parental factors and pregnancy, birth or childhood health outcomes. While single-nutrient studies have laid the foundation for dietary investigations, the approach of assessing overall diet and lifestyle is more comprehensive. Taken together, maintaining a healthy weight status, adopting a better-quality diet, reducing smoking exposure, and limiting sedentary lifestyles before and during pregnancy in both parents emerge as crucial factors in preventing adverse maternal and child health outcomes. Given the vast amount of information collected by the various cohorts featured in the nine articles, there remains many interesting hypotheses to explore that will advance research in this field. As these studies typically assessed exposures at a single time point, future studies may consider and examine changes (or trajectories) of diet, lifestyle, and sociodemographic exposures from preconception, pregnancy and postpartum periods. It may also be worth delving into the social determinants of maternal and child health such as community and family support, which could help with designing and implementing effective lifestyle interventions to optimize health and wellbeing.

Author contributions

SXL: Conceptualization, Writing—original draft. JSL: Conceptualization, Supervision, Validation, Writing—review and editing. L-WC: Conceptualization, Supervision, Validation, Writing—review and editing. AC: Conceptualization, Supervision, Validation, Writing—review and editing.

Conflict of interest

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Associations of maternal dietary patterns during pregnancy and fetal intrauterine development

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Dietary pattern is excellent in reflecting an individual's eating conditions. Longitudinal data on fetal growth can reflect the process of intrauterine growth. We aimed to evaluate the associations between maternal dietary patterns and intrauterine parameters in middle and late pregnancy. The present study was conducted within Jiangsu Birth Cohort (JBC) study. Dietary information was assessed with a food frequency questionnaire (FFQ) in the second and third trimester of gestation. B-ultrasound scans were performed to obtain fetal intrauterine parameters, including head circumference (HC), femur length (FL), abdominal circumference (AC), and estimated fetal weight (EFW). Exploratory factor analysis was used to extract dietary patterns. Multiple linear regression and linear mixed-effects model (LMM) were used to investigate the association between maternal dietary patterns and fetal growth. A total of 1,936 pregnant women were eligible for the study. We observed inverse associations of maternal "Vegetables and fish" and "Snack and less eggs" patterns during mid-pregnancy with fetal HC Z-score, respectively ("Vegetables and fish": $\beta = -0.09$, 95% CI −0.12, −0.06; "Snack and less eggs": $\beta = -0.05$, 95% CI −0.08, −0.02). On the contrary, "Animal internal organs, thallophyte and shellfish" pattern in the second trimester was associated with increased HC Z-scores ($\beta = 0.04$, 95% CI 0.02, 0.06). Consistently, score increase in "Vegetables and fish" pattern in the third trimester was inversely associated with the Z-scores of HC ($\beta = -0.05$, 95% CI −0.09, −0.02), while "Meat and less nuts" pattern was positively correlated with the Z-scores of HC ($\beta = 0.04$, 95% CI 0.02, 0.07). As compared to the fetus whose mothers at the lowest tertile of "Snack and less eggs" pattern in both trimesters, those whose mothers at the highest tertile demonstrated 1.08 fold (RR = 2.10, 95% CI 1.34–3.28) increased risk of small HC for gestational age (GA). No correlation was observed between maternal dietary patterns and other intrauterine parameters. Our results suggested the effects of maternal dietary patterns on fetal growth, particularly HC. These findings highlighted the adverse impact of unhealthy dietary pattern on fetal growth, might provide evidence for strategies to prevent intrauterine dysplasia and dietary guidelines during pregnancy.

KEYWORDS

prospective study, pregnancy, dietary patterns, B-ultrasound, intrauterine development

Introduction

Pregnancy requires an increased intake of energy and macronutrient for maternal and fetal needs (1). Several studies, including observational studies and clinical trials, have shown that maternal energy-protein imbalance, inadequate intake of fatty acid and vitamin B are associated with low birth weight (LBW), preterm birth (PTB), and congenital heart disease in offspring (2–4). Maternal undernutrition and overnutrition have adverse effects on fetal health (5). Even in the absence of malnutrition, maternal diet during pregnancy is paramount in achieving appropriate fetal growth and development (6–8). Previous studies have provided evidence on the associations between individual food or nutrient intake during pregnancy, such as fruits (9) and iron (10), and birth outcomes. However, food and nutrients are not consumed in isolation, and these ingredients in the diet may form complex synergies and interactions (11). The summary description of the overall dietary status better reflects individual's actual eating conditions. Dietary pattern, a semi-quantitative research method describing the overall diet, is particularly suitable for large-scale epidemiological studies (12). Thus, it has gradually become an indispensable method for research on dietary nutrition and health and wellbeing in recent years (13). Several studies have demonstrated the association between maternal dietary patterns and birth out-comes, including the anthropometry measurements of newborns, and the risk of PTB and born small for gestational age (SGA) (14–17).

Compared with the anthropometry measurements of newborns, the longitudinal data of fetal growth measured repeatedly can better reflect the continuous process of intrauterine growth (18). Growth of the fetus *in utero* determines the gratifying outcome of pregnancy, i.e., the birth of a healthy and viable child (19–21). Poor second and third trimester fetal growth has been associated with increased risks of PTB, LBW, and long-term adverse health outcomes (22–24). Normal fetal growth depends on genetic background, endocrine milieu, and the appropriate supply of oxygen and nutrients (25). However, few studies have investigated the influence of maternal dietary patterns during pregnancy on fetus intrauterine development.

Therefore, in the present cohort study of 1,936 mother-infant pairs, we described maternal dietary patterns in mid- to late-pregnancy, and prospectively investigated the associations between maternal dietary patterns and intrauterine growth parameters of fetus.

Materials and methods

Study population and design

Our research was based on the Jiangsu Birth Cohort (JBC) study, a prospective and longitudinal study that recruited women who are going to receive assisted reproductive technology (ART) treatment and those who are in their first trimester of spontaneous pregnancy (SP) at the Women's Hospital of Nanjing Medical University or Suzhou Affiliated Hospital of Nanjing Medical University. Detailed cohort design and data collection have been described previously (26). The study was approved by the Human Research Ethics Committee of Nanjing Medical University. The ethical approval code for the project is NJMUIRB (2017) 002. In addition, written informed consent was obtained from all participants.

Since April 2017, the cohort collected maternal dietary information with semi-quantitative food frequency questionnaire (FFQ, including 25-items) in the first [10–14 gestational week (GW)], second (22–26 GW), and third trimester (30–34 GW). From the second trimester of pregnancy to delivery, pregnant women undergo multiple routine ultrasound examinations in the hospital. Based on the distribution of ultrasound examinations time, we chose 3-time points (22–24, 30–32, and 34–36 GW) to achieve as much ultrasound data as possible.

By March 2020, a total of 2,667 single live births were born. Among them, dietary information of 2,183 mothers (81.85%) was collected in the second and third trimester. In addition, 2 mothers with implausible dietary information [total energy intake (TEI) <500 or >5,000 kcal/d] were excluded. Among 2,181 mother-infant pairs with maternal dietary data, 1,936 (88.77%) mothers had at least one B-ultrasound in the designated GWs. The flow chart of participants enrolled in the present study was shown in Supplementary Figure 1.

Assessment of dietary intakes during pregnancy

Dietary intakes during pregnancy were assessed by semi-quantitative FFQ (Supplementary Table 1), which was evaluated by well-trained investigators with the help of food models and food atlas (27). The responses were reviewed and corrected in time to ensure the completeness and validity of the questionnaires. The daily energy intakes were then calculated according to the Chinese Food Composition Table (28).

Before the analysis, we aggregated the 25 foods into 16 food groups to reduce complexity; these food groups were created based on the expected similar nutrient composition (28). The intake of each food was adjusted for TEI in the second (mean TEI = 2133.1 kcal/d), and third trimester (mean TEI = 2159.0 kcal/d) using the residual method after log-transformation (29). The validity of the FFQ was verified before the formal investigation. One hundred and forty-one pregnant women in middle pregnancy completed both the FFQ and the 3-day 24-h dietary recall (24HR), detailed data have been published elsewhere (30).

Assessment of outcome

The examination was completed by a professional ultrasound technician performing three ultrasound scans to obtain fetal intrauterine growth data and take the average value. Ultrasound parameters of fetal growth (millimeters) included head circumference (HC), femur length (FL), and abdominal circumference (AC). In addition, gestational age (GA) was calculated according to the interval between the self-reported date of last menstrual period and the date of the B-ultrasound examination. Additionally, estimated fetal weight (EFW), GA adjusted Z-scores and percentiles for fetal growth parameters were calculated according to the International Fetal and Newborn Growth Consortium for the 21st Century (INTER-GROWTH-21st) standards (31, 32). We chose the 10th centile as the cutoff of SGA and the 90th percentile as the large for GA (LGA) cutoff for each parameter since the 10th centile for AC or EFW was used to qualify a fetus as SGA, and the 90th percentile was used to qualify the fetus as LGA in a consensus definition published by an international committee (33).

Assessment of covariates

Data on mothers (demographic, lifestyle, and clinical factors) and infants (PTB, LBW, sex) were derived from structured questionnaires and electronic medical records (EMR). Questionnaires were collected by face-to-face interviews or telephone. Covariates included mode of conception (SP / ARTP), area of residence (urban, township, rural), household income (<50,000 CNY or 50,000–100,000 CNY or 100,000–200,000 CNY or >200,000 CNY), maternal education (<12/≥12 years), maternal age at conception, maternal pre-pregnancy BMI, parity (primipara / multipara), chronic diabetes (yes/no), gestational diabetes mellitus (GDM, yes / no), TEI, infant sex (male / female). In addition, the dietary patterns are mutually corrected. Notably, only two women reported smoking and eight women reported drinking during pregnancy in this study. Thus, smoking and drinking were not included as covariates.

Statistical methods

We used exploratory factor analysis to characterize maternal dietary patterns during middle and late pregnancy (34). Dietary patterns were derived by principal component extraction with the use of varimax rotation on the 16 food groups (35). To determine the number of factors to retain, we considered eigenvalues >1 (36), a breakpoint in the Scree test (37) and the interpretability of the factors (38). The dietary patterns identified in the two trimesters were similar in relation to the number of factors identified and the foods that loaded highly (Supplementary Table 2). Therefore, factor analysis was rerun on the geometric mean of food intake during the two pregnancy periods to represent maternal habitual dietary patterns. For each food group, loadings for factors represented the correlation between the food groups and a factor. The dietary patterns were labeled according to food groups that made major contributions to the factor (absolute value of factor loading >0.50 and in the top three of the food groups). Factor scores for each dietary pattern were calculated for each subject with summing the intake of food groups weighted by their factor loadings. In addition, factor loadings are correlation coefficients between each food group and the dietary pattern; hence, higher dietary pattern scores indicate greater adherence to the derived pattern (39).

Baseline characteristics were described as percentages or mean (SD). According to the tertiles of dietary pattern scores, all pregnant women were divided into three groups to compare the distribution of macronutrient intake. We performed linear trends across tertiles using linear regression (median intake for each tertile as variables included in the model). The intraclass correlation coefficient (ICC) and 95% CI were calculated by dietary pattern scores to assess the temporal variability of dietary patterns during pregnancy. The linear mixed-effects model (LMM) was used to examine the associations between maternal dietary pattern scores in the two trimesters and longitudinal indicators of intrauterine development (40). Analyses were adjusted for mode of conception (SP / ARTP), area of residence (urban, township,

TABLE 1 Characteristics of baseline demographic and lifestyle factors of 1936 mother-infant pairs.

Mothers' characteristics	Overall	Offspring's characteristics	Overall
Mode of conception		GW at delivery	39.43 (1.35)
SP	1,049 (54.2)	PTB*	81 (4.2)
ARTP	887 (45.8)	Birth weight (g)	3384.35 (443.31)
Area of residence		LBW (<2,500 g)	53 (2.7)
Urban	1,530 (79.3)		
Township	290 (15.0)	Male birth	1,014 (52.4)
Rural	110 (5.7)		
Household income (CNY)		HC (cm)	
<50,000	69 (3.6)	22–24 GW	21.39 (0.98)
50,000–100,000	435 (22.6)	30–32 GW	28.90 (1.15)
100,000–200,000	794 (41.2)	34–36 GW	31.51 (1.14)
>200,000	629 (32.6)		
Maternal education (years) < 12	355 (18.4)	AC (cm)	
Maternal pre-pregnancy BMI (kg/m^2)		22–24 GW	19.26 (1.17)
<18.5	230 (12.0)	30–32 GW	27.69 (1.36)
18.5–23.9	1,311 (68.3)	34–36 GW	31.60 (1.51)
24–27.9	306 (15.9)		
≥28	72 (3.8)	FL (cm)	
Maternal age at conception (years) ≥ 35	246 (12.7)	22–24 GW	4.16 (0.25)
Primipara	1,531 (79.1)	30–32 GW	5.97 (0.26)
Chronic diabetes	14 (0.7)	34–36 GW	6.72 (0.27)
GDM	517 (26.7)		
Anemia	188 (9.71)	EFW (g)	
Maternal TEI (100 kcal/d)		22–24 GW	668.58 (77.21)
Second trimester	21.33 (5.33)	30–32 GW	1742.28 (240.95)
Third trimester	21.59 (5.36)	34–36 GW	2574.98 (335.38)

*Gestational age (GA) < 37 GW.
SP, spontaneous pregnancy; ARTP, assisted reproductive technology pregnancy; GDM, gestational diabetes mellitus; TEI, total energy intake; GW, gestational week; PTB, preterm birth; LBW, low birth weight; HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight.

rural), household income (<50,000 CNY or 50,000–100,000 CNY or 100,000–200,000 CNY or >200,000 CNY), maternal education (<12/≥12 years), maternal age at conception (year), maternal pre-pregnancy BMI (continuous), parity (primipara / multipara), chronic diabetes (yes/no), GDM (yes/no), TEI, infant sex (male / female). In addition, the dietary patterns were mutually corrected. False discovery rate (FDR) (41) was utilized to correct for multiple tests, and FDR-p < 0.05 was set as the significance threshold. To avoid the potential confounding effects of maternal diabetes and anemia, we excluded mothers with such conditions in the sensitivity analyses. Maternal diabetes included preexistent diabetes and GDM (42), and anemia was defined as hemoglobin levels <110 g/L (43). In addition, a stratified analysis was performed according to the mode of conception, and heterogeneity was tested. All analyses were conducted in R software (Version 3.6.1, R Foundation for Statistic Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

Basic characteristics

Demographic characteristics of the 1,936 enrolled mother-infant pairs were summarized in Table 1. The JBC study was originally designed to investigate the heterogeneity of assisted vs. natural pregnancy in perinatal outcomes and child health, with 45.8% (n = 887) of mothers conceived after assisted reproduction in this analysis. The majority of women live in cities (79.3%) and a medium socioeconomic status level household (63.8%). Fewer than one in five women have <12 years of education (18.4%). Approximately two-thirds (n = 1,311) of women within a normal weight before pregnancy and 246 (12.7%) women were over 35 years old at conception. In addition, 1,531 (79.1%) mothers were primiparous. And the number of mother with GDM and anemia were 517 (26.7%) and 188 (9.71%), respectively. Baseline information on offspring

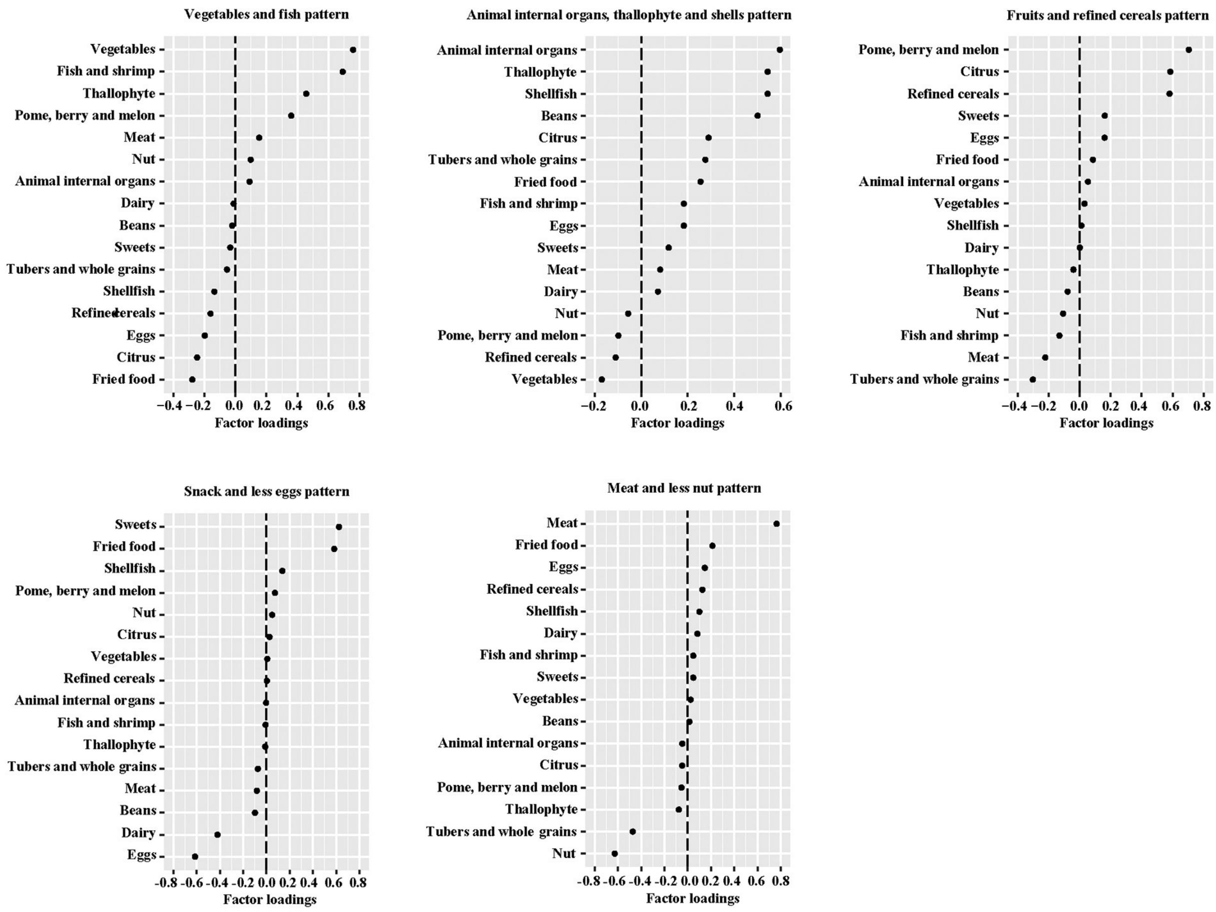

FIGURE 1
Factor loadings of averaged* food groups in middle and late pregnancy for five dietary patterns. *The geometric mean of food groups in two trimesters of pregnancy.

indicated that the incidence of PTB (GA $<$ 37 GW) and LBW (birth weight $<$ 2,500 g) was 4.2% ($n = 81$) and 2.7% ($n = 53$), respectively. The proportion of male infants (52.4%) was slightly higher than that of female infants.

Maternal dietary patterns

Five dietary patterns were identified by using factor analysis (Figure 1), which accounted for 46.4% of the total changes in dietary intake. The "Vegetables and fish" pattern was characterized by higher intakes of dietary fiber, minerals, and high-quality protein, explaining 10.2% of the variation in the dietary data. The "Animal internal organs, thallophyte and shellfish" pattern, which explained 10.0% of the variation, is rich in micronutrients, cholesterol and animal protein. In addition, "Fruits and refined grains" pattern, "Snack and less eggs" pattern, and "Meat and less nuts" pattern explained 9.1, 8.1, and 8.0% of the variation, respectively. In the evaluation of temporal variability of diets across pregnancy, all dietary patterns showed high consistency (ICC $>$ 0.40) from mid- to late-gestation in our study population (Supplementary Table 3), especially the "Vegetables and fish" pattern (ICC = 0.631). Macronutrient intakes of 1,936 mothers were described according to tertiles of dietary pattern scores (Supplementary Table 4). Compared to women in the lowest tertile of the "Vegetables and fish" pattern, women in the highest tertile had higher intakes of protein (second trimester: 18.77% compared with 16.15% energy; third trimester: 18.90% compared with 16.57% energy) and dietary fiber (second trimester: 7.29 g compared with 6.51 g/1,000 kcal; third trimester: 7.34 g compared with 6.25 g/1,000 kcal). We observed that women with a greater adherence to the "Animal internal organs, thallophytic and shellfish" pattern or "Meat and less nuts" pattern (third tertile) had a higher mean intake of cholesterol. Women in the highest tertile of "Snack and less eggs" pattern score had the lowest cholesterol intake than all other tertiles of dietary

TABLE 2 Adjusted associations of maternal dietary patterns in the second and third trimester of pregnancy with fetal growth indicators.

Dietary patterns	HC Z-score		AC Z-score		FL Z-score		EFW Z-score	
	Beta (95% CI)	FDR-*p*	Beta (95% CI)	FDR-*p*	Beta (95% CI)	FDR-*p*	Beta (95% CI)	FDR-*p*
Second trimester Vegetables and fish	**−0.09 (−0.12, −0.06)**	**<0.001**	0.004 (−0.02, 0.03)	0.959	−0.001 (−0.03, 0.03)	0.998	−0.02 (−0.05, 0.01)	0.332
Animal internal organs, thallophyte and shellfish	**0.04 (0.02, 0.06)**	**0.002**	0.01 (−0.01, 0.03)	0.523	−0.001 (−0.02, 0.02)	0.998	0.02 (−0.001, 0.04)	0.181
Fruits and refined grains	−0.01 (−0.04, 0.02)	0.748	0.01 (−0.01, 0.04)	0.613	−0.01 (−0.03, 0.02)	0.898	0.01 (−0.02, 0.03)	0.851
Snack and less eggs	**−0.05 (−0.08, −0.02)**	**0.002**	−0.01 (−0.03, 0.02)	0.748	−0.01 (−0.04, 0.02)	0.650	−0.02 (−0.05, 0.01)	0.291
Meat and less nuts	0.03 (0.01, 0.06)	0.146	−0.01 (−0.04, 0.01)	0.542	0.01 (−0.01, 0.04)	0.638	−0.005 (−0.03, 0.02)	0.922
Third trimester Vegetables and fish	**−0.05 (−0.09, −0.02)**	**0.009**	0.01 (−0.02, 0.04)	0.803	0.01 (−0.03, 0.04)	0.896	−0.004 (−0.03, 0.02)	0.896
Animal internal organs, thallophyte and shellfish	0.01 (−0.01, 0.04)	0.615	−0.01 (−0.03, 0.01)	0.700	−0.01 (−0.03, 0.01)	0.700	−0.005 (−0.03, 0.02)	0.876
Fruits and refined grains	−0.03 (−0.06, 0.01)	0.219	0.002 (−0.02, 0.03)	0.963	0.001 (−0.03, 0.03)	0.963	−0.005 (−0.03, 0.02)	0.896
Snack and less eggs	−0.04 (−0.07, −0.01)	0.133	0.005 (−0.02, 0.03)	0.896	−0.03 (−0.06, 0.01)	0.349	−0.005 (−0.03, 0.02)	0.896
Meat and less nuts	**0.04 (0.02, 0.07)**	**0.013**	−0.001 (−0.03, 0.02)	0.963	0.03 (0.01, 0.05)	0.165	0.01 (−0.01, 0.03)	0.751

Analyses were adjusted for mode of conception, area of residence, household income, maternal education, maternal age at conception, maternal pre-pregnancy BMI, parity, chronic diabetes, GDM, TEI, and infant sex. In addition, the dietary patterns were adjusted for each other.
HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight; FDR, false discovery rate; TEI, total energy intake; GDM, gestational diabetes mellitus.
Bold values means a statistically significant difference in results.

patterns. In addition, protein intake declined along with the increased score of "Snack and less eggs" pattern (p for trend < 0.001).

Maternal dietary patterns and fetal growth indicators

Associations of maternal dietary patterns in the second and third trimester with fetal growth index were shown in Table 2. In the second trimester, maternal "Vegetables and fish" ($\beta = -0.09$, 95% CI −0.12, −0.06) and "Snack and less eggs" ($\beta = -0.05$, 95% CI −0.08, −0.02) pattern were associated with decreased fetal HC Z-score from mid-to late-gestation. On the contrary, each score increases in "Animal internal organs, thallophyte and shellfish" pattern was associated with 0.04 (0.02, 0.06) in Z-scores of fetal HC. We then investigated maternal dietary patterns in the third trimester in relation to intrauterine growth parameters in late pregnancy. Consistently, per score increase in "Vegetables and fish" pattern in the third trimester was inversely associated with the Z-scores of HC ($\beta = -0.05$, 95% CI −0.09, −0.02) in late pregnancy, while "Meat and less nuts" pattern was positively correlated with the Z-scores of HC ($\beta = 0.04$, 95% CI 0.02, 0.07) were positively correlated with this pattern score. However, no correlation was observed between maternal dietary patterns and AC, FL, and EFW. In addition, we investigated maternal dietary patterns in relation to offspring birth weight after further adjusting for GW at delivery (Supplementary Table 5). No significant association was observed between maternal dietary patterns during pregnancy and offspring birth weight. We further carried out sensitivity analyses by excluding women who were complicated with chronic diabetes or GDM (Supplementary Table 6), as well as women who were diagnosed with anemia during pregnancy (Supplementary Table 7), and the main results remained stable. In addition, we conducted stratified analyses by mode of conception (Supplementary Table 8). Though some associations were not statistically significant when splitting the study population, the main results were consistent in both groups and no heterogeneity was observed.

As these dietary patterns were significantly associated with fetal HC following adjustment for covariates, Supplementary Table 9 illustrates the associations of fetal HC with intakes of food groups. After adjusting for covariates, the effects of food intake on fetal HC remained largely consistent with the dietary patterns it constituted, although not all statistically significant.

Adherence to the same dietary pattern in both trimesters and fetal HC

To assess the effect of adherence to the same dietary pattern from middle to late pregnancy and fetal HC, we categorized participants into tertiles according to their scores on the dietary patterns in both second and third trimester (Table 3). As compared to the fetus whose mothers at the lowest tertile of the score on "Vegetables and fish" pattern in both trimesters,

TABLE 3 Adjusted associations of tertiles of dietary patterns in the second and third trimester with fetal HC Z-score.

Dietary patterns	*N*	HC Z-score	
		Beta (95% CI)	FDR-*p*
Vegetables and fish	343	Ref	
Lowest tertile in both trimesters			
Highest tertile in both trimesters	368	**−0.28 (−0.43, −0.14)**	**0.001**
Animal internal organs, thallophyte and shellfish	322	Ref	
Lowest tertile in both trimesters			
Highest tertile in both trimesters	349	0.08 (−0.06, 0.22)	0.326
Fruits and refined grains	304	Ref	
Lowest tertile in both trimesters			
Highest tertile in both trimesters	311	−0.01 (−0.16, 0.15)	0.926
Snack and less eggs	335	Ref	
Lowest tertile in both trimesters			
Highest tertile in both trimesters	350	**−0.19 (−0.33, −0.05)**	**0.016**
Meat and less nuts	299	Ref	
Lowest tertile in both trimesters			
Highest tertile in both trimesters	316	**0.18 (0.04, 0.33)**	**0.019**

Analyses were adjusted for mode of conception, area of residence, household income, maternal education, maternal age at conception, maternal pre-pregnancy BMI, parity, chronic diabetes, GDM, TEI, and infant sex. In addition, the dietary patterns were adjusted for each other. Ref, reference group, which is the group of mothers with the lowest tertile of dietary pattern scores in both trimesters.
HC, head circumference; FDR, false discovery rate; TEI, total energy intake; GDM, gestational diabetes mellitus.
Bold values means a statistically significant difference in results.

those whose mothers at the highest tertile demonstrated 0.28 decreased Z-score in fetal HC ($\beta = -0.28$, 95% CI −0.43, −0.14). Similar associations exist between "Snack and less eggs" pattern and HC Z-score. Additionally, HC Z-score of the fetus in the highest tertile of the mother's "Meat and less nuts" pattern increased by 0.18 (0.04, 0.33) as compared with the lowest tertile.

We observed 10.66% of HC in late pregnancy below the 10th centile and 7.59% above the 90th centile with INTERGROWTH-21st. Further analyses investigating associations of dietary patterns with small and large HC for GA were carried out. As compared to the fetus whose mothers at the lowest tertile of "Snack and less eggs" pattern in both trimesters, those whose mothers at the highest tertile in both trimesters demonstrated 1.08 fold (RR = 2.10, 95% CI 1.34–3.28) increased risk of small HC for GA after adjusting for potential confounders (Table 4). No significant associations were observed between dietary patterns and the risk of large HC for GA.

Discussion

The present study prospectively investigated the associations between maternal dietary patterns across the second to third trimester and intrauterine growth parameters in middle and late pregnancy in a Chinese birth cohort study. Notably, our study demonstrated the positive associations of maternal "Animal internal organs, thallophyte and shellfish" and "Meat and less nuts" patterns with fetal HC; and the negative correlation between "Vegetables and fish" and "Snack and less eggs" patterns and fetal HC. Further, these effects persisted after we excluded mothers with diabetes or anemia. No heterogeneity was observed in this association between groups of different conception methods, which suggested the effects of dietary patterns on fetal growth were not significantly different among ART and SP populations. We cannot exclude the possibility of the relatively modest sample size in the stratification analyses causing underestimation of the significance of true associations due to statistical power (44). In addition, the effects were more significant if one adhered to the same pattern across the second and third trimester. It should also be noted that high adherence to the "Snack and less eggs" pattern increases the risk of small HC for GA. However, no correlation was observed between maternal dietary patterns and AC, FL, EFW and birth weight.

"Animal internal organs, thallophyte and shellfish" and "Meat and less nuts" patterns are rich in meat and meat products, which contribute significantly to the intake of cholesterol, protein and essential minerals such as iron and zinc (45). Cholesterol plays a pivotal role in many aspects of brain development. The brain has the highest cholesterol content compared with other organs (25% of total body cholesterol), while representing only about 5% of total body weight (46). Analysis of 5,702 pregnant women in the Generation R Study showed that lipid levels in the first trimester were positively associated with neonatal HC (47). Additionally, zinc has multiple roles in brain growth, differentiation, and repair (48). One prospective study of 7,644 pregnant women in Foshan, China also showed that maternal serum zinc levels at 24 GW were positively correlated with neonatal HC (49). Notably, the level of zinc in shellfish is much higher than that in fish and shrimp, which may lead to their different effects on HC (28). Observational study including 538 children aged 3–4 in rural Nepal showed a positive correlation between animal food intake and HC (50). Clinical intervention trial of 88 infants further demonstrated that the increase in HC from 7 to 12 months for supplemented with meat group was higher than cereal-complementary group, and protein and zinc intakes were predictors of head growth (51). One observational study assessed offspring's HC among vegetarian and omnivorous pregnant women and reported that offspring's HC of vegetarian mothers was smaller than that of omnivorous mothers (52), which also suggested the potential effects of animal protein on fetal HC. Thallophyte and shellfish are not only rich in protein and micronutrients, but also a quality source of iodine (53, 54). Iodine is an essential micronutrient and a component of the thyroid hormones, which regulate growth and development from conception to adulthood (55, 56). A study conducted in a pregnancy cohort of 2087 women found that high urinary

TABLE 4 Adjusted associations of tertiles of dietary patterns in the second and third trimester with small and large HC for GA of fetus.

Dietary patterns	*N*	Small HC for GA		Large HC for GA	
		RR (95% CI)	FDR-*p*	RR (95% CI)	FDR-*p*
Vegetables and fish					
Lowest tertile in both trimesters	343	Ref		Ref	
Highest tertile in both trimesters	368	1.40 (0.93, 2.10)	0.556	0.44 (0.25, 0.80)	0.061
Animal internal organs, thallophyte and shellfish					
Lowest tertile in both trimesters	322	Ref		Ref	
Highest tertile in both trimesters	349	0.84 (0.56, 1.26)	0.900	0.86 (0.52, 1.43)	0.939
Fruits and refined grains					
Lowest tertile in both trimesters	304	Ref		Ref	
Highest tertile in both trimesters	311	0.83 (0.52, 1.33)	0.900	0.78 (0.44, 1.38)	0.900
Snack and less eggs					
Lowest tertile in both trimesters	335	Ref		Ref	
Highest tertile in both trimesters	350	**2.10 (1.34, 3.28)**	**0.013**	1.03 (0.63, 1.69)	0.979
Meat and less nuts					
Lowest tertile in both trimesters	299	Ref		Ref	
Highest tertile in both trimesters	316	0.60 (0.39, 0.93)	0.182	1.27 (0.71, 2.25)	0.900

Analyses were adjusted for mode of conception, area of residence, household income, maternal education, maternal age at conception, maternal pre-pregnancy BMI, parity, chronic diabetes, GDM, TEI, and infant sex. In addition, the dietary patterns were adjusted for each other. Ref, reference group, which is the group of mothers with the lowest tertile of dietary pattern scores in both trimesters.
HC, head circumference; GA, gestational age; FDR, false discovery rate; TEI, total energy intake; GDM, gestational diabetes mellitus.
Bold values means a statistically significant difference in results.

iodine concentration in the second trimester was associated with higher HC of fetal during pregnancy (57). Our findings are in line with the above studies, and the adherence to "Meat and less nuts" pattern across both trimesters demonstrated more distinct effects on increased fetal HC.

Moreover, we found that maternal "Vegetables and fish" and "Snack and less eggs" patterns had a lowering effect on the HC of fetus, the latter also increasing the risk of small HC for GA. Fiber-rich in "Vegetables and fish" pattern increases post-meal satiety and reduces food intake behavior (58). Fish and shrimp were not only rich in nutrients such as marine n-3 fatty acids, vitamin D, and selenium, but can also be a source of pollutants such as methylmercury, arsenic and polychlorinated biphenyls (59, 60). Study based on data from the Child Health and Development Study in the San Francisco Bay Area found that high polychlorinated biphenyl exposure *in utero* was associated with reduced HC at birth (61). As reported by the China Fisheries Statistical Yearbook (62), lean fish species are common food fish in Jiangsu Province, China (62). One prospective cohort study in Italy of 114 mother-infant pairs reported a negative association between maternal consumption of lean fish during pregnancy and neonatal HC (63). Notably, thallophyte and shellfish may contain mercury and persistent pollutants, but meanwhile their nutrient substances such as high levels of zinc and iodine are beneficial for fetal growth (28, 53, 54). The "Snack and less eggs" pattern is an unhealthy diet characterized by low cholesterol and protein. Results from a cohort study of 1,151 women in the southern US demonstrated that adherence to a dietary pattern characterized by fast food, snacks, sweets, and soft drinks during pregnancy reduced offspring head neonatal HC (64). In addition, snack food products are often nutrient-poor, high in salt or sugar, and not recommended for pregnant women (65). Similar to cholesterol (46), protein plays an indispensable role in the development of fetal brain anatomy and physiology (66). A randomized controlled parenteral nutrition study in very early preterm infants also showed that post-natal high-protein diet could improve offspring's HC at 28 days (67).

It was worth noting that our results suggested effects of maternal dietary patterns with growth index in fetal being observed only associated with HC, but not with AC, FL, EFW, and birth weight. Head growth is an independent process and proceeds independently of skeletal growth and fat acquisition (68). FL, AC and body weight are not effective indicators for evaluating head development. Randomized controlled trial of 196 women showed that dietary and lifestyle interventions during pregnancy were associated with offspring's HC but not offspring's weight, and the association persisted until offspring 1-year-old (69). A pilot trial of portable ultrasound with 47 second-trimester women in Ecuador found a significant association between maternal diet and fetal HC, while EFW was not affected by maternal diet (70). In addition, two birth cohort studies in the U.S. reported that dietary pattern in the mid- to late-trimester has no effect on the birth length or weight of offspring

(64, 71), but were associated with HC at birth (64). As far as AC was concerned, the dietary pattern in the third trimester of pregnancy has no effect on the AC of the offspring even up to 54 months of age (72).

A key strength of our study is the longitudinal evaluation of embryonic growth, providing data on fetal growth across pregnancy. Further, prospective and longitudinal data collection allowed examining the temporal associations of maternal dietary patterns and subsequent fetal development. In addition, the use of dietary patterns, which provides an insight into the overall quality of the diet, a feature single-food or nutrient studies cannot provide (12). Finally, a wide range of potential confounding factors was evaluated and controlled in the analysis. Some potential limitations of the research merit discussion. First, the limited items in the FFQ and is prone to be biased by poor participant recall of dietary intake. The FFQ used in this study was scientifically designed and its implementation process was strictly controlled. Moreover, we have confirmed the high validity of the questionnaire in a pre-survey. Second, we did not include maternal B-ultrasound data in the first tri-mester in the current study as the B-ultrasound before 14 GW only provides the crown-rump length (CRL) to assess the GA and fetal size. Additionally, meta-analysis also showed that ultrasound data in the middle and late trimesters rather than the early trimester have predictive value for birth outcomes (73). Third, we did not collect HC, AC and FL at birth, which hindered the evaluation of accuracy of intrauterine ultrasound parameters. However, the EFW and birth weight showed well consistency (data not shown), which may reflect the accuracy of B-ultrasound data to some extent. Finally, despite the strengths of our study, its findings should be interpreted with some caution. Our survey was conducted in China, where food culture is significantly different from other countries, especially Western countries. Therefore, the generalization of our findings to other countries remains to be established.

Conclusion

In the prospective and longitudinal JBC study, our results suggested the effects of maternal dietary patterns on fetal growth, particularly HC. These findings highlighted the adverse impact of unhealthy dietary pattern during pregnancy on fetal growth, might provide evidence for strategies to prevent intrauterine dysplasia and dietary guidelines during pregnancy. This study also validates the practicality of "dietary pattern" for research and health guidance, which takes into account the correlation structure of the food groups and does not focus on selected aspects of a diet. The observed associations between maternal dietary patterns and fetal growth highlighted research on maternal nutrition evaluated by "dietary pattern" in the field of intrauterine growth and even post-natal health. Furthermore, our findings may have important clinical and public health implications. Considering the high prevalence of fetal growth restriction and its potential negative impact on lifelong health, improving maternal diet is of utmost importance. Therefore, awareness of the importance of a healthy dietary pattern should be raised among pregnant women. Future prospective studies with longer follow-up are warranted to determine whether maternal dietary patterns may impact longer-term child growth beyond intrauterine development.

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 of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL, RQ, YD, and QL: conceptualization. RQ: methodology and writing original draft preparation. RQ and YL: formal analysis. RQ, QL, YD, YJ, JD, CS, HL, SL, ST, LH, XX, CL, and ZW: investigation. ZH and YL: resources and funding acquisition. TJ, HM, GJ, YX, YL, FZ, and ZH: data curation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.985665/full#supplementary-material

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The relationship between maternal employment and stunting among 6–59 months old children in Gurage Zone Southern Nation Nationality People's region, Ethiopia: A comparative cross-sectional study

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Background: Motivating proper nutrition during childhood is the basis for optimal health, learning, productivity, and social wellbeing throughout life. Stunting is among the major public health problems. According to the Ethiopian mini demographic and health survey, the prevalence of stunting among under five children was 37%. In addition, stunting has a trans-generational effect on a mother's nutritional status. However, evidence on the causal contribution of maternal employment to stunting among under five children is not well understood in Ethiopia. This study aimed to compare the stunting status and associated factors among under five children of employed and unemployed mothers in the Gurage Zone, Southern Ethiopia, in 2021. A community-based comparative cross-sectional study was conducted among 671 (330 employed and 341 unemployed) randomly selected mother–child pairs in the Gurage Zone, Southern Ethiopia. A pretested semi-structured tool and validated anthropometric measurements were used to collect the data. The data were entered into Epi Data version 3.1 and exported to Statistical Package for Social Science (SPSS) version 23.0 for analysis. Frequency, percent, mean, median, and *SD* were computed and presented by using tables and figures. A bivariable and multivariable binary logistic regression analysis was conducted to assess the association between factors and outcome variables.

Results: In this study, a total of 671 mother–child pairs (330 (94.60%) employed and 341 (97.70%) unemployed) participated, with a total response rate of 96%. Among the total participants, about 70 (21.2%) [95% CI: (17.0, 25.5)] and 98 (28.8%) [95% CI: (23.0, 33.4)] of children of employed and unemployed mothers, respectively, were stunted. Mothers' level of education, primary and secondary [AOR = 1.79, 95% CI: (0.8, 3.7), age between 25 and 29 years [AOR = 0.08, 95% CI: (0.006, 0.904)], monthly family income > 5,000 birr [AOR = 0.42, 95% CI: (0.00, 0.64)], and children aged between 6 and 23 months [AOR = 2.9; 95% CI: (1.48, 5.80)] were predictors of stunting among the children of employed mothers. Compared to the mothers who did not receive nutritional education [AOR = 2.5; 95% CI: (1.10, 5.60)], monthly family income of 2,000 ETB [AOR = 2.64; 95% CI: (1.34, 5.19)], sex of child (girl) [AOR = 2.3; 95% CI: (1.30, 3.80), and mothers educational status of read-and-write only [AOR = 2.9, 95% CI: (1.40, 5.80)] were predictors of stunting among the children of unemployed mothers. The nutrition intervention should focus on encouraging women's education as it increases the probability of being employed, improving the income of families by using different income-generating strategies, and strengthening the existing essential nutrition counseling strategy. Likewise, further research work on the difference between employed and unemployed mothers on stunting status is also recommended to researchers.

KEYWORDS

stunting, employment, associated factor, children, Gurage Zone, Ethiopia

Introduction

Stunting is defined as a long-term lack of adequate nutrition in children, which limits linear growth and leads to collective growth deficits (1–3). It is the most common type of undernutrition and is regarded as a major public health issue in the country (4, 5). Stunting is an anthropometric gauge regularly used to compute a child's long-term nutritional condition. It would be defined as *Z*-scores of less than 2 SDs of height for age (6–9). Proper nutrition is crucial for healthy growth and development. It ensures proper organ formation and function, a strong immune system, and neurological and cognitive development. It is also the foundation of survival. The effect of proper nutrition during childhood is trans-generational (not only in early life but also across adulthood) (7).

Food insecurity, inadequate maternal and child care, poor health services, and living circumstances, or improper feeding practice cause measurable unfavorable effects on body function and clinical outcomes (10–12). There are various causes of stunting; these causes are versatile and tangled with each other, hierarchically related and intergenerational. Stunting among children depends on the multifaceted interactions of various factors such as socio-demographic, environmental, reproductive, institutional, cultural, political, and regional (13, 14).

Because of the intergenerational crash of chronic malnutrition, childhood stunting is connected with the poor-nutritional status of future mothers and an advanced risk of death (15). In low-income settings, micronutrient consumption of women is insufficient due to the limitation of resources, and it increases the risk of child mortality (16). As a result, women's employment has a positive effect because it increases household income, which improves household nutrition in general and the nutritional status of women in particular (17). In addition to the multiple roles of women in the health and welfare of all family members, women's employment has a direct effect on child care, the nutritional status of children, and the mother herself (10, 18, 19).

In 2018, 22% of under five children were stunted globally (20). In developing countries, one out of four children are stunted (3, 18). Ethiopia has the second highest rate of stunting in the Sub-Saharan Africa (19). Worldwide, 8–11 million under five children die each year (8, 20–22). A total of 45% of these deaths are attributed to stunting, which is mostly avoidable through economic development and public health measures (3, 12, 14, 19, 23, 24).

According to the 2019 Ethiopia, mini demographic and health survey (EMDHS), 37% of under-five children are short for their age or stunted and 12% are severely stunted. The prevalence of stunting generally increases gradually with age, from 22% among children aged 6–8 months old up to 44% of children aged 48–59 months, and it is also slightly higher among boys than in girls (40% vs. 33%) (4).

According to the World Bank estimate, in Ethiopia, 16% of all repetitions in primary school are connected to stunting. Stunted children are delayed by 1.1 y in school education (25, 26). A study from Ethiopia provides evidence that due to children undernutrition, Ethiopia loses an estimated 55.5 billion Ethiopian birr each year. This is equivalent to 16.5% of the GDP. There were an estimated 4.4 million additional clinical episodes associated with undernutrition in children under the age of five at a cost of ETB 1.8 billion (27).

Stunting in children is declining with much effort made by various stakeholders. However, Ethiopia is not on track to realize the national nutrition program (NNP) II target and the Sequota declaration to reduce stunting at the rate of 26% by 2020. Besides, there is a great disparity in stunting rates across regions, residences, and economic status. Hence, stunting remains a public health concern in Ethiopia and more intervention is considered necessary to accelerate learning (28). Involving women in income-generating activities such as employment increases household income, with the resultant advantage of increasing women's status and power of decision-making (14).

In addition, there is an agreement that income earned by a mother or maternal employment has a direct effect on childcare, the nutritional status of children, and the mothers themselves (10). Furthermore, maternal employment empowers women economically and socially, and is in line with sustainable development goal 8, which aims at promoting economic growth and productive employment for all. In addition, sustainable development goal 2 aims at ending hunger, achieving food security, and improving nutrition (20).

Although previous literature shows that a high risk of stunting is associated with socioeconomic classes (14), there is a dearth of literature connecting maternal employment with childhood stunting in Ethiopia, which needs to be supported by solid evidence. Thus, this study is aimed at understanding the relative contributions of maternal employment to childhood stunting.

Materials and methods

Study setting and design

This community-based comparative cross-sectional study was conducted in the Gurage Zone, 158 km away from Addis Ababa, the capital city of Ethiopia, and 345 km from Hawassa, the capital city of the Southern Nation Nationality People's region (SNNPR). In the district, there are three sub-cities and seven kebeles (which refer to the lower-level administrative divisions) under these sub-cities. It has a total population of 72,929 living within 14,585 households. A total of 11,377 of them were estimated to be under five children, and 9,772 were aged between 6 and 59 months. The study was conducted in May 2021, in the Gregorian calendar.

Population and eligibility criteria

The findings of this survey are projected for all mother—child pair aged 6–59 months in the Gurage Zone, while those children aged 6–59 months from a randomly selected kebele were the study population. Those children aged 6–59 months old who have resided in the study area for at least 6 months and above and who have volunteered to participate in the study were considered as study participants, while those children whose mothers were unable to respond to the interview due to severe illness were excluded. Sample size determination.

The sample size was determined by considering both objectives; for the first objective, we assumed the prevalence of stunting (P) among children of unemployed and employed mothers was 26.5 and 18.5%, respectively, from previous studies (18), f () = 7.84, when the power = 80%, and = 5% considering a 10% non-respondent rate and a 1.5 design effect, using a statistical formula.

$$\eta = (p1q1 + p2q2)\ f((\alpha, \beta))/((p1 - p2)^2$$

yield sample size of 698.

While the sample size for the second objective was estimated using the sample size for a cross-sectional study to compare the factor variable with stunting under Epi-info version 7 software. Assumptions were taken into consideration; mothers' educational status (14), mothers' employment status (18), and sex of children (29) as factors; confidence level = 95%, power (1-): 80%, ratio = 1:1 (employed and unemployed), and a design effect of 1.5, giving up the largest sample size of 647 for unemployed mothers at an adjusted odds ratio (AOR) of 2, which is less than that calculated by the double population proportion formula. Therefore, the final sample size was 698 (349 employed and 349 unemployed).

Sampling procedures

A multi-stage sampling technique was used to randomly select 698 child–mother pairs from a randomly selected household. The sample size was proportionally allocated to randomly selected sub-cities. Then, from each sub-city, a pre-specified number of kebeles were selected, and the sample

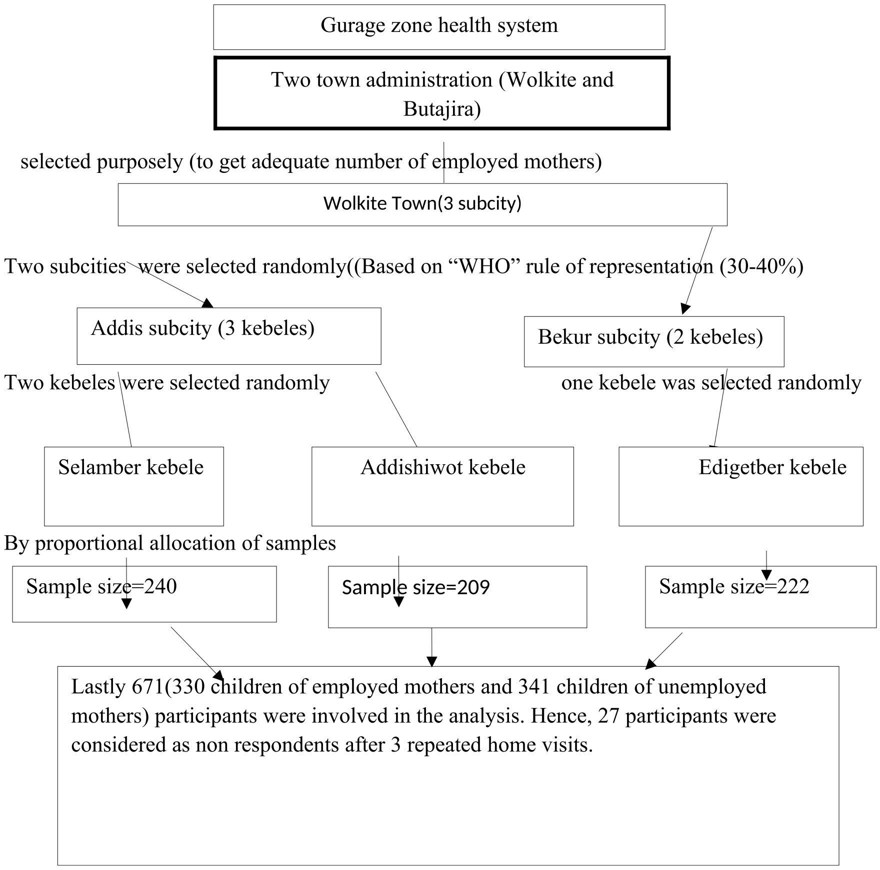

FIGURE 1
Schematic presentation of the sampling procedure for a study on the relationship between maternal employment and stunting among 6–59-month-old children in Gurage Zone SNNPR, Ethiopia 2021.

was further allocated proportionally to each randomly selected kebele. A total of 3 kebele were included [Based on the "WHO" rule of representation (30–40%)] (see **Figure 1**).

After that, to select the allocated sample of participants from each kebele, we applied systematic random sampling. The sample frame containing the full list of households with children aged 6–59 months was obtained from the list (registered 2 weeks prior to the actual data collection process for this purpose). When there were two 6–59-month-old children in a household, one was selected randomly by lottery method. When the respondent was not available at the time, the data collectors made about 3 visits.

Data collection tools and procedure

A pretested structured interviewer-administered questionnaire containing variables assessing socio-demographic variables, household economic status, maternal health status, and child health-related factors, was used to collect data from the mother or caregiver of the child. After reviewing relevant literature from prior related studies, the questionnaire was prepared in English and translated to the local language (Amharic), and administered in translated form. The questionnaire was pretested a week before the actual survey in an analogous setting in Butajira town on 5% of the calculated sample size and an amendment of the tool was done based on the result from the pretest. After interviewing the mothers of the selected children, the anthropometric measurement for height/length was measured in accordance with WHO guidelines. A portable stand-meter (SECA) was used to measure older children (older than 2 years) while younger children (less than 2 years) were measured using a calibrated length board. The body parts were in touch with the measuring board in proper anatomical position. The child's body at the occiput, shoulder blades, buttocks, and heels were in touch with the board and recorded to the nearest 0.1.

Variables of the study

The dependent variable of this study is stunting. Maternal health and health service-related factors such as antenatal care (ANC) follow-up, nutritional information, child health-related factors such as breastfeeding practice, meal frequency, immunization status, and diarrhea exposure.

Quality control of data

The questionnaire was pretested and administered in the local language. An adequate number of data collectors and supervisors were employed for actual data collection and trained on how they proceeded, and close supervision was undertaken throughout the process. The completeness and consistency of the collected data were checked on a daily basis.

Operational definitions/measurement/

Stunted—Children whose height-for-age *Z*-score is below minus two standard deviations (-2 *SD*) from the median of the WHO standard (16, 20).

Definition of terms

A caregiver is the most responsible person that provides child care when the mother is out of the home for work. A mother is considered to be an “employed mother” if she reports earning income since the birth of the current eligible child until the data collection period by working either in a government, NGO, public, private sector, or other self-managed income-generating work. A mother is considered “unemployed” if she reports having had no work since the birth of her current eligible child until the data collection period, whether in the government, NGO, public, or private sector, or from other self-managed income-generating work.

Processing and analysis of data

The data were coded and entered into the statistical software Epi Data version 3.1 before being exported to the Statistical Package for Social Science (SPSS) version 23.0 for analysis. The analysis was done; frequency, percent, mean, median, and standard deviation were computed, and presented by using tables and figures. A bivariable and multivariable binary logistic regression analysis was conducted to assess the association between the factors and outcome variables. The variables were checked for normality, and multicollinearity (using statistically significant correlations and a higher variance inflation factor above 10). Factors with a *p*-value below 0.20 in bivariate were considered for the final logistic regression model to address all possible confounders. Model fitness was tested by using the Hosmer-Lemeshow goodness-of-fit (0.689 and 0.446) for employed and unemployed, respectively, which were good fits for the data). Crude and adjusted odd ratios with 95% confidence intervals were reported. Independent predictors were declared at a *P*-value below 0.05.

Ethical considerations

Ethical clearance was obtained from the Institutional Health Research Ethical Review Committee at Wolkite University. An official support letter was submitted to those who are concerned. The study, its purpose, procedure, and duration, the rights of the respondents, and possible risks and benefits of the study were clearly explained to each participant using the local language. At last, written informed consent was obtained from participants before they participated in the study. All COVID-19 pandemic prevention standard precautions were followed, including data confidentiality.

Results

Socio-demographic and economic characteristics

This study was undertaken among 671 mothers (330 (94.6%) employed and 341 (97.7%) unemployed) who have children aged 6–59 months in southern Ethiopia, with a total response rate of 96%. The respondents’ average age was 32.1 years (+ 5.8), and the age range was 24–45. A total of 301 (91.2%) employed and 326 (95.6%) unemployed were married; 148 (44.8%) employed and 151 (44.3%) unemployed were Muslim; 130 (39.4%) employed and 145 (42.5%) unemployed were Orthodox; 192 (58.2%) employed and 49 (14.4%) unemployed mothers had attended college or higher; and 208 (63%) and 267 (78.3%) employed and unemployed mothers had family sizes of 4–6. More than half (59%) of the employed mothers had a family income of > 5,000 ETB per month, whereas around two-thirds (68.3%) of the unemployed mothers earn between 2,000 and 5,000 ETB (see **Table 1**).

Characteristics of 6–59-month-old children of employed and unemployed mothers

Among the total 154 (46.7%) children of employed and 160 (46.9%) children of unemployed mothers, 105 (31.8%) children of employed and 97 (28.4%) children of unemployed mothers were aged 6–23 months, whereas 255 (68.2%) children of employed and 244 (71.6%) children of unemployed mothers were aged 24–59 months. In total, 326 (98.8%) children of

TABLE 1 Socio-demographic characteristics of mothers who have 6–59 months old children, in Gurage Zone SNNPR Ethiopia, 2021 (n = 671).

Variables	Employed (N = 330) Count (%)	Unemployed (N = 341) Count (%)	Total (N = 671) Count (%)
Maternal age			
20–24 years	9 (2.73%)	5 (1.46%)	14 (2.08%)
25–29 years	127 (38.50%)	122 (35.78)	249 (37.11%)
30–34 years	81 (24.53%)	80 (23.6%)	161 (24%)
≥ 35	113 (34.24)	134 (39.3)	247 (36.81)
No of family			
1–3	14 (4.2)	5 (1.5%)	19 (2.8%)
4–6	208 (63%)	267 (78.3%)	475 (70.8%)
>6	108 (32.7%)	69 (20.2%)	177 (26.4%)
Marital status			
Marred and live together	301 (91.2%)	326 (95.6%)	627 (93.4%)
Divorced	14 (4.2%)	4 (1.2%)	18 (2.7%)
Widowed	11 (3.3%)	9 (2.6%)	20 (2.98%)
Never marred	4 (1.2%)	2 (0.6%)	6 (0.9%)
Religion			
Orthodox	130 (39.4%)	145 (42.5%)	275 (41%)
Muslim	148 (44.8%)	151 (44.3%)	299 (44.2%)
Catholic	14 (4.2%)	19 (5.6%)	33 (4.9%)
Protestant	38 (11.5%)	26 (7.6%)	64 (9.5%)
Family income			
<2,000 ET birr	60 (18.2%)	108 (31.7%)	166 (24.7%)
2,000–5,000 ET birr	74 (22.4%)	233 (68.3%)	313 (46%)
>5,000 ET birr	196 (59.4%)	0 (0%)	192 (28.6)
Educational status			
Read and write	46 (13.9%)	90 (26.4%)	136 (20.27%)
Primary to secondary	100 (30.3%)	202 (59.2%)	302 (45.0%)
College and above	184 (55.8%)	49 (14.4%)	233 (34.73%)
Educational status of husband's			
Read and write	10 (3.0%)	2 (0.6%)	12 (1.8%)
primary to secondary	93 (28.2%)	210 (61.6%)	303 (45.2%)
College and above	227 (68.8%)	129 (37.8%)	356 (53.1%)

employed and 332 (93%) children of unemployed mothers were vaccinated for age. Regarding the feeding patterns of half of the children, 167 (50.6%) and 173 (50.7%) of children of employed and unemployed mothers, respectively, were breastfed eight times per day. In total, 228 (69.1%) and 255 (74.8%) of children of employed and unemployed mothers, respectively, had taken complementary diets three to four times per day.

Maternal characteristics

Regarding service utilization during pregnancy, all mothers in both groups have reported that they have gotten ANC services at health facilities at least once. A total of 179 (54.2%) employed and 253 (74.2%) unemployed mothers reported visiting a health facility four or more times during their most recent pregnancy. Concerning nutrition information received during any service delivery time, 246 (74.5%) employed mothers and 284 (83.3%) unemployed mothers reported receiving nutrition information. Regarding delivery service, 322 (97.6%) and 324 (95%) of employed and unemployed mothers, respectively, gave birth at the health facility.

Prevalence of stunting among 6–59-months-old children of employed and unemployed mothers

Among the total participants, about 70 (21.2%) [95% CI: (17, 25.5)] and 98 (28.8%) [95% CI: (23, 33.4)] children of employed and unemployed mothers, respectively, were stunted.

Factors associated with stunting among children of employed mothers

The association between stunting and factor variables were assessed using a step-wise backward binary logistic regression model. Variables with a p-value below 0.2 in the bivariable logistic regression analysis were considered for the multivariable logistic regression model.

In bivariate analysis, the age of mothers, maternal education, husband education, family income, age of the child, frequency of breastfeeding, diarrhea, frequency of ANC visit, and nutrition information were associated with stunting at p-value $\leq$ 0.2 and have been a candidate for multivariate logistic regression analysis. In the multivariate analysis, maternal education, maternal age, child age, family income, and frequency of breastfeeding showed a statistically independent significant association with stunting at a p-value < 0.05.

Children whose mothers attended primary and secondary level education [AOR = 1.79, 95% CI: (0.8, 3.7)] were 1.8 times more likely to be stunted compared to children whose mothers attend college and above. Children whose mothers' age ranged between 25 and 29 [AOR = 0.08, 95% CI: (0.009, 0.648)] were 92% protected from stunting compared to children whose mothers' age ranged between 20 and 24 (see Table 2). Children from families with a monthly income of 2,000–5,000 ETB [AOR = 0.045, 95% CI: (0.013, 0.155)] and > 5,000 ETB [AOR = 0.042, 95% CI: (0.014, 0.129)] were 95.5 and 95.8%, respectively, less likely to be stunted as compared to children from families with a monthly income of < 2,000 ETB (see Table 2). Children aged 24–59 months [AOR = 0.37, 95% CI: (0.11, 0.78)] were 63% less likely to be stunted compared with children aged between 6 and 23 months. Likewise, children who breastfeed $\geq$ 8 times per day [AOR = 0.081, 95% CI: (0.027, 0.247)] were 91.9% less likely to be stunted as compared to the children who breastfeed < 8 times per day (see Table 2).

Factors associated with stunting among children of unemployed mothers

In bivariate analysis maternal education, family income, age of the child, sex of the child, and nutrition education were significantly associated with stunting at a p-value of $\leq$ 0.2 and 95% CI. Those variables significantly associated ($p \leq 0.2$) were considered as a candidate for multivariate analysis to control the potential confounding variable. In the final model, sex of the child, nutrition information, maternal education, and family income had a statistically significant association with stunting at a p-value of < 0.05 and 95% CI (see Table 3).

The multivariate analysis revealed that the odds of being stunted were 2.5 times higher [AOR = 2.5, 95% CI: (1.1, 5.6)] among children of unemployed mothers who had no exposure to nutrition education compared with those children of unemployed mothers who had received nutrition education. Children of unemployed mothers whose mothers were only able to read and write [AOR = 2.9, 95% CI: (1.4, 5.8)] were 2.9 times more likely to be stunted compared to children of unemployed mothers whose mothers had attended primary and secondary school. Likewise, children of unemployed mothers whose family monthly income < 2,000 ETB [AOR = 2.64, 95% CI: (1.34, 5.19)] were nearly three times more likely to be stunted as compared with the children whose family monthly income was greater or equal to 2,000 ETB. And a girl child [AOR = 2.3, 95% CI: (1.3, 3.8)] is two times more likely to be stunted compared with a boy (see Table 3).

Discussion

This article quantified and compared the burden of stunting and its predictors among children of employed and unemployed mothers. A considerable proportion of children of employed and unemployed mothers [21.2%, 95% CI: (17, 25.5) and 28.8%, 95% CI:: (23, 33.4)] were stunted, which showed that the prevalence of stunting is slightly higher among children of unemployed mothers. It is consistent with other study findings from Wolayta Sodo, town administration, Southern Ethiopia (18.5 and 26.5%), respectively (14), and Wilayat Zone, Southern Ethiopia, 21.8 and 22.6%, respectively (18). This might be due to socio-demographic/economic/and cultural similarities between these study areas. However, other survey reports from Adama town, central Ethiopia (2017) (28 and 39.5%), respectively (10) show that the possible reason for this difference could be the time gap between the studies, as an intensive intervention in childhood.

In this study, we found that children of mothers of lower education levels were nearly 3 times more likely to be stunted compared with those of secondary and above levels. It was relatively consistent with the findings from Adama Town, central Ethiopia (10), Wolayta Zone, southern Ethiopia (18), and Uganda (20). The possible explanation for this may be that as women's level of education increases their awareness of child nutrition, child care practices, healthcare utilization during illness, and immunization service utilization improves, and that in turn affects children's nutritional status (10,14,17,19).

TABLE 2 Bivariate and multivariate analysis for stunting among employed mothers in Gurage Zone, SNNPR, Ethiopia 2021 (n = 671).

Variables	Category	Stunted		COR [95% CI]	AOR [95% CI]	*P*-value
		Yes	Not			
Maternal education	Read and write	14	32	0.69 (0.34,1.42)	0.14 (0.04,0.55)	≤0.26
	Primary to secondary	13	87	2.04 (1.03,4.01)	1.79 (1.20,3.70)	≤0.03*
	College and above	43	141	1	1	
Monthly family income in ETB	<2,000	8	52	1	1	
	2,000–5,000	12	62	0.79 (0.3,2.0)	0.04 (0.01,0.15)	≤0.00**
	>5,000	50	146	0.45 (0.2,1.0)	0.04 (0.01,0.13)	≤0.00**
Age of child	6–24 months	13	92	1	1	
	24–59 months	57	168	0.42 (0.21,0.80)	0.37 (0.11,0.78)	≤0.01**
Maternal age	20–24 years	6	2	0.74 (0.36,1.48)	0.49 (0.17,1.43)	≤0.19
	25–29 years	24	103	0.75 (0.01,0.39)	0.08 (0.01,0.64)	≤0.02*
	30–34 years	19	62	0.74 (0.51,1.85)	0.65 (0.23,1.85)	≤0.42
	<=35 years	21	93	1	1	
Frequency breast feeding	<8 times per/day	63	104	1	1	
	≥8 times per day	7	156	0.07 (0.03,0.16)	0.08 (0.03,0.25)	≤0.00**
Diarrhea in the last 2 weeks	Yes	5	45	1	1	
	No	65	215	0.37 (0.14,0.96)	0.35 (0.10,1.25)	≤0.11
ANC visit	<4 times	23	128	1	1	
	≥4 times	47	132	0.50 (0.29, 0.88)	0.74 (0.30,1.87)	≤0.54
Nutrition information	Yes	61	185	1	1	
	No	9	75	2.74 (1.29, 5.80)	1.81 (1.90, 5.20)	≤0.46

COR, Crude odds ratio; AOR, Adjusted odds ratio. *$p < 0.05$, **$p \leq 0.01$.

TABLE 3 Bivariate and multivariate analysis for stunting among unemployed mothers in Gurage Zone, SNNPR, Ethiopia, 2021 (n = 671).

Variables	Stunted		COR with 95% CI	AOR with 95% CI	*P*-value
	Yes	No			
Sex of child					
Male	56	95	1	1	
Female	42	148	2.0 (1.2, 3.3)	2.3 (1.3,3.8)	≤0.01*
Nutrition information					
Yes	87	197	1	1	
No	11	46	1.8 (1.3, 3.7)	2.5 (1.1, 5.6)	≤0.02*
Maternal education					
Read and write	13	77	3.2 (1.7,6.3)	2.9 (1.4, 5.8)	≤0.01**
Primary to secondary	72	130	1	1	
College and above	13	36	1.5 (1.2, 6.31)	1.4 (01.6, 3.2)	≤0.31
Monthly family income					
<2,000 ET birr	41	67	1.88 (1.157, 3.08)	2.64 (1.34, 5.19)	≤0.01**
≥2,000 ET birr	57	176	1	1	
Age of child					
6–23	31	66	1	1	
24–59	67	177	1.2 (0.7, 2.0)	1.3 (1.3,3.8)	≤0.12

COR, Crude odds ratio; AOR, Adjusted odds ratio. *$p < 0.05$, **$p < 0.01$.

In addition, the likelihood of being stunted is lower among children of younger employed mothers [AOR = 0.08, 95% CI: (0.01, 0.64)]. It is consistent with a survey report from Wolayta Sodo southern Ethiopia (18). The possible explanation is at a younger age, the number of family size particularly children is limited which enables the mother to give sufficient time to care for her children compared with late age (14,18). On the contrary, as the age of children of employed mother increase the likelihood of being stunted lowers [AOR = 0.37, 95% CI: (0.11, 0.78)]. This was supported by the study conducted in the Wolayta Zone, where the prevalence of stunting was significantly higher in the age group of 6–23 months compared to the older children (14). The possible justification for this may be the intergenerational effect of stunting affects children to be stunted at an early age without intensive intervention.

This study finding also showed that as family income increases (>2,000 ETB), the likelihood of children of employed and unemployed mothers being stunted is lessened. This is in line with the study finding from the Wolayta Zone, southern Ethiopia (18). This indicates increasing income increases food security at the household level, thus decreasing stunting. Moreover, children from low-income households had low access to adequate dietary intake in kinds and amounts and also decreased purchasing power of the family, and a shortage of other important materials and utilities (30).

Children of an unemployed mother who had no exposure to nutrition education were 2.5 times more likely to be stunted compared with those children of mothers who had been exposed to nutritional education. This finding is in line with the findings of a previous study (18). This implies that nutrition information is the best intervention in bringing behavioral change which gives healthy feeding practice that in turn plays a significant role in better nutritional status of children (30). In addition, girls were two times more likely to be stunted compared to the boys. This was supported by a study conducted in a different part of Ethiopia (18, 30, 31) whereas, it contradicted other study findings, that being girls were less likely to be stunted (6, 19, 32). The reason for this discrepancy may be due to unmeasured factors on care giving behaviors of mothers, because of preference of sex in a country like Ethiopia (30).

Strength and limitation

This is the first comparative study carried out at community level in Gurage Zone, The limitation of this study comprises since the study used the data since birth like breastfeeding practice, Vit-A supplementation, and others, which may confront memory lapse (recall bias), and the Shortage of similar studies limited us to making further comparative discussion.

Conclusion and recommendations

In our study prevalence of stunting was 21.2%, 95% CI: (17, 25.5) and 28.8%, 95% CI: (23, 33.4) for children of employed and unemployed, respectively. This finding is lower compared with the regional, national, and WHO cut-off point of 40% set for stunting. In this study, maternal education, maternal age, family income, frequency of breastfeeding, and child age had a statistically significant association with stunting among children of employed mothers, whereas nutritional information, maternal education, family income, and sex of the child had a statistically significant association with stunting among children of unemployed mothers, thus nutrition intervention should focus on encouraging women education as it increases the probability of being employed, improving income of family by using different income-generating strategies, and strengthening the existing essential nutrition counseling strategy. Likewise, further research work on the difference between employed and unemployed mothers on stunting status is also recommended to researchers.

Data availability statement

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

Ethics statement

Ethical clearance was obtained from the Institutional Health Research Ethical Review Committee, Wolkite University. An official support letter was submitted to those who are concerned. The study, purpose, procedure and duration, rights of the respondents and possible risks and benefits of the study were clearly explained to each participant using the local language. Finally written informed consent was obtained from participants before they participated in the study. The data confidentiality and all COVID-19 pandemic prevention standard precautions were kept.

Author contributions

All the authors participated in the design, data analysis, drafting, and revising the manuscript, have agreed on the journal to which the manuscript was submitted, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.964124/full#supplementary-material

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Association of low birthweight and small for gestational age with maternal ferritin levels: A retrospective cohort study in China

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Background: Birthweight have profound impacts on health status throughout lifetime, however, the relationship between maternal ferritin level in pregnancy and birthweight of the newborn remains controversial.

Objective: This retrospective cohort research was to analyze the association between maternal ferritin levels during pregnancy with birthweight outcomes, primarily for low birthweight (LBW) and small for gestational age (SGA).

Methods: Newborns weighing lower than 2,500 grams were defined as LBW. SGA is defined as birthweight lower than the 10^{th} percentile of the distribution of newborns' birthweight of the same gestational age. Multivariable logistic regressions have been used to explore the association of maternal ferritin levels and birthweight related outcomes, in which the ferritin concentration was logarithm transformed in the model. We further used restricted cubic spline models to explore linear/non-linear dose–response manners of ferritin level and birthweight outcomes.

Results: A total of 3,566 pregnant women were included in the study. In the results of the present study, we observed that maternal ferritin levels were linearly associated with the risk of LBW (p-trend = 0.005) and SGA (p-trend = 0.04), with the adjusted odds ratios (ORs) of 1.78 (95% CI 1.37–2.32) for LBW and 1.87 (95% CI 1.38–2.54) for SGA with an increase in Ln-ferritin concentrations per unit. The adjusted ORs across quartiles of ferritin levels were 2.14 (95% CI 1.03–4.47) for Quartile 2, 3.13 (95% CI 1.47–6.69) for Quartile 3, and 3.63 (95% CI 1.52–8.68) for Quartile 4 for LBW. The adjusted ORs of LBW and SGA among women using supplemental iron were 0.56 (95% CI 0.38, 0.85) and 0.65 (95% CI 0.40, 1.05) compared with non-users, respectively.

Conclusions: Our findings found a linear dose–response relationship between ferritin levels and an increased risk of poor birthweight outcomes, suggesting that maternal ferritin level during pregnancy may provide an additional predictor for differentiating poor birthweight related outcomes. Further exploration should be conducted to ensure maternal ferritin thresholds and iron supplement doses.

KEYWORDS

ferritin, cohort study, pregnancy nutrition, low birthweight, small for gestational age

Introduction

Birthweight is the key to evaluating fetal growth (1). Poor birthweight due to intrauterine growth and development limitations may contribute to adverse birth outcomes. Low birthweight (LBW) was the major cause of morbidity and mortality in newborns (1). Low birthweight is a global public health problem, which involves a wide range and has short-term and also long-term impact on the early growth and development of individuals, as well as the occurrence of chronic diseases in adolescence and adulthood. The prevalence of low birthweight remains high, this phenomenon adds a heavy burden to the medical and health system (2). The incidence rate of low birthweight reflects the nutritional status of pregnant women and fetuses in a place or country, as well as the status and the quality of maternal and child's health care work. Therefore, fetal weight undergrowth is an important neonatal outcome, and it is important to identify its potential influencing factors to prevent adverse health effects throughout life time.

The nutrition status of pregnant woman during pregnancy critically determines the nutrition of the fetus and contributes significantly to the health of the fetus and newborn. Serum ferritin is a protein that indicates the level of iron reserve in the body (3). Poor ferritin level is a common nutritional problem during pregnancy and is associated with inadequate intake anemia or certain chronic diseases (4). Ferritin itself has important physiological activities which is not only a carrier of iron (3). Iron, on the other hand, is a powerful pro-oxidant that catalyzes the production of reactive oxidative species (ROS) (5). Excess iron intake can lead to impaired placenta function because of oxidative damage (4). Existing epidemiological evidence demonstrates that higher serum ferritin is associated with an increased risk of LBW in late pregnancy (6). Some researchers found that both low and high ferritin levels measured in pregnancy were add risks to the occurrence of LBW and small for gestational age (SGA) among newborns with small sample size (7), and hypothesized the relationship between iron stores and total health risk would be U-shaped, similar to most other nutrients (8). Obstetricians pay attention to ferritin levels during pregnancy, pregnant women are encouraged to take iron supplements when ferritin levels are low (9). In China, the prevalence of anemia in non-pregnant women was 17.4%, in women during the first trimester was 21.6%, and in women during the third trimester was 10.5% (10). As a result, the spontaneous go to pharmacy for iron contained supplements by pregnant women is common in the context of high anemia rates. Because pregnancy is an especially sensitive period, the type of food consumed by pregnant women and the independent choice of various doses of nutritional supplements will greatly affect the level of ferritin during pregnancy.

In conclusion, the results of previous researches on iron status and the risk of LBW have no consistent conclusion. Additionally, there is no evidence of the dose–response relationship between serum ferritin concentration and birthweight outcomes. Furthermore, research on iron overload that utilizes large sample sizes is limited among the Chinese population. This study was conducted to investigate the relationship between maternal serum ferritin levels and birthweight of newborns, to indicate the possible outcome risk caused by iron nutrition status, to provide a scientific basis for a scientific diet, nutritional supplements, or pregnancy care.

Methods

Study population

This retrospective cohort study was performed at the Zhongnan Hospital of Wuhan University, China. The medical information of pregnant women who delivered in Zhongnan Hospital of Wuhan University from January 2014 to September 2021 were retrospectively reviewed, and information on pregnant women who admitted to the hospital for prenatal examinations was also collected. Inclusion criteria: (1) $\geq$18 years old; (2) the results of serum ferritin test during pregnancy were available; (3) the woman delivered a single fetus in our hospital; and (4) the data were complete. Exclusion criteria: (1) multiple births, stillbirths, lost visitors; (2) lack of information on newborn birthweight. This study applied for informed consent exemption and was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (Approval No.:2022141K).

Assessment of serum ferritin and Fe supplemental use

Maternal blood samples were tested for serum ferritin by the hospital laboratory. The serum ferritin concentration was detected by the chemiluminescence method performed on Abbott™ 3517. In order to ensure the precision and accuracy of ferritin detection in clinical laboratory, we conduct inner-laboratory quality control at two concentration levels daily. At the same time, the laboratory participated in the inter-laboratory evaluation plan organized by the Clinical Laboratory Center of the National Health Commission and the Clinical Laboratory Center of Hubei Provincial Health Commission to ensure that the results were comparable. All the ferritin data was extracted from the patient's first ferritin test during pregnancy in our hospital, the information of Fe supplemental use was from medical order in hospital information service.

Birthweight outcomes

Gestational age was obtained from medical records as the number of days between delivery date and last menstrual period. Preterm birth was referring to a single live birth occurring at 36 weeks of gestation or earlier (11). Newborns weighing lower than 2,500 grams were defined as LBW (12). According to a global reference (13), SGA is defined as birthweight lower than the 10^{th} percentile of the distribution of newborns' birthweight of the same gestational age. Severe SGA was referring to birthweight lower than the 5^{th} percentile of the distribution of birth weight in the same week, and mild SGA was defined as 5^{th}–9^{th} percentile of the birthweight distribution in the same week.

Covariable

Maternal demographic and socioeconomic characteristics and lifestyle information were standardized and collected by trained nurses. The gestational weeks at the test time were also reviewed. Medical records on delivery (e.g., parity, gestational age, and infant gender) and complications of pregnancy (gestational hypertension and gestational diabetes mellitus) during pregnancy or diagnosed on admission were surveyed and reviewed by experienced obstetricians.

Statistical analysis

The median value of each ferritin quartile was as a continuous variable in adjusted models for p-trend values. For outliers (exceeding the mean ± 3SD), the measured ferritin concentrations were replaced with the mean ± 3SD. Multivariable logistic regression models were used to analyze odds ratios (ORs) of birthweight outcomes across increasing quartiles of serum ferritin concentrations. Furthermore, we explored the dose–response relationships between serum ferritin levels and the risk of birthweight outcomes by restricted cubic spline models (14). Knots were placed at the 25th, 50th, 75th, and 95th percentiles of the ferritin distribution, and the reference value was set at the 50th percentile. All models were adjusted for potential confounders: maternal age at delivery (continuous), pre-pregnancy BMI (<18.5, 18.5–23.9, 24.0–27.9, ≥28.0), hypertension (yes or no), education (≤middle school, high school, ≥college), gestational diabetes mellitus (yes or no) and neonatal gender (male or female). Missing data of variables were categorized into an additional group to avoid losing participants caused by missing values of confounders. Stratified analyses were performed by including serum ferritin concentrations and corresponding pregnancy trimester at test time in the logistic regression models. We have conducted sensitivity analyses to verify the robustness of the results, we re-performed the analysis which limited to women freed of hypertensive disorders or gestational diabetes during the pregnancy. To further examine the combined association of ferritin concentrations and Fe supplement use with LBW, participants were stratified into three groups based on ferritin concentrations classified as low (tertile 1, ≤15.4 ng/mL), medium (tertile 2, 15.4–38.9 ng/mL), and high (tertile 3, ≥38.9 ng/mL), we conducted logistic regression to estimate ORs of LBW with non-users in the medium ferritin group as a reference. We performed statistical analyses by SAS 9.4.

Results

In this retrospective cohort study, 6,553 women had maternal ferritin test records before delivery who also had an admission record as an outpatient at the hospital because of "pregnancy" related diagnosis. Two thousand and eighty five women who did not have a medical record of delivery were excluded from the study. Twenty two stillbirths and 580 women who had multiple deliveries were also excluded from this analysis (Figure 1). Finally, the present study including 3,566 pregnant women in the analyses. The median (range) serum ferritin concentration in the studied population was 24.33 (<1–793.07) ng/mL, 1,146 of them reported iron supplement use. Characteristics according to quartiles of maternal ferritin concentrations are shown in Table 1.

In the adjusted models, with an increase in Ln-ferritin concentration per unit, the adjusted OR of LBW was 1.78 (95% CI 1.37–2.32) while the OR was 2.05 (1.27–3.32) for LBW (term) (Table 2). For those women whose ferritin concentration were in the highest quartile, the OR was 3.63 (1.52–8.68; p-trend < 0.001) for LBW and 5.50 (1.21–25.02; p-trend = 0.004) for LBW (term). The ORs of LBW and LBW

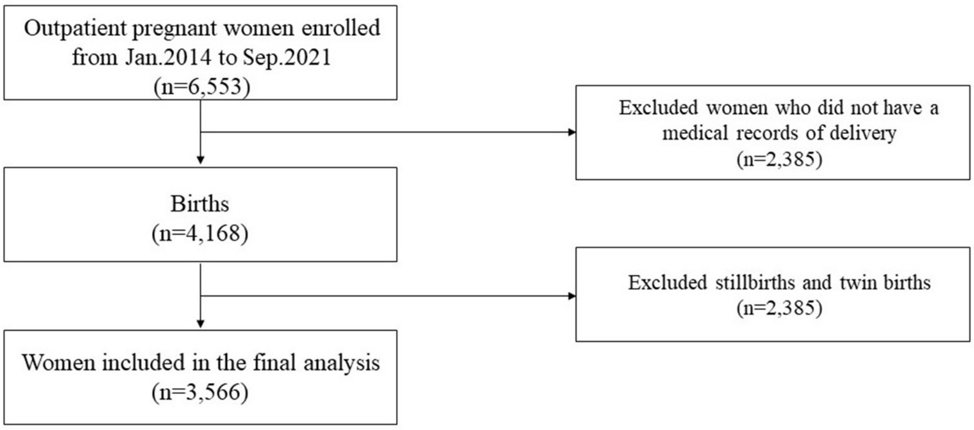

FIGURE 1
Study flowchart.

(term) categories were increased across quartiles of ferritin concentration and the associations were significant in each quartile compare to the lowest quartile. The adjusted OR of LBW (preterm) was 1.64 (95% CI 1.21–2.24) for each additional unit increase of Ln-ferritin concentration. For those women whose ferritin concentration were in the highest quartile, which was suggestively significant associated with LBW (preterm), the OR was 2.46 (0.90–6.76; p-trend = 0.01). In the stratified analysis for pregnancy trimesters, the p trend for adjusted ORs of LBW was significant in the 2nd (p-trend = 0.003) and the last trimesters (p-trend <0.001). In the middle trimester, the OR of LBW of whose ferritin concentration were in the highest quartile was 3.49 (1.54, 7.95). The OR for whose ferritin concentration in the highest quartile of in the last trimester was 26.99 (10.64, 68.45).

The adjusted OR of SGA was 1.87 (95% CI 1.38–2.54) with an increase in Ln-ferritin concentration per unit in the adjusted models, and was 3.82 (1.43–10.21; p-trend< 0.001) for women whose ferritin level were in the highest quartile group. The ORs of SGA were increased across quartiles of ferritin concentration and the associations were significant in each quartile while the lowest quartile as reference. For the SGA category, increased ferritin concentration posed a greater threat to the occurrence of severe SGA, resulting in OR 2.30 (1.47–3.61) with an increase in Ln-ferritin levels per unit, an OR of 14.07 (1.34–147.77; p-trend = 0.001) for women whose ferritin were in the highest quartile (Table 3). In the stratified analyses for pregnancy trimesters, the p-trend for adjusted ORs of LBW was significant in the 2nd trimester (p-trend = 0.003) and 3rd trimester (p-trend < 0.001). In the 2nd trimester, the OR of SGA for women whose ferritin concentration were in the highest quartile was 3.81 (1.50, 9.66) and p trend was 0.002 (Supplementary Table S1).

Positive associations of maternal ferritin levels with the risk of birthweight outcomes were observed in the studied population, and the ORs were increasing with higher quartile groups of ferritin level of birthweight outcomes. Spline regression analysis shows significant linear associations for serum Ln-ferritin concentrations and risk of LBW ($p = 0.005$), LBW (term) ($p = 0.04$), and LBW (preterm) ($p < 0.0001$), small for gestational age ($p = 0.0006$), mild SGA ($p = 0.03$), and severe SGA ($p = 0.02$) (Figure 2), which indicates positive associations between maternal ferritin concentrations and ORs of LBW and SGA with a linear manner.

The adjusted ORs of LBW and SGA restricted to women who were without gestational diabetes and hypertension disorders, were lower based on the adjusted model in the sensitivity analyses, the estimated results and statistical significance are consistent with the preliminary analysis (Supplementary Table S2).

Additionally, the adjusted OR (95% CI) of LBW and SGA among women using supplemental iron was 0.56 (0.38, 0.85) and 0.65 (0.40, 1.05) compared with non-users, respectively (Supplementary Table S3). The present study suggests that Fe supplementation use for pregnant women in the high ferritin group were not associated with higher risk of LBW.

Discussion

This is the first and largest retrospective cohort study to investigate the relationship between maternal ferritin concentration and birthweight among mainland Chinese pregnant women. Our results showed that the risk of low birthweight is significantly increased in pregnant women with higher ferritin concentration. We further investigated the dose–response relationship between maternal ferritin and the risk of low birthweight for the first time. In this study, it was suggested that elevated maternal ferritin levels during pregnancy were

TABLE 1 Basic characteristics according to quartiles of maternal ferritin concentrations.

	All individuals ($n = 3{,}566$)	Quartiles of ferritin concentration			
		Q1 ($n = 891$) ≤12.10 ng/mL	Q2 ($n = 892$) 12.10–24.35 ng/mL	Q3 ($n = 892$) 24.35–50.61 ng/mL	Q4 ($n = 891$) ≥50.61 ng/mL
Maternal characteristic					
Age at delivery, y					
Mean (SD)	31.2 (4.22)	30.84 (4.22)	31.11 (4.33)	31.14 (4.18)	30.98 (4.17)
Median (range)	30 (18–53)	30 (18–49)	31 (18–53)	30 (21–50)	30 (21–46)
≤25	237 (6.6%)	73 (8.2%)	58 (6.5%)	50 (5.6%)	56 (6.2%)
26–29	1,191 (33.4%)	295 (33.1%)	295 (33.1)	283 (31.7%)	318 (35.7%)
30–34	1,426 (40.0%)	357 (40.1%)	355 (39.8%)	373 (41.8%)	341 (38.3%)
≥35	712 (20.0%)	166 (18.6%)	184 (20.6%)	186 (20.9%)	176 (19.8%)
Pre-pregnancy BMI, kg/m^2					
Mean (SD)	21.34 (3.09)	21.00 (2.73)	21.22 (2.96)	21.43 (3.19)	21.65 (3.37)
Median (range)	20.8 (13.4–49.4)	20.6 (13.7–39.8)	20.8 (14.6–45.1)	21.0 (15.1–49.4)	21.1 (13.4–38.3)
<18.5	422 (11.8%)	104 (11.7%)	103 (11.5%)	103 (11.5%)	112 (12.5%)
18.5–23.9	1,937 (54.3%)	459 (51.5%)	481 (53.9%)/	504 (56.5%)	493 (55.3%)
24.0–27.9	349 (9.8%)	72 (8.1%)	76 (8.5%)	92 (10.3%)	109 (12.2%)
≥28.0	98 (2.8%)	13 (1.5%)	14 (1.6%)	28 (3.1%)	43 (4.8%)
Missing data	760 (21.3%)	243 (27.2%)	218 (24.4%)	165 (18.5%)	134 (15.0%)
Parity					
Nulliparous	1,936 (53.5%)	451 (49.9%)	456 (50.4%)	493 (54.5%)	536 (59.3%)
Multiparous	1,680 (46.5%)	453 (50.1%)	448 (49.6%)	411 (45.5%)	368 (40.7%)
Education					
Compulsory and lower	154 (4.3%)	48 (5.4%)	40 (4.5%)	31 (3.5%)	35 (3.9%)
High school or equivalent	310 (8.7%)	101 (11.3%)	70 (7.8%)	67 (7.5%)	72 (8.1%)
Graduate or higher	2,864 (80.3%)	664 (74.5%)	710 (79.6%)	736 (82.5%)	754 (84.6%)
Missing data	238 (6.7%)	78 (8.8%)	72 (8.1%)	58 (6.5%)	30 (3.4%)
Trimester at ferritin test					
1st trimester	1,008 (28.3%)	32 (3.6%)	74 (8.3%)	277 (31.1%)	625 (70.1%)
2nd trimester	1,416 (39.7%)	347 (38.9%)	423 (47.4%)	425 (47.6%)	221 (24.8%)
3rd trimester	1,142 (32.0%)	512 (57.5%)	395 (44.3%)	190 (21.3%)	45 (5.1%)
Fe supplements use					
Non-user	2,421 (67.9%)	580 (65.1%)	583 (65.4%)	603 (67.6%)	655 (73.5%)
Iron supplements	1,145 (32.1%)	311 (34.9%)	309 (34.6%)	289 (32.4%)	236 (26.5%)
Neonatal characteristic					
Gender					
Male	1,914 (53.7%)	480 (53.9%)	457 (51.2%)	488 (54.7%)	489 (54.9%)
Female	1,652 (46.3%)	411 (46.1%)	435 (48.8%)	404 (45.3%)	402 (45.1%)

Q, quartile.

associated with a higher risk of LBW and SGA in a linear dose–response manner.

The positive associations between concentrations of serum ferritin, used in medical practice to indicate iron storage and anemia status, with LBW and SGA in our study were in accordance with previous studies (6, 7, 15–19). Goldenberg et al. found that participants in high ferritin group was associated with lower birthweight when the low ferritin group was as reference among 580 black women (6). Hubel et al. demonstrated that elevated maternal

TABLE 2 Risk of low birthweight and subcategories associated with maternal serum ferritin concentration.

Variables	OR (95% CI) for ferritin concentration					p-trend
	Q1 (n = 891) ≤12.10 ng/mL	Q2 (n = 892) 12.10–24.35 ng/mL	Q3 (n = 892) 24.35–50.61 ng/mL	Q4 (n = 891) ≥50.61 ng/mL	Per unit† (n = 3,566)	
Low birthweight						
n (%)	36 (4.0%)	70 (7.8%)	96 (10.8%)	98 (11.0%)	300 (8.4%)	
Crude	Ref. (OR = 1)	**2.74 (1.29, 5.84) ***	**3.01 (1.42, 6.34) ***	**3.32 (1.61, 6.83) ***	**1.53 (1.20. 1.95)**	**0.001**
Adjusted‡	Ref. (OR = 1)	**2.14 (1.03, 4.47) ***	**3.13 (1.47, 6.69) ***	**3.63 (1.52, 8.68) ***	**1.78 (1.37, 2.32)**	**<0.001**
Low birthweight (term)						
n (%)	3 (<1%)	9 (1.0%)	10 (1.1%)	15 (1.7%)	37 (1.0%)	
Crude	Ref. (OR = 1)	2.99 (0.81, 11.10)	**3.23 (0.88, 11.74) Δ**	**4.87 (1.40, 16.91) ***	**1.61 (1.13, 2.28)**	**0.009**
Adjusted‡	Ref. (OR = 1)	**7.97 (0.96, 66.00) Δ**	**7.53 (0.80, 70.56) Δ**	**5.50 (1.21, 25.02) ***	**2.05 (1.27, 3.32)**	**0.004**
Low birthweight (preterm)						
n (%)	15 (1.7%)	26 (2.9%)	38 (4.3%)	34 (3.8%)	113 (3.2%)	
Crude	Ref. (OR = 1)	**2.47 (0.96, 6.41) Δ**	**2.78 (1.03, 7.51) ***	**2.47 (0.91, 6.74) Δ**	**1.39 (0.98, 1.97) Δ**	**0.088Δ**
Adjusted‡	Ref. (OR = 1)	1.59 (0.70, 3.60)	**2.66 (1.17, 6.02) ***	**2.46 (0.90, 6.76) Δ**	**1.64 (1.21, 2.24)**	**0.011 ***

Q, quartile. † Per unit increase in the natural logarithm transformed serum ferritin concentration (ng/mL). ‡ Adjusted for iron supplements in pregnancy, maternal age at delivery, parity, pre-pregnancy body-mass index, hypertensive disorders in pregnancy, gestational diabetes mellitus, education, and infant sex. $^{\Delta}p < 0.1$; $^{*}p < 0.05$. OR values in bold indicate statistically significance marginally significant.

TABLE 3 Risk of small for gestational age and subcategories associated with maternal ferritin concentration.

Variables	OR (95% CI) for ferritin concentration					p-trend
	Q1 (n = 891) ≤12.10 ng/mL	Q2 (n = 892) 12.10-24.35 ng/mL,	Q3 (n = 892) 24.35-50.61 ng/mL	Q4 (n = 891) ≥50.61 ng/mL	Per unit† (n = 3,566)	
SGA						
n (%)	14 (1.6%)	25 (2.8%)	26 (2.9%)	30 (3.4%)	95 (2.7%)	
Crude	Ref. (OR = 1)	**1.79 (0.92, 3.47) Δ**	**1.75 (0.90, 3.40) Δ**	**2.06 (1.08, 3.93) ***	**1.26 (1.01, 1.56)**	**0.047**
Adjusted‡	Ref. (OR = 1)	**2.42 (1.08, 5.43) ***	**3.32 (1.40, 7.86) ***	**3.82 (1.43, 10.21) ***	**1.87 (1.38, 2.54)**	**<0.001**
Severe SGA						
n (%)	4 (<1%)	10 (1.1%)	15 (1.7%)	12 (1.3%)	41 (1.1%)	
Crude	Ref. (OR = 1)	2.48 (0.77, 7.95)	**3.50 (1.15, 10.65) ***	**2.77 (0.88, 8.69) Δ**	**1.33 (0.96, 1.85)**	**0.086**
Adjusted‡	Ref. (OR = 1)	**8.51 (1.06, 68.36) ***	**26.69 (3.06, 232.56) ***	**14.07 (1.34, 147.77) ***	**2.30 (1.47, 3.61)**	**0.001**
Mild SGA						
n (%)	10 (1.1%)	15 (1.7%)	11 (1.2%)	18 (2.0%)	54 (1.5%)	
Crude	Ref. (OR = 1)	1.48 (0.66, 3.33)	**1.03 (0.43, 2.46) Δ**	1.73 (0.79, 3.80)	1.19 (0.90, 1.58)	0.274
Adjusted‡	Ref. (OR = 1)	1.60 (0.63, 4.10)	1.15 (0.40, 3.34)	2.57 (0.81, 8.17)	**1.53 (1.02, 2.30)**	**0.024**

Q, quartile. † Per unit increase in the natural logarithm transformed maternal serum ferritin concentration (ng/mL). ‡ Adjusted for iron supplements in pregnancy, maternal age at delivery, parity, pre-pregnancy body-mass index, hypertensive disorders in pregnancy, gestational diabetes mellitus, education, and infant sex. $^{\Delta}p < 0.1$; $^{*}p < 0.05$. OR values in bold indicate statistically significance marginally significant.

ferritin levels were increased 3-fold risk of intrauterine growth restriction (IUGR) (18). Akkurt et al. reported that the maternal ferritin level was higher in the IUGR group than in the appropriate for gestational age (AGA) group (59 ng/mL vs. 32 ng/mL, $p < 0.001$) (16). A prospective cohort study was conducted among 573 pregnant women which discovered a negative association between high plasma ferritin and low birthweight (15). The fact that previous studies were in small sample sizes with <600 participants, our data from a large retrospective cohort study provide strong scientific evidence in a Chinese population. In the present study, the median serum ferritin concentration (median = 24 ng/mL) was comparable to values from previous studies, from which the mean/median levels ranged from

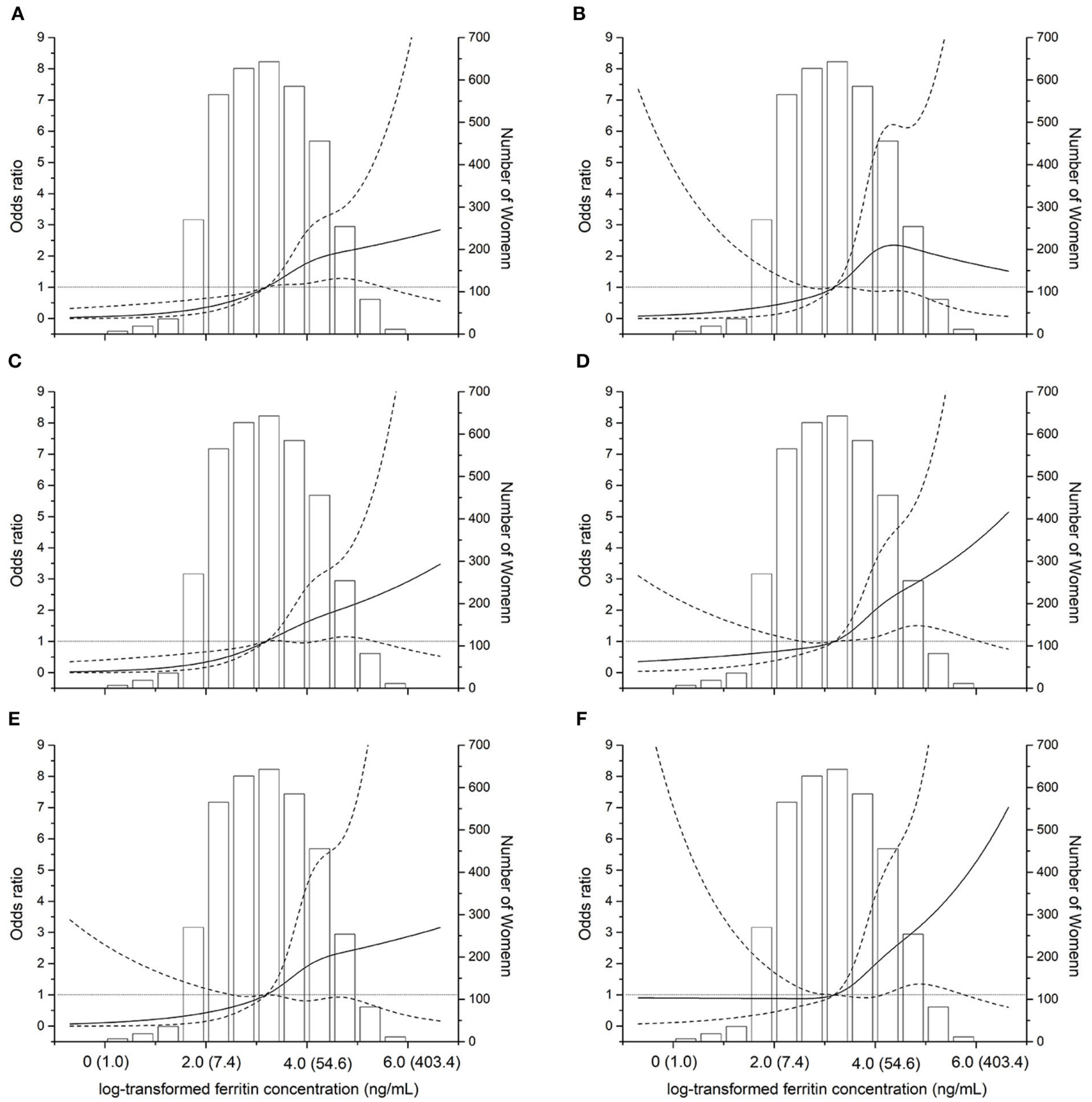

FIGURE 2
Dose–response relationships between maternal ferritin concentrations and the risk of adverse birth outcomes. The restricted cubic spline for the association between serum ferritin and incident of LBW **(A)**. LBW (term) **(B)**. LBW (preterm) **(C)**. SGA **(D)**. Severe SGA **(E)**. Mild SGA **(F)**. The solid lines represent odds ratios (ORs) based on restricted cubic splines for the log-transformed levels of maternal ferritin, the dotted lines represent the confidence interval. The bars represent histograms of maternal ferritin concentration distribution among the total population. The numbers in parentheses show the maternal concentrations before log-transformation. The horizontal gray line represents OR = 1.

18 to 43 ng/mL across pregnancy (6, 15, 17, 20, 21). As a result, the consistency between studies indicates the adverse association between maternal ferritin concentrations and birthweight effects persisting in Chinese and other ethnic populations. Of note, the positive association of ferritin and LBW and SGA was observed in the 2nd and/or 3rd trimesters in the stratified analysis (Supplementary Table S1), and this phenomenon is consistent with previous research (8).

In the present study, we observed an increased risk of LBW and SGA as the maternal ferritin concentration increased in a linear dose-response manner. However, there was a hypothesis that iron exhibits a U-shaped risk of adverse health effect curves similar to other internal nutrients, which was not consistent with the results in our study. This discrepancy is probably have multiple explanations because of the double character of maternal ferritin both as an iron storage marker and acute stage reactant (7, 22), such as oxidative stress (7, 23), inflammation and infection (22, 24), hemoconcentration (7, 25). A higher ferritin concentration in pregnant women was also found to be associated with a higher risk of preterm delivery and gestational diabetes in previous studies, it may add risk of health risk as a whole (26).

The present study suggests that Fe supplementation use is beneficial to birthweight-related outcomes, however, for pregnant women without iron deficiency may be not helpful for reducing the risk of LBW. In fact, the evidence supporting the guidance for universal supplementation of iron among gestational women has been controversial (8). In the context of a high global anemia rate in pregnant women, iron deficiency accounts for 20–50% of anemia occurrences (27, 28). Comparative evidence suggests that iron supplementation improves hematologic biomarkers such as hemoglobin and ferritin (7, 29). However, there are also studies reported that routine iron supplementation in non-anemic gestational woman has no benefit on pregnancy outcomes, and caution is advised against Fe supplementation already (8). The discrepancy was possibly due to different body iron stores in the studied populations. Thus, iron supplementation among women with high maternal ferritin was not associated with significantly decreased risk of LBW.

There are notable strengths of the present study. For the first time, our study revealed whether maternal serum ferritin was associated with an increased risk of birthweight related outcomes in a retrospective cohort study based on a large sample size among Chinese population. We disclosed that as maternal ferritin concentrations rise, it would reversely associate with fetal weight growth that add risks of LBW and SGA, the second and third trimesters should be highly focused on. Thus, an assessment of iron status during pregnancy is needed to make appropriate individualized iron supplementation recommendations to prevent negative outcomes because of maternal iron deficiency and iron overload.

Nevertheless, this study also has potential limitations. First, we only used maternal ferritin as a marker of maternal iron status among the studied pregnant women. Among markers of iron status, serum ferritin has been the most used markers in epidemiologic studies (8); however, including other markers (transferrin et al.) would be more comprehensive for interpreting the results. Second, information on the intake dose of iron supplements and diet was absent. Third, we did not have a biological sample of the studied population, which could be further tested for oxidative stress and inflammation status.

In conclusion, maternal ferritin levels during pregnancy may provide an additional predictor for distinguishing fetuses with potential poor birthweight related outcomes. Moreover, high ferritin values should also be monitored by prenatal care due to adverse perinatal outcome. Further exploration should be conducted to ensure maternal ferritin thresholds and iron supplement doses.

Data availability statement

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

Author contributions

YZZ and JHM initiated the project. YT conducted the research and analyzed the data and wrote the initial draft of the paper. YS extract and review the data. JWK, JL, JD, FW, DX, XLQ, JJG, YJL, and CW contributed to revisions. All authors approved the final manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1002702/full#supplementary-material

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Association between modes of delivery and postpartum dietary patterns: A cross-sectional study in Northwest China

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Objective: Puerperae' dietary patterns (DPs) during the puerperium may be influenced by the mode of delivery, but population studies on this topic are scarce. This study aims to explore the relationship between DPs and different modes of delivery among puerperae.

Methods: A cross-sectional study was conducted on 3,345 parturients in Lanzhou, China. The postpartum food intake was measured by a food frequency questionnaire (FFQ). Factor analysis was used to determine the DPs. Multiple linear regression was employed to examine the association between the mode of delivery and DP.

Results: In this study, two DPs, i.e., traditional and modern DPs, were identified. Traditional DP was characterized by high energy-adjusted intake of tubers, coarse cereals, rice, whole grains, fishery products, and eggs. Modern DP included a high intake of coffee, non-sugary drinks, wine, tea, and fishery products. Compared with participants with vaginal delivery (reference category), cesarean section had an inverse association with modern DP (β: −0.11, 95% CI: −0.36, −0.09). A significant interaction was found between education level, monthly household income, alcohol drinking, and modes of delivery. The inverse association between cesarean section and modern DP or the intake of coffee was significant among puerperae with higher or lower monthly household income. However, the inverse association between cesarean section and traditional DP was only found among puerperae with higher monthly household income. Moreover, among the participants with high education, cesarean section was positively associated with intake of vegetables.

Conclusion: Cesarean puerperae with higher levels of education and those with lower and higher monthly household income had less unhealthy foods intake than those who had vaginal delivery. They need to be accounted for in educational programs and interventions focused on healthy diet recommendations in puerperium.

KEYWORDS

parturient, dietary pattern, cesarean delivery, dietary behavior, postpartum period

Introduction

Diet during the peripartum period is important to the health of mother and child (1) and provides an opportunity to change their old unhealthy eating habits (2). Dietary patterns (DPs), rather than individual food groups, foods, or nutrients, provide a more comprehensive approach to assess both health and environmental outcomes related to the diet (3). A high-quality diet, such as the healthy eating pattern of the Mediterranean diet, is internationally recommended for pregnant and breastfeeding women (4). Nevertheless, several studies on a national or international scale showed that pregnant women do not generally follow the recommended healthy diet (5–11), which can contribute to the suboptimal intake of key nutrients essential to the health of mother and child (1).

Evidence suggested that food intake patterns may be influenced by the physiological and behavioral demands of pregnancy and postpartum (2, 12–15). The mode of delivery is an important factor that can influence a woman's postnatal behavior and quality of life owing to different painful conditions. Compared with women who have vaginal delivery, the risk of reduction in health and wellbeing during postpartum period is higher among women who had a cesarean section (16). Moreover, Chinese cesarean delivery rate in China is highest in the world (17, 18). Therefore, many studies focus on the postnatal nutritional care of cesarean puerperae (19). Some studies found that women who had a cesarean section are offered oral fluids and food. Moreover, some studies determined that coffee can be given to patients to enhance the recovery of their gastrointestinal function after elective cesarean section (20, 21). However, studies that investigated the association between vaginal delivery and postpartum diet are still scarce.

A limited number of studies have focused on the postnatal dietary patterns (DPs) (21, 22) in parturients with different delivery modes. It is unknown to what degree delivery modes affect postnatal DPs in China. Therefore, this study aims to examine the relationship between DPs and mode of delivery of puerperae to provide a scientific basis for health promotion and interventions focused on healthy diet recommendations in puerperium (22, 23).

Materials and methods

Study design and sample collection

This study is a cross-sectional survey conducted at the maternity outpatient clinic of Lanzhou Maternity and Child Health Hospital in Gansu Province from October 2019 to April 2021. A convenience sampling method was used in this study. A questionnaire survey was conducted by the hospital's obstetrician and gynecologist on women who underwent puerperal examinations at the hospital. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Chongqing Medical University (record number 2018-131). All participants provided their written informed consent.

Literature demonstrated that the cesarean section rate in China is approximately 36.7% (24). According to the formula of sample size calculation,

$$N = \left(Z_{\alpha}^{2} \times p \times q\right) / d^{2}$$

p is 0.367. $q = 1 - p = 0.633$. The margin of error (d) = 0.10 × p = 0.0367, and α is 95%. The calculated sample size was 2,703, considering the possibility of 15% non-response rate. The minimum sample size needed for this study was calculated to be 3,180.

Puerperae who (1) consented to participate in the survey and (2) gave birth 42 days previously were included in this study. Exclusion criteria were as follows: puerperae (1) who experienced serious complications, (2) with cognitive disorders and (3) who refused to participate in the investigation. A total of 3,345 responses were included in the analysis after the subjects with less than one pregnancy (n = 143), who were younger than 20 years (n = 14), who had a questionnaire with incomplete answers (n = 583) and who chose to give birth other than vaginally or by cesarean section (n = 83) were excluded (**Figure 1**). Ultimately, 3,345 participants were enrolled.

Dietary assessment and food grouping

A qualitative food frequency questionnaire (FFQ) was used to assess the dietary intake of puerperae participating in this

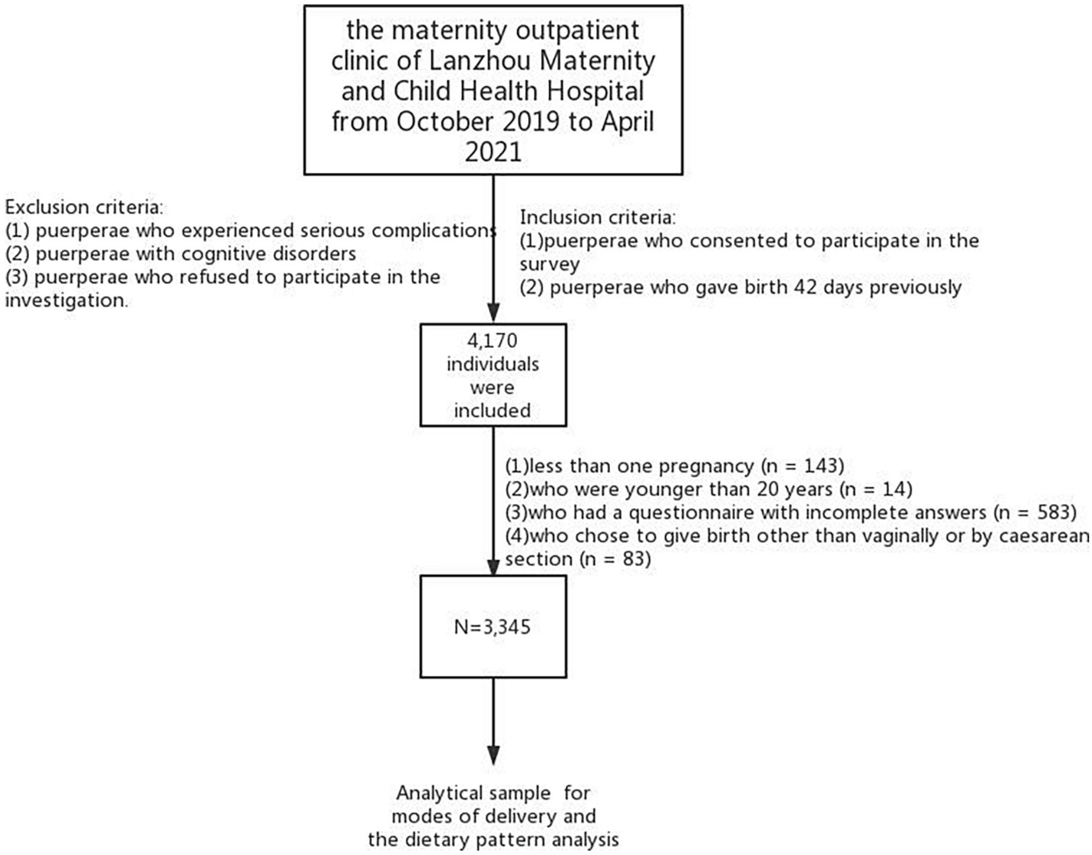

FIGURE 1
Participant flow chart.

study on their 42nd day after delivery. Of all the dietary assessment methods: 24-h recall, food record, food history, and FFQ, the last is a reliable and inexpensive data collection method, which has been widely allows the identification and evaluation of food patterns in epidemiological studies and can assess diet quality (25). All the foods included in the current analysis were selected according to the Dietary Guidelines for Chinese lactating women and common postpartum practices reported by previous studies (26). The final version was modified by epidemiologists, statisticians, multidisciplinary experts in nutrition, and a health management professor to ensure the content of the questionnaire was valid and had used in previous studies (26–28). A total of 78 foods items were included in the FFQ. In the analysis the food items were categorized into 21 food groups based on the similarity of nutrition profiles and cooking method. The 21 food groups were vegetables, fruits, freshwater fish, seafood, red meat, poultry, processed meat, milk, dairy desserts, eggs, sugary drinks, non-sugary drinks, tea, coffee, wine, rice, wheat, coarse cereals, potatoes, whole grains and cakes and confectionery. We did not collect data on the amount consumed in the FFQ, thus we calculated only the daily consumption frequency for each food group. Although the FFQ has not been validated, the food items included in the FFQ were similar to other validated FFQ in China (29). All participants were asked to record their habitual intake frequency for each food group within the last year according to the following categories:

1– Less than once a month
2– Once a month
3– Two to three times a month
4– Once a week
5– Two to three times a week
6– Four to six times a week
7– Once a day
8– Twice a day
9– Three to four times a day
10– More than five times a day

For the presented analyses, the information on food consumption frequency was transformed into the number of times each food was consumed over a week. These food groups are listed in **Supplementary Table 7**.

Mode of delivery

The questionnaire categorized the mode of delivery into five types (cesarean delivery, normal delivery, delivery by forceps, breech delivery, and vacuum extraction). Given that the number of cesarean and normal deliveries accounted for 97.36% of the total number of deliveries, those who chose other delivery methods were excluded. Finally, 2,187 cesarean and 1,158 vaginal puerperae were included in the analysis.

Covariates

The sociodemographic characteristics and health-related lifestyles were also obtained through the questionnaire. The sociodemographic variables were as follows: age (20–34 years/35 years or above), ethnicity (Han/minority) and residence (urban/rural). Marital status was recorded as primary marriage or other (remarried, divorced, or other). Educational level was recorded as two categories: secondary education or below (senior high school or below) and tertiary education (university or above). The average monthly household income was categorized as <¥4,500, ¥4,500–¥9,000 or >¥9,000 (30). Dietary caregivers were divided into three categories, including self/husband, in-laws/parents and maternity matron/nanny. The prepregnancy body mass index (BMI) was calculated on the basis of the self-reported preconception weight. BMI was rated as follows: <18.5 kg/m^2, thin; 18.5–24.9 kg/m^2, normal; 25.0–29.9 kg/m^2, overweight; and 30.0–40.0 kg/m^2, obese (31). Suffering from a postpartum disease and alcohol drinking were classified into two categories, i.e., yes or no. Singleton or twin pregnancies was classified into two categories, i.e., singleton pregnancies or twin pregnancies. Smoking status was divided into three categories, including current smoker, ex-smoker, and non-smoker.

Statistical analysis

All statistical analyses were performed using STATA (version 17, StataCorp, College Station, TX, USA) and the software GraphPad Prism 8. Demographic characteristics were described using frequencies and percentiles, which were all categorical variables. Chi-square test was used to compare the distributions of the delivery modes in lower versus higher DPs categories (split at the median of DP scores). DPs' Chi-square and multiple linear regression were utilized for categorical variables and continuous variables, respectively. Differences between the mode of delivery and demographic characteristic variables were analyzed using chi-square tests. The intake of the 21 food groups was included in the factor analysis (32). A factor analysis (principal component extraction with varimax rotation) of specific items revealed four factors (with eigenvalue >1), explaining 64.0% of the total variance. Finally, two DPs were determined in accordance with factor interpretability, which explained 52.6% of the total variance. Food groups with component loading ≥| 0.30| are shown in **Table 1**. The factors were rotated with varimax to improve the interpretability and minimize the correlation between the factors. Participants were assigned a pattern-specific factor score, which was calculated as the sum of the product of the factor loading coefficients and standardized daily intake of each food associated with the pattern. Factor loadings were included in the calculation of pattern scores.

Multiple linear regression was conducted to verify the association between the variables describing the mode of delivery (independent variables) and dietary intake pattern (dependent variables). A set of multiple linear regression models was built: Model 1 – adjusting the age groups; Model 2 – further adjusting the residence, education, income, and dietary caregivers and Model 3 – further adjusting the prepregnancy BMI and suffering from a postpartum disease based on Model 2.

The multiplicative interaction between dietary intake and demographic characteristics (i.e., marital status, parity, and education level) was tested by adding the product of the variables to the multivariable model.

TABLE 1 Component loadings for dietary patterns.

	Component 1[a]	Component 2[b]
Vegetables	0.553	
Fruits	0.586	
Poultry	0.554	0.342
Fishery products	0.512	0.43
Processed meat products	0.511	0.467
Fish	0.501	0.426
Red meat	0.441	0.394
Dairy desserts	0.593	0.339
Milk	0.563	0.322
Tubers	0.691	
Coarse cereals	0.677	
Rice	0.668	
Whole grains	0.645	0.356
Eggs	0.625	
Wheat	0.616	
Cakes	0.57	0.465
Coffee		0.933
Non-sugary drinks		0.888
Wine		0.871
Sugary drinks		0.865
Tea		0.844

Component loadings for dietary patterns derived from qualitative food frequency questionnaire data completed by women who underwent postnatal check-ups.
[a]Component 1, called traditional dietary pattern, is characterized by high energy-adjusted intake of staple food (tubers, coarse cereals, rice, and whole grains), eggs, meat, fish and fishery products, fruits, and vegetables.
[b]Component 2, called modern dietary pattern, is characterized by high energy-adjusted intake of coffee, tea, drinks, and wine and low intake of meat and whole grains.

TABLE 2 Basic demographic characteristics.

Factor	Total $N = 3,345$	Delivery mode		P-value
		Vaginal delivery $N = 1,158$	Cesarean section $N = 2,187$	
Parity				0.002*
First birth	2,327 (69.6%)	766 (66.1%)	1,561 (71.4%)	
Second birth	1,018 (30.4%)	392 (33.9%)	626 (28.6%)	
Ethnicity				0.075
Han	3,006 (92.7%)	1,025 (91.6%)	1,981 (93.3%)	
Minority	236 (7.3%)	94 (8.4%)	142 (6.7%)	
Marital status				<0.001*
Primary marriage	3,213 (96.7%)	1,088 (94.9%)	2,125 (97.6%)	
Other marital status	110 (3.3%)	58 (5.1%)	52 (2.4%)	
Educational level				<0.001*
Secondary education and below	573 (17.2%)	254 (22.0%)	319 (14.6%)	
Tertiary education	2,765 (82.8%)	902 (78.0%)	1,863 (85.4%)	
Residence				<0.001*
Urban	3,008 (90.9%)	993 (87.3%)	2,015 (92.9%)	
Rural	300 (9.1%)	145 (12.7%)	155 (7.1%)	
Age				<0.001*
20–34	2,749 (82.2%)	876 (75.6%)	1,873 (85.6%)	
≥35	596 (17.8%)	282 (24.4%)	314 (14.4%)	
Dietary caregivers				0.032*
Themselves/husband	472 (15.2%)	187 (17.4%)	285 (14.0%)	
Parents/parents-in-law	1,944 (62.5%)	663 (61.7%)	1,281 (63.0%)	
Nanny/maternity matron	693 (22.3%)	225 (20.9%)	468 (23.0%)	
Monthly household income				0.076
≤¥4,500	853 (25.5%)	313 (27.0%)	540 (24.7%)	
¥4,501–9,000	1,181 (35.3%)	380 (32.8%)	801 (36.6%)	
>¥9,000	1,311 (39.2%)	465 (40.2%)	846 (38.7%)	
Pre-pregnancy BMI				<0.001*
Thin	503 (15.0%)	131 (11.3%)	372 (17.0%)	
Normal	1,993 (59.6%)	671 (57.9%)	1,322 (60.4%)	
Overweight	393 (11.7%)	179 (15.5%)	214 (9.8%)	
Obesity	456 (13.6%)	177 (15.3%)	279 (12.8%)	
Suffering from postpartum disease				0.035*
No	1,184 (73.5%)	436 (76.6%)	748 (71.8%)	
Yes	427 (26.5%)	133 (23.4%)	294 (28.2%)	
Singleton or twin pregnancies				<0.001
Singleton pregnancies	3,243 (97.3%)	1,068 (92.7%)	2,175 (99.7%)	
Twin pregnancies	90 (2.7%)	84 (7.3%)	6 (0.3%)	
Smoking				0.57
Current smoker	38 (1.1%)	16 (1.4%)	22 (1.0%)	
Ex-smoker	47 (1.4%)	15 (1.3%)	32 (1.5%)	
Non-smoker	3,237 (97.4%)	1,116 (97.3%)	2,121 (97.5%)	
Alcohol drinking				0.71
No	2,450 (78.2%)	847 (78.6%)	1,603 (78.0%)	
Yes	682 (21.8%)	231 (21.4%)	451 (22.0%)	

*$P < 0.05$.

Results

Characteristics of study participants

A total of 3,345 puerperal women were included in this survey. About 82.2% of puerperae were aged 20–34 years. In the sample, 69.6% of the participants were first birth, 82.8% obtained tertiary education, 62.5% had been taken into care by parents or parents-in-law, and 25.2% had a monthly household income of ≤¥4,500. Statistically significant modes of delivery differences in demographic characteristics were found in parity, marital status, education level, residence, and age. Per IOTF (international obesity task force) standards, prepregnancy BMI categories significantly differed ($p < 0.001$). Modes of delivery differences were also found in dietary caregivers, singleton or twin pregnancies and suffering from a postpartum disease ($p < 0.001$, Table 2).

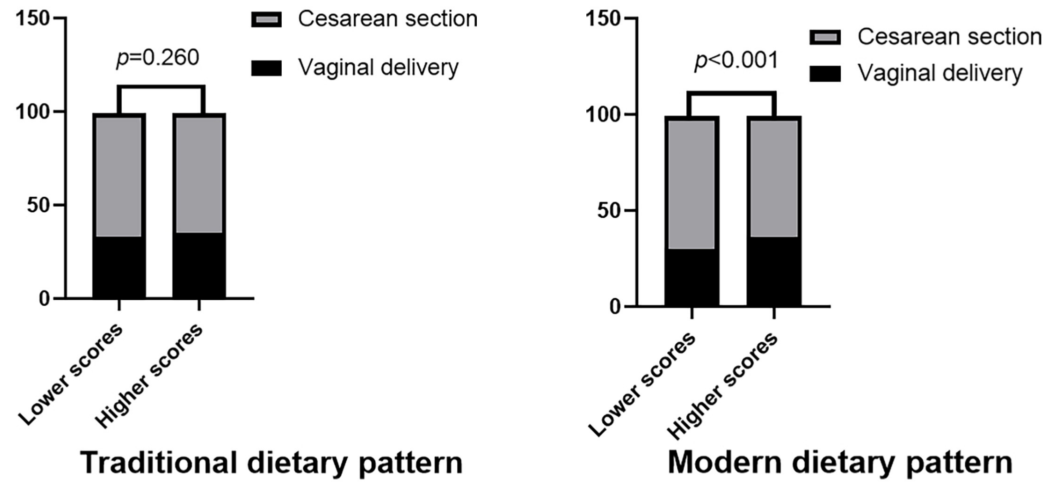

FIGURE 2
Associations between modes of delivery and postpartum dietary intake.

Dietary patterns

Two DPs, namely, traditional and modern DPs, were identified. Food with loading ≥ 0.3 on traditional DP included a high energy-adjusted intake of tubers (loading = 0.691), coarse cereals (loading = 0.677), rice (loading = 0.668), whole grains (loading = 0.645), fishery products (loading = 0.512), and eggs (loading = 0.625). Foods loaded on modern DP included a low intake of processed meat products (loading = 0.467) and cakes (loading = 0.465) and a high intake of coffee (loading = 0.933), non-sugary drinks (loading = 0.888), wine (loading = 0.871), tea (loading = 0.844), and fishery products (loading = 0.43). The food groups with a component loading ≥| 0.30| are shown in Table 1.

Association between mode of delivery and postpartum dietary intake

The delivery mode was associated with the modern DPs, such that vaginal puerperae were more likely to be in the upper half of the modern DPs compared to cesarean puerperae (Figure 2). The multiple linear regression results, including the β-coefficients (95% CI) between the delivery modes and dietary intake scores, are presented in Table 3. After the adjustment of the sociodemographic variables and health-related behaviors, compared with vaginal delivery (reference category), cesarean puerperae had an inverse association with modern DP (β:−0.11, 95% CI: −0.36, −0.09), indicating that the woman who delivered by cesarean section had low adherence to modern DP. However, no difference was observed in the dietary scores between the different delivery modes and traditional DP.

Subgroup analyses of the association between mode of delivery and postpartum dietary intake

The mode of delivery had no interaction with marital status, age, singleton, or twin pregnancies and smoking in relation to association with traditional DP, modern DP and the intake of vegetable, fruit, and coffee. However, we observed significantly inverse effects of monthly household income on the association between the cesarean section and traditional DP ($p = 0.025$) as well as modern DP ($p = 0.036$).

An inverse association between modes of delivery and the traditional DP was only found among puerperae with monthly household income >¥9,000. However, the inverse association between modes of delivery and the modern DP was observed among puerperae with monthly household income ≤¥4,500 or > ¥9,000 and non-drinking. Furthermore, a positively association between cesarean section and the intake of vegetable was found among tertiary education level. And, the observed inverse association between modes of delivery and the intake of coffee remained statistically significant among participants with monthly household income ≤¥4,500 or >¥9,000 (Tables 4, 5 and Supplementary Table 1).

Discussion

This study analyzed DPs in a sample of parturients in Lanzhou Maternal and Child Health Hospital on their 42nd day after childbirth and the association among mode of delivery, DP and food intake. In this study, two DPs (e.g., traditional and modern DPs) were identified. This study also found that modes of delivery had an inverse association with modern DP.

TABLE 3 Associations between modes of delivery and postpartum dietary intake.

	Model 1[a]		Model 2[b]		Model 3[c]	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Traditional dietary pattern						
Vaginal delivery (Ref)						
Cesarean section	−0.02 (−0.13, 0.06)	0.629	0.01 (−0.11, 0.07)	0.762	−0.02 (−0.05, 0.07)	0.477
Modern dietary pattern						
Vaginal delivery (Ref)						
Cesarean section	−0.07 (−0.24, −0.07)	<0.001*	−0.06 (−0.16, −0.08)	0.006*	−0.11 (−0.36, −0.09)	0.001*

[a]Model 1 adjusted for age.
[b]Model 2 further adjusted for residence, education, income and dietary caregivers.
[c]Model 3 further adjusted for pre-pregnancy BMI, suffering from postpartum diseases, singleton or twin pregnancies, monthly household income, smoking, and alcohol drinking.
*$P < 0.05$.

TABLE 4 Subgroup analyses of associations between modes of delivery and postpartum dietary intake[#].

Factor	Traditional dietary pattern	P^1	Modern dietary pattern	P^1	Vegetable	P^1
Marital status						
Primary marriage	−0.05 (−0.14, 0.05)	0.574	−0.16 (−0.27, −0.06)*	0.327	0.54 (−0.13, 1.22)	0.377
Other marital status	0.18 (−0.35, 0.72)		−0.13 (−0.35, 0.08)		2.47 (−1.70, 6.64)	
Age						
20–34	−0.04 (−0.14, 0.07)	0.713	−0.15 (−0.25, −0.06)*	0.716	0.52 (−0.22, 1.25)	0.559
≥35	−0.05 (−0.26, 0.17)		−0.50 (−1.11, 0.11)		0.99 (−0.56, 2.54)	
Education level						
Secondary education and below	−0.03 (−0.23, 0.17)	0.875	−0.14 (−0.41, 0.13)	0.790	−1.00 (−2.60, 0.60)	0.049
Tertiary education	−0.02 (−0.13, 0.08)		−0.14 (−0.24, −0.05)*		0.73 (0.00, 1.46)*	
Singleton or twin pregnancies						
Singleton pregnancies	−0.04 (−0.13, 0.06)	0.961	−0.15 (−0.25, −0.06)*	0.198	0.62 (−0.04, 1.29)	0.778
Twin pregnancies	−0.14 (−1.45, 1.17)		−0.96 (−2.36, 0.43)		0.97 (−8.85,10.80)	
Monthly household income						
≤4,500	−0.06 (−0.25, 0.12)	0.025	−0.29 (−0.51, −0.07)*	0.036	0.72 (−0.64, 2.08)	0.983
4,501–9,000	0.13 (−0.03, 0.29)		0.01 (−0.14, 0.15)		0.23 (−0.88, 1.35)	
>9,000	−0.18 (−0.33, −0.03)*		−0.22 (−0.36, −0.09)*		0.67 (−0.38, 1.72)	
Smoking						
Current smoker	−0.40 (−1.80, 1.00)	0.827	0.49 (−0.39, 1.36)	0.099	−3.33 (−12.66, 6.00)	0.555
Ex-smoker	0.07 (−2.41, 2.54)		−0.24 (−2.87, 2.40)		−1.32 (−10.58, 7.94)	
Non-smoker	−0.04 (−0.14, 0.05)		−0.16 (−0.25, −0.07)*		0.65 (−0.02, 1.32)	
Alcohol drinking						
No	−0.08 (−0.19, 0.03)	0.130	−0.24 (−0.34, −0.13)*	0.005	0.42 (−0.33, 1.18)	0.221
Yes	0.09 (−0.11, 0.29)		0.04 (−0.14, 0.22)		1.13 (−0.28, 2.54)	

[1]*P* for interaction.
*$P < 0.05$.
[#]Vaginal delivery as the reference group.

Furthermore, the modern DP score and the intake of coffee were inversely associated with modes of delivery among puerperae under 35 years of age. Among the participants with secondary education or lower, modes of delivery had an inverse association with intake of vegetables.

Our results were in accordance with the literature. Although some investigators advocated the adoption of a high-quality DP during the postnatal period, such as the Mediterranean diet model or healthy food pyramid (33), many maternal diets are unreasonable (1, 34–39). Two DPs were identified in this study. Specifically, the traditional DP, which was a high-quality DP, was characterized primarily by high consumption of rice, vegetables, fishery products, whole grains, dairy desserts, poultry, and fish. However, the modern DP was a low-quality DP

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TABLE 5 Subgroup analyses of associations between modes of delivery and postpartum dietary intake in the total sample#.

Factor	Fruits	P1	Coffee	P1
Marital status				
Primary marriage	−0.06 (−0.77 to 0.65)	0.139	−1.63 (−3.04 to −0.22)*	0.233
Other marital status	2.87 (−2.00 to 7.73)		3.93 (−3.33 to 11.19)	
Age				
20–34	−0.11 (−0.88 to 0.67)	0.145	−1.69 (−3.25 to −0.14)*	0.483
≥35	1.11 (−0.58 to 2.80)		−0.34 (−3.42 to 2.74)	
Education level				
Secondary education and below	−1.51 (−3.67 to 0.65)	0.005	−2.05 (−5.03 to 0.93)	0.372
Tertiary education	0.50 (−0.23 to 1.23)		−0.89 (−2.43 to 0.65)	
Singleton or twin pregnancies				
Singleton pregnancies	0.14 (−0.57 to 0.84)	0.507	−1.31 (−2.70 to 0.08)	0.209
Twin pregnancies	−2.22 (−12.27 to 7.83)		−13.18 (−29.81 to 3.45)	
Monthly household income				
≤4,500	−0.54 (−2.13 to 1.05)	0.208	−2.74 (−5.44 to −0.03)*	0.020
4,501–9,000	0.72 (−0.42 to 1.85)		1.44 (−0.95 to 3.83)	
>9,000	−0.12 (−1.19 to 0.95)		−3.12 (−5.31 to −0.93)*	
Smoking				
Current smoker	−4.05 (−14.22 to 6.13)	0.906	−7.64 (−23.19 to 7.92)	0.907
Ex-smoker	2.02 (−7.97 to 12.00)		−2.47 (−27.16 to 22.22)	
Non-smoker	0.11 (−0.60 to 0.82)		−1.42 (−2.82 to −0.02)*	
Alcohol drinking				
No	−0.10 (−0.90 to 0.71)	0.139	−1.70 (−3.25 to −0.14)*	0.548
Yes	0.53 (−0.91 to 1.96)		−0.60 (−3.64 to 2.44)	

1 *P* for interaction.
**P* < 0.05.
#Vaginal delivery as the reference group.

involving the consumption of a combination of wheat, coffee, sugary drinks, wine, cakes, and processed meat products. Thus, there is a gap between this DP and the diet recommended by Dietary Guidelines for Chinese lactating women (40). The nutritional status of a woman during lactation is not only critical for her health, but for future generations (41). Furthermore, the puerperium diet of Chinese women is determined by the culture of "zuo yuezi," some traditional eating behaviors the one month postpartum. During this period, their behavior in relation to diet, activity and hygiene is determined by the theory of traditional Chinese medicine (TCM). Several "zuo yuezi" practices are beneficial, including eating more, eating protein rich food. However, its recommendation to avoid cold foods (e.g., vegetables and fruits) is not consistent with the Dietary Guidelines for Chinese lactating women (42). In brief, the attention and interventions of the health team should continue into postpartum so that the adoption of healthy eating habits is guaranteed (43).

Various factors may affect the choice of postpartum DP (e.g., age, gender, and economic level) (30, 33), but the effect of mode of delivery on postnatal DP has attracted limited attention. This study found no association between traditional DP and delivery mode. However, compared with vaginal delivery, cesarean puerperae had an inverse association with modern DP. Compared with normal vaginal delivery, cesarean section was inversely associated with postpartum diseases, causing healthcare to pay attention to postoperative care in cesarean delivery (44). The postnatal health and wellbeing of woman who delivered by vaginal section is higher than those of woman who delivered by cesarean section (45). During the postpartum period, women who delivered by vaginal section spend more time on childcare, preparing foods for family and cannot take too much time on maintaining healthy diet (2, 46, 47).

This study determined that the intake of vegetables, fruits and coffee was correlated with cesarean section only when adjusting for age. Different from complications after vaginal delivery, postoperative ileus (POI) is a frequent occurrence after a cesarean section. Increased attention should be paid to the postpartum diet of cesarean puerperae to promote the return of the gastrointestinal function (48). The guidelines for postoperative cesarean section recommend a high intake of fruits and vegetables to prevent constipation (44). Moreover, a review published in 2021 showed that postoperative coffee consumption can likely reduce POI incidence after a cesarean section (20). Nevertheless, no correlation was observed in this study between the consumption of fruits, vegetables or coffee and delivery mode after the other confounding factors, including residence, education, income, and dietary caregivers, were controlled. This relationship was not from a causal effect and might be attributed to confounding factors.

In the subgroup analyses, the interaction between monthly household income and modes of delivery to traditional/modern DPs is interesting. The significantly inverse interaction was found between monthly household income and modern DPs among puerperae with higher or lower monthly household income. This finding was consistent with a qualitative research which thought that the diet of Chinese puerperae is susceptible to traditional beliefs regardless of income (42). In addition, this interaction also found among non-drinking cesarean puerperae. This suggests that daily drinking habits can influence the choices of modern DPs for cesarean puerperae. However, the inverse association between cesarean section and traditional DP was only found among puerperae with higher monthly household income. The possible cause is that Chinese traditional beliefs and practices believe that puerperae should eat more, eat protein rich food and avoid "cold" food (e.g., fruits and vegetables) (42). In this study, the cesarean puerperae with a high level of education were likely to increase the intake of vegetables, and this finding was consistent with the findings of a Spanish cross-sectional study (33, 49). Therefore, education on postpartum diet health knowledge for parturients with different levels of education and household income and their dietary caregivers should be strengthened.

Some limitations of this study should be addressed. Firstly, due to the cross-sectional study design it was not possible to claim the causal relationship between modes of delivery and DPs; therefore, prospective studies are needed to confirm the findings of this study. Secondly, food consumption data are from a qualitative FFQ, and two individuals with an identical consumption frequency may have different true consumptions of a particular food owing to differences in the consumed portion sizes (50, 51), this may have reduced the ability to assess the diet quality by FFQs. This loss of detail is inherent in qualitative FFQs. Thirdly, questionnaires had been completed by the medical staff may led to interviewer bias. Fourthly, the data of elective and emergency cesarean sections and pregnancy diet should be considered. Fifthly, it was difficult for us to conduct a follow-up study because of the COVID-19 pandemic and the fact that the investigators were the hospital's obstetrician and gynecologist, so the reliability of FFQ test was only conducted among a small number of participants. However, Qin et al. (52) demonstrated that portion size adds only limited information to the variance in food intake, suggesting that standard portion size specifications may not introduce a large error in the estimation of food intake. Secondly, the use of a questionnaire is limited owing to the misestimation in the consumption frequency for certain foods when FFQ is used. Thirdly, this study investigated only parturients in the northwest, lacking samples from multicenter surveys. However, obtaining such samples is not logistically and economically possible in this study, considering the number of respondents. Despite research limitations, they do not affect the importance of this study.

Conclusion

In conclusion, puerperium is a critical period for postpartum recovery. However, modern DP is a low-quality DP. Moreover, this study found that the choice of modern DP during this period is related to the mode of delivery. Furthermore, significant interaction exists among monthly household income, education level, and modes of delivery. Thus, based on our findings health professionals should pay attention to the dietary intake of those with a low literacy and those had normal vaginal delivery with lower and higher monthly household income.

Data availability statement

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

Ethics statement

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

Author contributions

LiZ and LW performed the statistical analysis, wrote the manuscript, and was primarily responsible for the final content. ZS, WW, and LaZ were involved in the data extraction and verification. YuZ, YS, SL, TW, and MS provided guidance and suggested revisions. YoZ provided critical updates to the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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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.2022.985941/full#supplementary-material

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Maternal gestational diabetes in singleton pregnancies conceived by ART may be modified by periconceptional B vitamins

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Background: The risk of maternal gestational diabetes mellitus (GDM) may be influenced by pregnancies conceived through assisted reproductive technology (ART). However, the influence of the dosage of B vitamins (folate, vitamin B6 and vitamin B12) on GDM weren't considered. Thus, we hypothesized that periconceptional B vitamins could modify maternal GDM in singleton pregnancies conceived by ART.

Methods: This study is a prospective cohort study using data from 3,252 women with singleton pregnancies and received a 75 g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. We included an interaction term in the multivariable logistic and linear regression models, respectively, to test our hypothesis.

Results: Women who underwent ART were significantly associated with the incidence of GDM compared with spontaneous pregnancy women. The adjusted odds ratio (aOR) was 1.59, and the 95% confidence interval (CI) was 1.08–2.34. ART pregnancies also elevated OGTT (oral glucose tolerance test) 1-h blood glucose levels and OGTT 2-h blood glucose levels ($P < 0.05$). A positive association between dietary vitamin B6 (aOR = 1.60, 95% CI: 1.13–2.27), dietary vitamin B12 (aOR = 1.88, 95% CI: 1.34–2.64) and dietary folate (aOR = 1.66, 95% CI: 1.19–2.32) with GDM risk comparing the highest to the lowest quartile (all $P_{trend} < 0.001$). The aORs of GDM for inadequate (< 400 μg/day), adequate (400–800 μg/day), and excessive (> 800 μg/day) supplemental folate intake were 1.00, 0.93, and 1.30, respectively ($P_{trend} = 0.033$). Since only the supplemental folate illustrates a statistically significant interaction with ART (P for interaction < 0.05), the association between ART and GDM and OGTT blood glucose levels stratifying by supplemental folate were further evaluated. These increased risks of GDM (aOR = 1.62, 95% CI: 1.39–3.39) and the regression coefficients (β) of 1-h blood glucose (β = 0.76, 95% CI: 0.39–1.13) and 2-h blood glucose (β = 0.60, 95% CI: 0.29–0.92) in the multiple linear regression model were significant only in the ART group with excessive supplemental folate (> 800 μg/day).

Conclusion: The risk of GDM is significantly elevated, particularly among those women who conceived ART with the intake of excessive supplemental folate (> 800 μg/day).

KEYWORDS

ART, gestational diabetes, B vitamins, blood glucose, interaction

Introduction

The number of pregnancies through assisted reproductive technology (ART) has been on the rise significantly since the mid-1980s when *in vitro* fertilization (IVF) became available in China (1). Following this, it is important to check the possible dangers to mothers and their offspring. Numerous studies have found that compared to women who conceive spontaneously, women who conceive though IVF appear at a higher risk of obstetric and perinatal complications (2–5). One of the most common and important pregnancy complications is gestational diabetes mellitus (GDM). The latest systematic review and meta-analysis showed a higher risk of GDM in women whose pregnancy is through ART than spontaneous (6). However, the study on the relationship between ART and OGTT blood glucose levels remains to be examined.

Maternal advanced age, obesity, multiple pregnancies, and polycystic ovary syndrome (PCOS) are the major risk factors for GDM. They are also frequently present in women who received ART, suggesting a potential association between GDM and ART (7–10). Some modifiable risk factors during pregnancy, in addition to BMI, include vitamin supplements. B vitamins are necessary for the One Carbon Cycle (C1) and are crucial for numerous metabolic pathways and methylation processes. Folate interacts closely with vitamin B6 and B12 for functional effects on the C1 network (11). Meanwhile, folate and vitamin B6 and B12 are crucial enzymatic cofactors in the synthesis of methionine from homocysteine (12, 13), and their lacking increases homocysteine concentrations in the blood (14, 15). Since elevated homocysteine is associated with insulin resistance, it leads to cause the risk of GDM (16, 17). Hence, our study investigated the effect for folate and vitamin B6 and B12 on GDM.

Although the previous study showed that folate supplementation and vitamin B12 were related to a higher probability of live birth among women who underwent ART (18, 19), the combined effect of B vitamins (folate, vitamin B6, and vitamin B12) and women who received ART on GDM has not been investigated till now. To address this gap, this study aimed to determine whether women who underwent ART are an independent risk factor for the development of GDM from a prospective cohort study. Moreover, it is further hypothesized that maternal B vitamins (folate, vitamin B6, and vitamin B12) intake from pre-pregnancy to the first trimester would alter the relationship between ART and GDM and maternal blood glucose levels.

Materials and methods

Study population and data sources

On May 1, 2019, a progressive prospective cohort study of pregnant women between 4 to 14 weeks was initiated. The data reported in this paper are as of February 21, 2022. A total of 3,980 pregnant women were recruited, and the details of this study have been described previously (20). All of the pregnant women in this study were part of the Qingdao Women and Children Hospital Health Cohort, a prospective cohort aimed at determining the impact of maternal dietary, environmental, and lifestyle exposures on the health of pregnant women and their children. During registration, questionnaire-based interviews were used to collect information on dietary information, social demographic status, reproductive variables, disease family history, the use of supplements, lifestyle factors, and illnesses. Throughout the follow-up visits during mid-pregnancy and late pregnancy, they provided information on lifestyle, dietary intake, and supplements.

Pregnant women were included with detailed information on the doses and duration of B vitamins supplements, the way of conception, and height and weight before to pregnancy. Following are the exclusion criteria: (1) Termination or abortion (n = 137); (2) missing the follow-up (n = 242) and loss the information of 75 g OGTT screening (n = 174); (3) history of diabetes (n = 14) or within 14 weeks of gestation diabetes (i.e., pregnant women whose fasting blood glucose value was higher than 5.1 mmol/L on the day of questionnaire collection) (n = 10); (4) height and weight of pregnant women before pregnancy is incomplete or missing (n = 16); (5) Dietary and supplemental information are incomplete, with unclear doses and duration (n = 135) (**Figure 1**). A total of 3,252 singleton births were considered for the final analysis. Among all the women in this study, 2,258 had complete three OGTT blood glucose levels, of which 2,031 were spontaneous conception and 227 received ART. Thus, 2,258 were included in the analysis of blood glucose levels (**Figure 2** and **Table 5**). Participation in the study was voluntary, and everyone was provided written informed consent.

Exposure and outcome measures

ART involves the *in vitro* handling of human oocytes and sperm, or embryos, intended to bring pregnancy (21). At enrollment, women responded to a semiquantitative food frequency questionnaire (FFQ) (22), reporting the frequency at which they consumed a specific portion of each of the 25 food or food group items during the past 6 months. They also reported their use of dietary supplements, including the brand, dose, and frequency. Intake of dietary folate, vitamin B6, and vitamin B12 from diet were calculated by multiplying the frequency of consumption by the nutrient content of a serving size determined from the food composition values available from the China Food Composition Tables (6th edition) (23). Total folate, vitamin B6 and B12, multivitamins and supplements and dietary sources were considered (24). FFQ was previously validated, which provides valid estimates of vitamins B6 and B12 intake with correlation coefficients between the FFQ and 1-week diet records of 0.58 for vitamin B6 (25), and 0.56 for vitamin B12 (26) intake. Furthermore, folate intake correlates well with prospectively collected diet records of 0.71 (27).

All participants were screened for GDM using a 75 g at 24–28 weeks gestation, according to the Ministry of Health (MOH) of China's Diagnostic Criteria for Gestational Diabetes Mellitus (WS311-2011) (28). MOH criterion cut-off values were consistent with the Consensus Panel recommendations of the International Association of Diabetes and Pregnancy Study Groups (29). In summary, GDM could be diagnosed if any of the following 75 g OGTT values were met or exceeded: fasting plasma glucose (FPG) $\geq$ 5.1 mmol/L, 1-h $\geq$ 10.0 mmol/L, or 2-h $\geq$ 8.5 mmol/L.

Covariates

We relied on self-reported data on maternal characteristics that could influence B vitamins intake and maternal risk of GDM. All multivariable models adjusted for maternal education (secondary school or less, high school, college/university, postgraduate and above), occupation (no, yes), women smoking and passive smoking during preconception to the first trimester (no, yes), age, pre-pregnancy BMI, and abortion history (no, yes), PCOS history (no, yes), GDM history (no, yes), and macrosomia (≥ 4 kg) (no, yes) are part of the personal medical history. Also, the family history of the disease includes diabetes and gestational diabetes (no, yes).

E-values were evaluated to estimate the association between ART and GDM risk so that the resistance of this study's results to unmeasured confounders could be assessed. The *E*-value is a sensitivity analysis representing the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome to explain a specific exposure-outcome association (30) fully.

Statistical analysis

Based on the way of fertilization, the study population was divided into two groups as indicated in **Figure 1**. As shown in **Table 1**, continuous and categorical maternal characteristics between spontaneous conception and ART women were compared. The Kolmogorov-Smirnov test and histograms were used to examine the distribution of continuous variables. Continuous variables having a normal distribution are displayed as means and standard deviations (mean ± SD). The median and interquartile range (IQR) are displayed for variables that significantly deviate from the normal distribution. Categorical variables are presented as frequencies with percentages. For regularly distributed continuous variables, differences were assessed using the Student's *t*-test. The Mann-Whitney *U*-test examined the differences between continuous variables with non-normal distribution. In order to assess the differences between categorical variables, the chi-square test was used.

Covariates in the multivariate models were selected based on a significant association at alpha < 0.05 level in bivariate models. The odds ratio (OR) and 95% confidence interval (CI) of GDM in ART vs. spontaneous conception were estimated using multivariable binomial logistic regression models. Multivariable linear regression models reporting regression coefficient (β) of fasting, 1-h OGTT glucose, and 2-h OGTT glucose levels between the two conception groups were used. All multivariable models were adjusted for maternal age, education, occupation, smoking, passive smoking, pre-pregnancy BMI, abortion history, PCOS, GDM history, macrosomia, family history of diabetes and family history of gestational diabetes.

Based on the distribution, the intake of folate, vitamin B6, and vitamin B12 were divided into quartiles. US Preventive Services Task Force (USPSTF) and WHO advise taking a daily folate supplement of 400–800 μg/day for all women who are consider becoming pregnant or are capable of becoming pregnant (31, 32). Furthermore, recent cohort studies in China indicated that taking folate supplements at

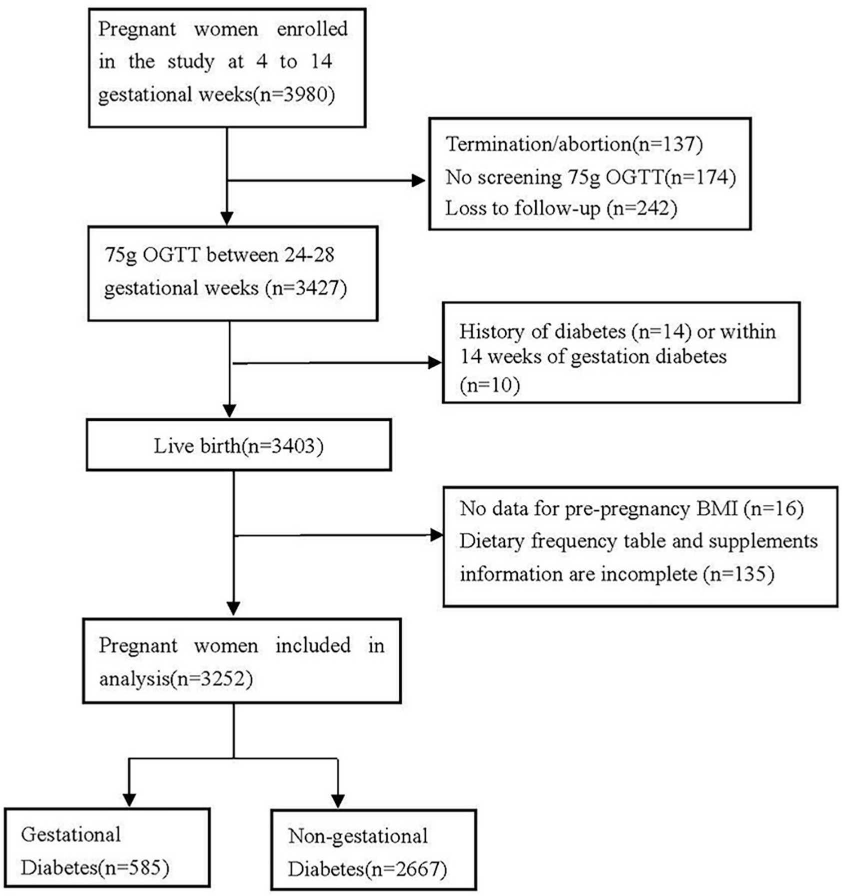

FIGURE 1
Flow chart of the screening process for the selection of eligible participants.

doses higher than 800 μg/day increased the risk of maternal GDM and hypertension (33, 34). The consumption of folate supplements in this study has been categorized as inadequate (< 400 μg/day), adequate (400–800 μg/day), and excessive (> 800 μg/day). ORs and 95% CIs were estimated for all three nutrients. Moreover, linear trends of GDM risk across the three nutrient intake categories were explored, by employing the median intake of each category as a continuous variable when fitting the models.

A multiplicative interaction term was included in the multivariable logistic and linear regression models to test our hypothesis that the three nutrients will change the incidence rate of GDM in ART women. However, the interaction between supplemental folate and ART on GDM and OGTT blood glucose levels is statistically significant (*P* for interaction < 0.05). The association between ART and GDM and OGTT blood glucose levels stratifying by supplemental folate was further evaluated: inadequate folate < 400 μg/day, adequate folate (400–800) μg/day, and excessive folate > 800 μg/day. No other effect modifiers were proposed, and no other interactions were investigated. All the data were analyzed with SPSS 22.0 software.

Results

Between 2019 and 2022, 3,252 eligible singleton pregnancies were among 3,980 women. 333 (10.24%) of these women underwent ART, while 2,919 (89.76%) conceived spontaneously. **Table 1** shows the characteristics of the study population. Distinctions exist between the ART and spontaneous conception groups. Women in the ART groups were likelier to have lower education level, nulliparous, no occupation and higher BMI. Regarding nutrient intake, the ART group possibly received higher doses of supplemental B6, total B6, supplemental B12, total B12, and total folate. Similarly, OGTT 1-h and OGTT 2-h blood glucose levels were greater than the spontaneous conception group (**Table 1**).

As shown in **Table 2**, in the unadjusted analysis, women who conceived ART exhibited almost double the odds of GDM than the spontaneous conception women (OR = 1.78, 95% CI: 1.37–2.31). After adjusting for maternal education, occupation, smoking, passive smoking, age, pre-pregnancy BMI, abortion history, PCOS, GDM history, macrosomia history, and family history of diabetes and gestational diabetes, the odds of GDM remained significantly higher in the ART group (aOR = 1.59, 95% CI: 1.08–2.34).

Fasting blood glucose levels between the ART and the spontaneous conception groups were not statistically different adjusting for variables. Neither were the regression coefficients in the multivariable linear regression models. However, OGTT 1-h and OGTT 2-h blood glucose levels were significantly higher in the ART group before adjustment, continuing the same trend after adjustment for covariates. The regression coefficients (β) of 1-h blood glucose (β = 0.43, 95% CI: 0.19–0.68) and 2-h blood glucose levels (β = 0.40, 95% CI: 0.19–0.60) in multiple linear regression are also statistically significant (**Figure 2**).

Comparing the highest to the lowest quartile, a significant relationship between dietary vitamin B6 and GDM (aOR = 1.60, 95% CI: 1.13–2.27) has been found. Similar results were observed for total vitamin B6 (aOR = 1.33, 95% CI: 1.00–1.77), including supplemental vitamin B6 sources. Both dietary vitamin B12 and total vitamin B12 exhibited a significant correlation with GDM in the highest quartile

TABLE 1 Demographic characteristics of women with spontaneous conception and ART.

Variables	Spontaneous conception (*n* = 2,919)	ART (*n* = 333)	*P*
Maternal age (years)			**<0.001**
<35	2,515 (86.16%)	249 (74.77%)	
≥35	404 (13.84%)	84 (25.23%)	
Educational level			**<0.001**
Secondary school or below	159 (5.45%)	43 (12.91%)	
High school	266 (9.11%)	48 (14.41%)	
College/university	2,053 (70.33%)	205 (61.56%)	
Postgraduate and above	441 (15.11%)	37 (11.11%)	
Occupation			**<0.001**
No	401 (13.74%)	94 (28.23%)	
Yes	2,518 (86.26%)	239 (71.77%)	
Parity			**<0.001**
Nulliparous	1,278 (57.39%)	168 (79.62%)	
Multiparous	949 (42.61%)	43 (20.38%)	
Previous GDM			0.058
No	1,910 (94.84%)	215 (97.73%)	
Yes	104 (5.16%)	5 (2.27%)	
Maternal smoking before or during pregnancy			0.711
No	2,896 (99.21%)	331 (99.40%)	
Yes	23 (0.79%)	2 (0.60%)	
Pre-pregnancy BMI group (kg/m^2)			**0.002**
<24	2,176 (74.55%)	222 (66.67%)	
≥24	743 (25.45%)	111 (33.33%)	
Previous delivery of babies ≥ 4 kg			0.085
No	1,820 (95.04%)	209 (97.66%)	
Yes	95 (4.96%)	5 (2.34%)	
PCOS			**< 0.001**
No	2,263 (89.98%)	212 (73.10%)	
Yes	252 (10.02%)	78 (26.90%)	
Dietary B6 (mg/day)	1.06 (0.65–1.51)	1.01 (0.58–1.57)	0.673
Supplemental B6 (mg/day)	1.90 (0.10–2.60)	2.40 (0.41–2.60)	**0.001**
Total B6 (mg/day)	2.87 (1.47–3.73)	3.18 (1.91–3.85)	**0.019**
Dietary B12 (μg/day)	1.69 (0.63–2.99)	1.70 (0.67–3.24)	0.357
Supplemental B12 (μg/day)	4.00 (0.26–4.87)	4.00 (0.60–5.20)	**0.025**
Total B12 (μg/day)	4.78 (2.55–6.49)	5.04 (3.72–6.65)	**0.029**
Dietary folate (μg/day)	174.50 (85.38–282.55)	189.44 (83.41–293.50)	0.371
Supplemental folate (μg/day)	800 (350–1,540)	800 (400–1,600)	IQR

(Continued)

TABLE 1 (Continued)

Variables	Spontaneous conception (*n* = 2,919)	ART (*n* = 333)	*P*
Total folate (μg/day)	843.05 (390.52–1404.96)	919.24 (527.11–1740.76)	**<0.001**
Fasting glucose (mmol/L)	4.53 (0.48)	4.64 (0.66)	0.120
OGTT 1-h glucose (mmol/L)	7.79 (1.61)	8.36 (1.86)	**<0.001**
OGTT 2-h glucose (mmol/L)	6.72 (1.32)	7.27 (1.60)	**<0.001**

Data are presented as n (%), mean ± SD or median (IQR). *P*-values are determined by chi-square, independent *t*-test or Mann–Whitney *U*-test. Bold values indicate statistically significant values.

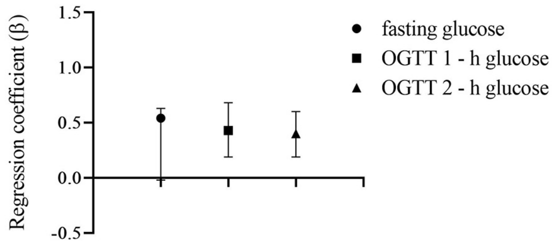

FIGURE 2
Association (regression coefficients ± 95% CIs) of ART with maternal OGTT glucose levels, reference to control group of women who conceived spontaneously. All models were adjusted education, occupation, smoking, passive smoking, age, pre-pregnancy BMI, abortion history, PCOS, GDM history, macrosomia, family history of diabetes and family history of gestational diabetes. Among all the 2,258 women of which 2,031 were spontaneous conception and 227 were receiving ART.

(aOR = 1.88, 95% CI: 1.34–2.64, and aOR = 1.52, 95% CI: 1.14–2.02) (P_{trend} < 0.05). The association between total vitamin B6 and GDM risk was entirely driven by dietary vitamin B6, similar to vitamin B12. Dietary folate and total folate intake were positively associated with GDM risk. The aORs of GDM for dietary folate and total folate intake were 1.66 (95% CI: 1.19–2.32) and 1.35 (95% CI: 1.02–1.77) (P_{trend} < 0.05). The aORs of GDM by supplemental folate intake were 0.93 (95% CI: 0.73–1.20) for 400–800 μg/day and 1.30 (95% CI: 1.01–1.68) for > 800 μg/day compared to intake < 400 μg/day (P_{trend} = 0.033) (**Table 3**).

Since only the interaction between supplemental folate and the ART on GDM and OGTT blood glucose levels was statistically significant (*P* for interaction < 0.05), we further stratified by supplemental folate: inadequate folate < 400 μg/day, adequate folate (400–800) μg/day, and excessive folate > 800 μg/day, and found that women with ART and excessive supplemental folate (> 800 μg/day) showed a slightly higher risk of developing GDM than women with spontaneous conception (aOR = 1.62, 95% CI: 1.39–3.39) (**Table 4**). Moreover, the increase in 1-h OGTT blood glucose risk (β = 0.76, 95% CI: 0.39–1.13) as well as 2-h OGTT blood glucose risk (β = 0.60, 95% CI: 0.29–0.92), were statistically significant only in women with excessive supplemental folate (> 800 μg/day) and ART (**Table 5**). All multivariable models adjusted for maternal age, education, occupation, smoking, passive smoking, pre-pregnancy BMI, abortion history, PCOS, GDM history, macrosomia, dietary vitamin B6, dietary vitamin B12, family history of diabetes and family history of gestational diabetes.

Discussion

This study demonstrated that women-conceived ART appears to be a risk factor for GDM and elevated blood glucose levels. We also found that ART was linked with GDM and higher blood glucose concentrations 1- and 2-h after OGTT in the 24–28 weeks, especially in women using excessive supplemental folate (> 800 μg/day).

Ashrafi et al. carried out a similar study and found that women who underwent ART had a higher risk of GDM than those who were spontaneously pregnant. However, they did not observe significant differences in blood glucose levels. The primary cause of the discrepancy is the various GDM judging standards. Their study followed the guidelines set forth by the American Diabetes Association (35), which called for two-step screening pregnant women at 24–28 weeks of gestation with a 50 g, 1-h oral glucose challenge test. If the screening test's results were abnormal (glucose ≥ 7.8 mmol/l or 140 mg/dl), a 100 g 3-h oral glucose tolerance test (OGTT) was then carried out in the 1–2 weeks that followed. Our study used one-step screening (i.e., a glucose-tolerance test in which the blood glucose level was obtained after the oral administration of a 75 g glucose load in the fasting state). It has been indicated that the two-step strategy led to lower diagnoses of GDM than the one-step approach (35). Another reason is that their sample size is relatively small, only including 360 women (36). Cai et al. found that IVF was associated with an increase in fasting blood glucose concentration in the second and third trimesters of pregnancy 2-h after OGTT, but only in women with a BMI of 25 kg/m^2 or higher (37). However, this study lacked a 1-h post-OGTT plasma glucose sample. Szymanska et al. observed an increase in fasting blood glucose levels during the first trimester of an IVF pregnancy but no increase in blood glucose levels during the second trimester. However, the study was limited to women with GDM (38).

Additionally, the results of the OGTT blood glucose test were examined in our study, and it was shown that women underwent

TABLE 2 Association of ART with maternal gestational diabetes mellitus.

	N (%)	Crude OR (95% CI)	*P*-value (95% CI)	Adjusted OR[a]	*P* -value
Spontaneous conception	2,919 (89.76)	1.00		1.00	
ART	333 (10.24)	1.78 (1.37–2.31)	**<0.001**	**1.59 (1.08–2.34)**	**0.019**

OR, odds ratio; CI, confidence internal.
[a]Adjusted for education, occupation, smoking, passive smoking, age, pre-pregnancy BMI, abortion history, PCOS, GDM history, macrosomia, family history of diabetes and family history of gestational diabetes. Bold values indicate statistically significant values.

TABLE 3 Odds ratios (OR) and 95% confidence intervals (CI) of GDM by quartile of B vitamins.

Nutrients	GDM/pregnancy	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)	P_{trend}
Dietary B6 (mg/day)				**<0.001**
Q1 (0.05–0.65)	134/817	1.00	1.00	
Q2 (0.66–1.06)	124/807	0.93 (0.71–1.21)	1.16 (0.81–1.66)	
Q3 (1.07–1.52)	160/824	1.23 (0.95–1.58)	1.56 (1.10–2.22)	
Q4 (1.53–3.32)	167/804	**1.34 (1.04–1.72)**	**1.60 (1.13–2.27)**	
Supplement B6 (mg/day)				0.228
Q1 (0–0.27)	151/918	1.00	1.00	
Q2 (0.28–1.98)	142/779	1.13 (0.88–1.46)	1.17 (0.88–1.55)	
Q3 (1.99–2.60)	169/896	1.18 (0.93–1.50)	1.05 (0.80–1.38)	
Q4 (2.61–9.30)	123/659	1.17 (0.89–1.52)	1.26 (0.94–1.68)	
Total B6 (mg/day)				**0.029**
Q1 (0.14–1.59)	131/810	1.00	1.00	
Q2 (1.60–2.98)	142/816	1.09 (0.84–1.42)	0.97 (0.71–1.33)	
Q3 (2.99–3.78)	137/806	1.06 (0.82–1.38)	1.04 (0.78–1.40)	
Q4 (3.79–10.50)	175/820	**1.41 (1.09–1.81)**	**1.33 (1.00–1.77)**	
Dietary B12 (μ g/day)				**<0.001**
Q1 (0.05–0.63)	128/819	1.00	1.00	
Q2 (0.64–1.69)	140/816	1.12 (0.86–1.45)	1.36 (0.96–1.94)	
Q3 (1.70–3.01)	134/809	1.07 (0.82–1.39)	1.34 (0.94–1.90)	
Q4 (3.02–9.80)	183/808	**1.58 (1.23–2.03)**	**1.88 (1.34–2.64)**	
Supplement B12 (μ g/day)				0.076
Q1 (0–0.41)	149/919	1.00	1.00	
Q2 (0.42–4.00)	160/953	1.17 (0.95–1.44)	1.17 (0.92–1.48)	
Q3 (4.01–5.00)	158/736	1.48 (0.66–3.30)	1.00 (0.37–2.70)	
Q4 (5.01–9.33)	118/644	1.27 (0.93–1.75)	1.32 (0.93–1.87)	
Total B12 (μ g/day)				**0.002**
Q1 (0.13–2.68)	125/812	1.00	1.00	
Q2 (2.697–4.87)	138/809	1.13 (0.87–1.47)	1.03 (0.75–1.41)	
Q3 (4.88–6.59)	141/814	1.15 (0.89–1.50)	1.09 (0.81–1.47)	
Q4 (6.60–14.84)	181/817	**1.56 (1.22–2.01)**	**1.52 (1.14–2.02)**	
Dietary folate (μ g/day)				**<0.001**
Q1 (5–87)	139/831	1.00	1.00	
Q2 (88–178)	122/808	0.89 (0.68–1.15)	1.10 (0.78–1.57)	
Q3 (179–284)	147/808	1.11 (0.86–1.43)	1.33 (0.94–1.87)	
Q4 (285–1,396)	177/805	**1.40 (1.10–1.80)**	**1.66 (1.19–2.32)**	
Supplement folate (μ g/day)				**0.033**
<400	164/977	1.00	1.00	
400–800	238/1,399	1.02 (0.82–1.26)	0.93 (0.73–1.20)	
>800	183/876	**1.31 (1.04–1.65)**	**1.30 (1.01–1.68)**	
Total folate (μ g/day)				**0.027**
Q1 (14–409)	133/812	1.00	1.00	
Q2 (410–850)	143/814	1.09 (0.84–1.41)	0.97 (0.71–1.36)	
Q3 (851–1,499)	139/813	1.05 (0.81–1.37)	1.02 (0.77–1.36)	
Q4 (1,500–2,778)	170/813	**1.35 (1.05–1.74)**	**1.35 (1.02–1.77)**	

P_{trend}, Tests for trend were performed using the median of the interval for each quartile. Reference to control group of women who was no-GDM.
[a]Adjusted for education, occupation, smoking, passive smoking, age, pre-pregnancy BMI, abortion history, PCOS, GDM history, macrosomia, family history of diabetes and family history of gestational diabetes. Bold values indicate statistically significant values.

TABLE 4 Association of ART with maternal gestational diabetes mellitus, stratified by supplemental folate.

	Spontaneous/ART	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)	*P*
Supplemental folate (μg/day)				
<400	903/74	1.29 (0.71–2.33)	1.07 (0.54–2.14)	0.840
400–800	1,263/136	1.65 (1.09–2.52)	1.17 (0.68–2.00)	0.575
>800	753/123	2.15 (1.42–3.27)	**1.62 (1.39–3.39)**	**0.043**

OR, odds ratio; CI, confidence internal. Reference to control group of women who conceived spontaneously in the respective supplemental folate group.
[a]All models adjusted for adjusted education, occupation, smoking, passive smoking, age, pre-pregnancy BMI, abortion history, PCOS, GDM history, macrosomia, dietary vitamin B6, dietary vitamin B12, family history of diabetes and family history of gestational diabetes. Bold values indicate statistically significant values.

TABLE 5 Association of ART with maternal glucose concentrations, stratified by supplemental folate.

	Fasting glucose[b] (mmol/L)		OGTT 1-h glucose[b] (mmol/L)		OGTT 2-h glucose[b] (mmol/L)	
	β [a] (95% CI)	*P*	β [a] (95% CI)	*P*	β[a] (95% CI)	*P*
Supplemental folate (μg/day)						
<400	0.03 (–0.15 to 0.21)	0.750	0.13 (–0.45 to 0.70)	0.667	0.14 (–0.31 to 0.60)	0.529
400–800	–0.01 (–0.14 to 0.11)	0.826	-0.09 (–0.51 to 0.33)	0.668	0.02 (–0.34 to 0.37)	0.935
>800	0.07 (–0.05 to 0.17)	0.247	**0.76 (0.39–1.13)**	**<0.001**	**0.60 (0.29–0.92)**	**<0.001**

β, regression coefficients; CI, confidence internal. Reference to control group of women who conceived spontaneous conception.
[a]All models adjusted for adjusted education, occupation, smoking, passive smoking, age, pre-pregnancy BMI, abortion history, PCOS, GDM history, macrosomia, dietary vitamin B6, dietary vitamin B12, family history of diabetes and family history of gestational diabetes.
[b]Among all the 2,258 women of which 2,031 were spontaneous conception and 227 were receiving ART. Bold values indicate statistically significant values.

ART would experience an increase in 1-h and 2-h blood glucose levels with no effect on fasting blood glucose. Gestational abnormal glucose metabolism is associated with a remarkably increased risk of adverse perinatal outcomes, even when levels are below GDM thresholds (39–41), and it is worth noting to observe the magnitude of these effects.

According to previous research, the risk of GDM may be increased by the relative deficiency of vitamin B6 and the comparatively low intake of vitamin B12 (42, 43). However, a positive correlation has been found between total vitamin B6 and total vitamin B12 in the highest quartile and the risk of GDM. This may be due to the fact that the supplements' contents were primarily the focus of the earlier research. However, our study's association between total vitamins B6 and B12 on GDM risk was entirely driven by dietary vitamins B6 and B12.

Both dietary folate and supplemental folate are statistically associated with GDM. Nevertheless, 10 years cohort study showed no statistically significant association between dietary folate before pregnancy and the prevalence of GDM (44). Given that sufficient dietary folate (> 400 μg/day) is expected to be rare in our sample, only 13.10% of our sample exhibited dietary folate intakes meet the recommended daily allowance (45). It is predicted that different associations between dietary folate and GDM in the study may be due to the different folate intakes of various populations. According to the USPSTF and WHO recommendations (31, 32), in this investigation, supplemental folate of > 800 μg/day is considered to be excessive, revealing that excessive folate supplementation would increase the incidence rate of GDM. Consistent with our study results, a cohort conducted in China showed that periconceptional folate supplement use of more than 800 μg/day from pre-pregnancy through mid-pregnancy was related to elevated GDM risk (34). The existing research on the relationship between B vitamins (folate, vitamin b6, and vitamin b12) and GDM is still controversial, more in-depth studies across multiple populations are needed to verify these results.

Previous studies have also considered the folate impact on women with ART, showing that folate can improve total and mature oocyte counts (46), embryo quality (47), pregnancy rates (48) and increase the likelihood of embryo survival (19, 49) after infertility treatment. However, these studies did not consider the effect of folate supplementation on perinatal diseases in pregnant women received ART. Numerous studies have demonstrated that folate supplementation, particularly excessive supplemental folate (> 800 μg/day), can alter the incidence of GDM in spontaneous conception women (34, 44, 50). Our research enriches fields related to ART and folate supplementation and showed that pre-pregnancy to first trimester folate supplements could modify the effect of ART on GDM risk and blood glucose levels.

The strengths of our study include a unique design and aim, specifically evaluating whether women on B vitamins exhibit a higher risk of GDM after ART. Moreover, using of a prospective cohort, which reduces the effects of selection or recall bias. To avoid information bias, women with hypertension or diabetes mellitus, as well as major influences of GDM were excluded. The *E*-value for the association between the women who underwent ART and GDM risk was 1.83, suggesting that a potential confounder must have relatively strong associations with both women who underwent ART and GDM risk to fully explain the association between supplemental folate intake and GDM risk.

This study has some limitations. The plasma homocysteine levels of B vitamins in pregnant women were not measured to support our conclusions. As a result, there is a possibility of misclassification. However, significant efforts were made to ensure reliable vitamin B data were collected on time by trained medical personnel with meticulous follow-up. Furthermore, self-reported folate from supplements was correlated with plasma folate and was regarded as a reliable indicator of folate exposure (51). Also, a relatively small sample size limits our ability to investigate the relationship between B vitamins and ART at different levels, and the generalizability of the findings to other regions needs further validation. Therefore, it is necessary to perform such study on a larger population.

Conclusion

ART appears to be an independent risk factor for GDM and elevated blood glucose levels. Our findings reinforce the need to advise women contemplating ART to avoid excessive folate supplements (>800 μg/day) to reduce their risk of GDM and hyperglycemia-related adverse outcomes. Women who seek fertility therapy should be counseled about this potential risk, and efforts should be taken to regulate the dose of folate supplementation throughout pregnancy. Pregnant women who underwent ART should have their health care during pregnancy, focusing more on blood glucose fluctuations.

Data availability statement

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

Ethics statement

Ethical approval for this study has been obtained from the Ethics Committee of Qingdao Women's and Children's Hospital (Number: 019–2019-FEKY). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ML and HW conceived, designed, and supervised the cohort study. YW and YC conceptualized idea for the manuscript. ML, HW, and XD were involved in design of questionnaire and protocol as well as supervision of data collection, analyzed, and interpreted the data. GL contributed to the preparation of the manuscript. All authors critically revised the article for intellectual and scientific content and approved this submission for publication.

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Conflict of interest

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

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BMI growth trajectory from birth to 5 years and its sex-specific association with prepregnant BMI and gestational weight gain

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Objective: The purpose of the study was to identify the latent body mass index (BMI) z-score trajectories of children from birth to 5years of age and evaluate their sex-specific association with prepregnant BMI and gestational weight gain (GWG).

Methods: This was a retrospective longitudinal cohort study performed in China. In total, three distinct BMI-z trajectories from birth to 5years of age were determined for both genders using the latent class growth modeling. The logistic regression model was used to assess the associations of maternal prepregnant BMI and GWG with childhood BMI-z growth trajectories.

Results: Excessive GWG increased the risks of children falling into high-BMI-z trajectory relative to adequate GWG (OR=2.04, 95% CI: 1.29, 3.20) in boys; girls born to mothers with prepregnancy underweight had a higher risk of low-BMI-z trajectory than girls born to mothers with prepregnancy adequate weight (OR=1.85, 95% CI: 1.22, 2.79).

Conclusion: BMI-z growth trajectories of children from 0 to 5years of age have population heterogeneity. Prepregnant BMI and GWG are associated with child BMI-z trajectories. It is necessary to monitor weight status before and during pregnancy to promote maternal and child health.

KEYWORDS

BMI-z trajectory, children aged 0–5 years, prepregnant BMI, gestational weight gain, latent class growth model

1. Introduction

The high prevalence of childhood overweight or obesity is a significant public health issue (1). According to the World Health Organization reports (2), an estimated 5.7% or 38.9 million children under the age of 5 around the world were affected by overweight in 2020. The Report on the Status of Nutrition and Chronic Diseases of Chinese Residents (2020) (3) shows that the prevalence of childhood overweight or obesity was 19% among children aged 6–17 and 10.4% among children under the age of 6. Early childhood overweight or obesity is critical for lifelong health (4, 5). Most prior studies examining the associated gene and environmental determinants of childhood overweight or obesity have focused on childhood BMI at just one point in time (6–8). Compared with the developmental assessments at a single time point, longitudinal child growth trajectories comprehensively evaluate the growth and development level of children from a dynamic perspective and detect abnormal growth in a timely manner (9).

Most studies showed that childhood growth trajectories have population heterogeneity (10–12). The early childhood growth trajectories were proved to be predictive of obesity risk in later life (13), cardiometabolic risk (14, 15), and adult diabetes (16). A recent birth cohort study evaluated childhood BMI z-score trajectories from age of 2 to 18 and showed that preschool age is a critical window that could predict growth patterns during puberty (17). Therefore, it is necessary to closely monitor the early childhood growth trajectories, focusing on those at higher risk of later overweight or obesity status, and helping to target specific groups for early intervention.

Accumulating evidence has supported that prepregnant BMI and gestational weight gain (GWG) may influence childhood overweight or obesity (18–21). Most studies showed that excessive GWG might increase the risk of childhood OWOB (22–24). However, the association between inadequate GWG with childhood BMI status remains unclear (25). Furthermore, there are still gaps in our knowledge regarding the associations of prepregnant BMI and GWG with BMI growth trajectories in early childhood. Therefore, the primary aim of this study was to identify the latent BMI-z growth trajectories of children from birth to 5 years of age in different genders and evaluate their independent association with prepregnant BMI and GWG.

2. Methods

2.1. Study subjects

The present study was a retrospective longitudinal cohort study. The study was approved by the Ethics Committee of Xuzhou Maternity and Child Health Care Hospital (No.201901).

Participants were singleton offspring born at term in Xuzhou Maternity and Child Health Care Hospital between 1 January 2016 and 31 December 2016. The inclusion criteria included (1) singleton offspring born at 28–42 completed weeks of gestation; and (2) mother–child pairs with recorded information, such as maternal gestational age, education level, prepregnant BMI, GWG, delivery type, child sex, birth weight, feeding mode in 6 months, and children physical check with at least 4 height/length and weight measurement recorded at 1 year (±2 months), 2 years (±2 months), 3 years (±3 months), 4 years (±3 months), and 5 years (±3 months). Exclusion criteria included (1) offspring born with congenital disabilities or postnatal diseases that could interfere with body composition development and (2) offspring with missing covariate data. Figure 1 depicts the study cohort derivation. A total of 2,190 mother–child pairs were enrolled in this study, and written informed consent was obtained from the parents of the subjects at recruitment.

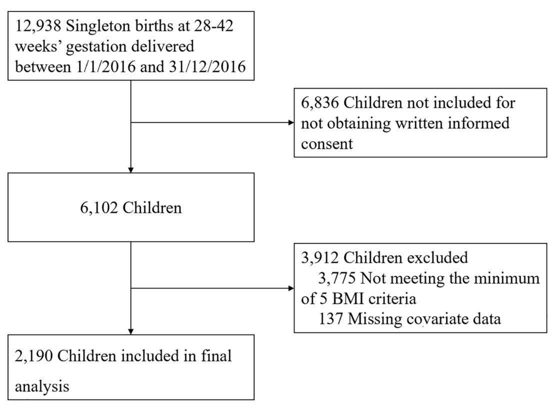

FIGURE 1
Study cohort derivation.

Data of mothers and children were collected retrospectively from the Jiangsu Maternal and Child Health Management Information System, including the maternal and child health information on prenatal, antenatal, and child healthcare electronic records with the standard quality control measures.

2.2. Prepregnant BMI and GWG

Height (m) and weight (kg) before pregnancy were collected at enrollment and calculated prepregnant BMI (kg/m^2). BMI was calculated as weight (kg) divided by square of the length/height (m^2). According to the BMI standards for Chinese adults (26), mothers were categorized as underweight with a BMI of <18.5 kg/m^2, adequate weight with 18.5 kg/m^2 ≤ BMI < 24.0 kg/m^2, overweight with 24.0 kg/m^2 ≤ BMI < 28.0 kg/m^2, and obese with BMI ≥ 28.0 kg/m^2. Based on their prepregnant BMI, GWG (kg) was calculated by subtracting prepregnancy weight (kg) from maternal weight at delivery (kg) and was categorized based on the standard of recommendation for weight gain during the pregnancy period (WS/T801-2022): underweight mothers (BMI < 18.5 kg/m^2) who gained 11.0–16.0 kg, normal-weight mothers (18.5 kg/m^2 ≤ BMI < 24.0 kg/m^2) gained 8.0–14.0 kg, overweight mothers (24.0 kg/m^2 ≤ BMI < 28.0 kg/m^2) gained 7.0–11.0 kg, and obese mothers (BMI ≥ 28.0 kg/m^2) gained 5.0–9.0 kg were categorized as adequate GWG; mothers who gained weight above or below this criterion were categorized as excessive or inadequate GWG, respectively. The BMI-z values that were more than ±5 were set to missing.

2.3. Child BMI-z

Children's weight and length/height were measured at each annual healthcare visit by trained staff. Body weight was measured using a digital scale (measuring range: 5–150 kg, measurement resolution: 0.1 kg, and measurement accuracy: ±0.3%). Recumbent length was obtained at the first-year and second-year visits, and standing height was obtained for those 3 years or older, all to the nearest 0.1 cm. BMI z-scores (BMI-z) were generated based on the age and sex-specific BMI reference from the WHO Child Growth Standards (2006).

2.4. Confounding factors

The potential confounding factors included maternal and children information. Maternal information included household income (￥), mother's education, prepregnancy BMI (kg/m^2), age at pregnancy (years), type of delivery, and parity. In terms of children's information, gestational age of delivery (years), infant feeding mode from birth to 6 months, and time of complementary foods introduction (months) were considered. Child birth weight was categorized as <2.5 kg, 2.5–4 kg, and ≥ 4 kg. Infant feeding mode from birth to 6 months was classified as

10.3389/fnut.2023.1101158

exclusive breastfeeding (27), mixed feeding, and formula feeding. The time of complementary food introduction was classified as ≤5 months, 6 months, and ≥ 7 months.

2.5. Statistical analysis

The latent class growth modeling (LCGM) approach was used to identify the subgroups shared a similar underlying trajectory based on the children's BMI z-scores with the Mplus 8.0. Model fit indices include Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC) and sample size adjusted BIC (aBIC), entropy, and a value of p for bootstrapped likelihood ratio test (BLRT) and Vuong-Lo–Mendell–Rubin likelihood ratio test (VLRT). The smaller the first three indices, the better the model fitting effect. The significant *value of p* for BLRT and VLRT indicates that a model with $k-1$ class should be rejected in favor of a model with k classes. The value of entropy >0.70 and the number of subjects in each trajectory group ≥5% indicate a good model fit. The maximum likelihood robust estimator was used to account for missing data when fitting the trajectories. Three distinct BMI-z trajectories were determined for both genders using LCGM.

Prepregnant BMI and GWG were compared among latent BMI trajectory groups using the chi-square test for proportions and the ANOVA F test for means. Logistic regression models were used to examine the association of prepregnant BMI and GWG with child BMI-z growth trajectory in different genders with the adjustment for the potential confounding factors, including household income, mother's education, age at pregnancy, type of delivery, parity, birth weight, and time of complementary food introduction. Covariate selection was based on a compulsory entry procedure and other potential confounders identified in the literature (28). Crude and adjusted odd ratios (ORs), along with 95% confidence intervals (CIs), were calculated. Data were analyzed using Statistic Product Service Solutions 23.0. All statistical tests were two-sided, and a *value of p* of <0.05 was considered statistically significant.

3. Results

The study population consisted of 2,190 mother–child pairs, of which 1,165 were boys and 1,025 were girls. Table 1 summarizes the maternal and child characteristics of the participants. A higher rate of exclusive breastfeeding in the first 6 months was found in girls than in boys (53.2 vs. 51.1%), and a higher proportion of girls with the time of complementary food introduction at 6 months was found (56.0 vs. 51.9%).

The number of classes and the shape of the BMI z-scores trajectories pattern were estimated according to the data of 1,165 boys and 1,025 girls. Complete BMI-z data were available for 1,043 (89.5%) boys and 917 (89.5%) girls, and the remaining children had one missing BMI-z data. The proportions of missing BMI-z data at each time point are shown in Supplementary Table 1. We tested from one to four possible trajectory classes. Considering the model fit indices, the three-class model was identified as the optimal model for both boys and girls. Supplementary Table 2 shows the fit statistics for the trajectory classes estimated.

Boys and girls shared similar patterns of growth trajectories but differed in their proportions. For the three latent trajectories, boys were more likely to have stable and moderate growth trajectories than girls. According to the relative position of the estimated three trajectories and combining professional significance, Class 1 was named as "moderate-BMI-z" (69.5% for boys and 63.9% for girls), Class 2 as "high-BMI-z" (11.6% for boys and 14.5% for girls), and Class 3 as "low-BMI-z" (18.9% for boys and 21.6% for girls). Moderate-BMI-z trajectory group represented children who had relatively stable BMI-z scores around 0 with a low increasing trend. The high-BMI-z trajectory group exhibited a relatively high initial BMI-z, a rapid increase until the age of 2 years, and a slight decrease after that, with the overall BMI-z ranging from 1 to 2.5. The low-BMI-z trajectory group was characterized by a relatively low initial BMI-z value, which tends to decrease rapidly until the age of 2 years and then increases slightly into the normal range, with the overall BMI-z ranging from −1.5 to −0.5. Figure 2 shows the BMI-z growth trajectory for trends and sizes of the three kinds of trajectories. Supplementary Table 3 shows the parameter estimation results of the LCGA model for children's BMI-z growth trajectory.

Table 2 presents the distribution of prepregnant BMI and GWG overall and according to child BMI-z growth trajectory classes stratified for sex. The average prepregnant BMI was $20.83 \pm 2.58\,kg/m^2$, and the maternal mean GWG was 15.53 ± 5.85 kg. The prevalence of maternal prepregnancy overweight and obesity was 8.4 and 1.6%, respectively, and GWG was classified as excessive for 60.8% of mothers and inadequate for 8.6%. Mothers with excessive GWG were more likely to have children within the high-BMI-z trajectory group among boys ($p = 0.018$). Mothers with prepregnancy underweight were more likely to have children within the low-BMI-z trajectory group among girls ($p = 0.001$).

Table 3 shows the independent association of prepregnant BMI and GWG with child BMI-z growth trajectory. After adjusting for household income, mother's education, age at pregnancy, type of delivery, parity, birth weight, time of complementary food introduction, and defining the moderate-BMI-z trajectory group as the reference category, boys of maternal excessive GWG were more likely to have high-BMI-z trajectory than their adequate GWG counterparts (OR = 2.04, 95% CI:1.29, 3.20); girls born to the mothers with prepregnancy underweight were more likely to have low-BMI-z trajectory than girls born to the mothers with prepregnancy adequate weight (OR = 1.85, 95% CI: 1.22, 2.79).

4. Discussion

This study was conducted to identify the childhood BMI-z trajectories from birth to 5 years among children born at term in Xuzhou Maternity and Child Health Care Hospital between 1 January 2016 and 31 December 2016 in different genders and to assess the association between BMI-z trajectories with prepregnant BMI and GWG. In total, three main findings are worthy of further attention and discussion. Data from this retrospective longitudinal cohort study showed that childhood BMI-z trajectories from birth to 5 years could be classified into three latent groups for both boys and girls, characterized as moderate-BMI-z trajectory group, high-BMI-z trajectory group, and low-BMI-z trajectory group. Prepregnant BMI and GWG were significantly associated with childhood BMI-z trajectories. Excessive GWG predicted the increased risk for the high-BMI-z trajectory group for boys, and prepregnancy underweight predicted the increased risk for the low-BMI-z trajectory group for girls.

With the application of longitudinal data analysis methods in childhood growth trajectories, accumulating studies have documented the potential heterogeneity of childhood growth trajectories (29, 30). The growth trajectory of early childhood is particularly important.

TABLE 1 Population characteristics of participants (*N*=2,190).

	All children *n*=2,190	Boy *n*=1,165	Girl *n*=1,025	*p*-value
	n (%)	*n* (%)	*n* (%)	
Maternal characteristics				
Household income per month, ￥				0.41
<2,500	110 (5.0)	57 (4.9)	53 (5.2)	
2,500–4,000	140 (6.4)	82 (7.0)	58 (5.7)	
≥4,000	1940 (88.6)	1,026 (88.1)	914 (89.2)	
Mother's level of education				0.52
Junior high or below	296 (13.5)	158 (13.6)	138 (13.5)	
High school/technical secondary school	425 (19.4)	225 (19.3)	200 (19.5)	
Junior college/vocational college	508 (23.2)	284 (24.4)	224 (21.9)	
College degree or above	961 (43.9)	498 (42.7)	463 (45.2)	
Age at pregnancy, years				0.04*
18~	417 (19.0)	209 (17.9)	208 (20.3)	
25~	1,096 (50.0)	569 (48.8)	527 (51.4)	
≥30	677 (30.9)	387 (33.2)	290 (28.3)	
Type of delivery				0.24
Vaginal	1,019 (46.6)	529 (45.4)	491 (47.9)	
Cesarean	1,170 (53.4)	636 (54.6)	534 (52.1)	
Parity				0.06
0	1,375 (62.8)	710 (60.9)	665 (64.9)	
1+	815 (37.2)	455 (39.1)	360 (35.1)	
Child characteristics				
Gestational age of delivery, weeks				0.26
<37	106 (4.8)	62 (5.3)	44 (4.3)	
≥37	2084 (95.2)	1,103 (94.7)	981 (95.7)	
Child birth weight, kg				<0.001*
<2.5	35 (1.6)	16 (1.4)	19 (1.9)	
2.5–4	1857 (84.8)	951 (81.6)	906 (88.4)	
≥4	298 (13.6)	198 (17.0)	100 (9.8)	
Infant feeding mode from birth to 6 months				0.49
Exclusive breastfeeding	1,140 (52.1)	595 (51.1)	545 (53.2)	
Mixed feeding	924 (42.2)	498 (42.7)	426 (41.6)	
Formula feeding	126 (5.8)	72 (6.2)	54 (5.3)	
Time of complementary foods introduction, months				0.05
≤5	516 (23.6)	298 (25.6)	218 (21.3)	
6	1,179 (53.8)	605 (51.9)	574 (56.0)	
≥7	495 (34.6)	262 (22.5)	233 (22.7)	

*$p < 0.05$.

Children at risk for overweight and obesity may have unique developmental trajectories during early childhood (31), which may influence the subsequent development of overweight or obesity and other health issues (14, 32). The classification and description of early childhood BMI-z growth trajectory in previous studies (33–36) can be roughly summarized into three types, including stable-moderate BMI-z growth trajectory, stable-low BMI-z growth trajectory, and stable-high BMI-z growth trajectory, which are consistent with the trajectories observed in our study. Furthermore, similar to these studies, it was concluded that children with stable-moderate BMI-z growth trajectory were in the majority, approximately 60% account, with the average BMI-z score range of around 0. However, Zhang et al. (37) reported four latent BMI-z growth trajectory patterns from birth to the age of 60 months. In addition to the three categories mentioned above, a catch-up BMI-z growth trajectory was also identified. The reason this result differs from our study may be due to the different fitting methods used (38). In future research, it would be beneficial to examine the application of different longitudinal data analysis methods to childhood growth trajectories.

In our analysis, after adjusting for the potential confounders, we found that boys of mothers with excessive GWG were significantly associated with an increased risk of high-BMI-z trajectory from birth to 5 years of age. Similarly, a retrospective longitudinal cohort study of 71,892 children suggested that children's high and increasing BMI

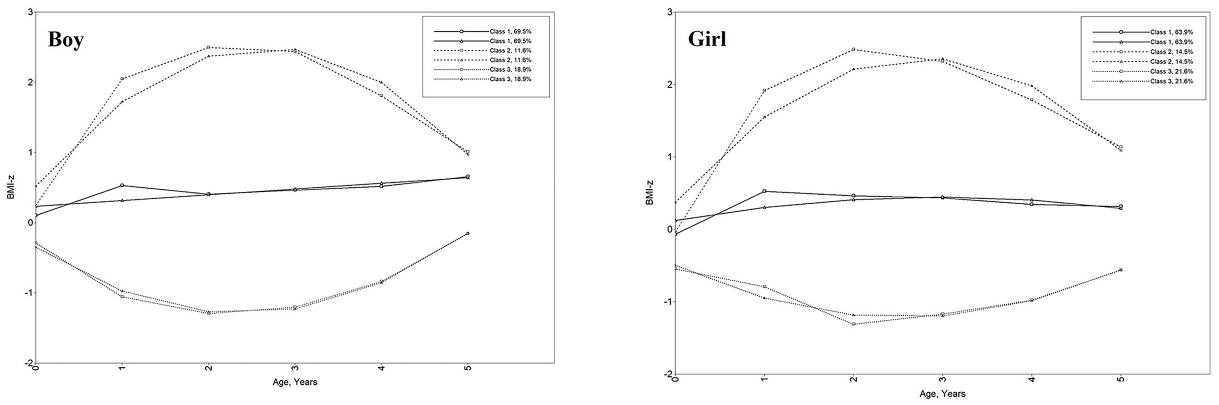

FIGURE 2
Child BMI-z growth trajectories from birth to 5years. Class 1: moderate-BMI-z trajectory, Class 2: high-BMI-z trajectory, Class 3: low-BMI-z trajectory. Line of circle symbol represents sample means; line of triangle symbol represents estimated means.

TABLE 2 Distribution of prepregnant BMI and GWG overall and according to child BMI-z growth trajectory classes stratified for sex.

	Mean±SD or *n* (%)				
	All	Class 1	Class 2	Class 3	*p*-value
Boys					
Prepregnant BMI, kg/m^2	20.86 ± 2.57	20.92 ± 2.62	21.06 ± 2.53	20.53 ± 2.38	0.085
Prepregnant BMI category					
Underweight	169 (14.5)	119 (14.7)	17 (12.6)	33 (15.0)	0.564
Adequate weight	876 (75.2)	607 (74.9)	99 (73.3)	170 (77.3)	
Overweight	101 (8.7)	69 (8.5)	17 (12.6)	15 (6.8)	
Obesity	19 (1.6)	15 (1.9)	2 (1.5)	2 (0.9)	
GWG, kg	15.32 ± 5.82	15.25 ± 5.88	16.18 ± 5.92	15.07 ± 5.44	0.172
GWG					
Adequate	357 (30.6)	265 (32.7)	31 (23.0)	61 (27.7)	0.018
Inadequate	105 (9.0)	72 (8.9)	7 (5.2)	26 (11.8)	
Excessive	703 (60.3)	473 (58.4)	97 (71.9)	133 (60.5)	
Girls					
Prepregnant BMI, kg/m^2	20.80 ± 2.58	20.81 ± 2.55	21.28 ± 2.69	20.44 ± 2.55	0.009
Prepregnant BMI category					
Underweight	156 (15.2)	92 (14.0)	12 (8.1)	52 (23.5)	0.001
adequate weight	768 (74.9)	501 (76.5)	116 (77.9)	151 (68.3)	
Overweight	84 (8.2)	50 (7.6)	19 (12.8)	15 (6.8)	
Obesity	17 (1.7)	12 (1.8)	2 (1.3)	3 (1.4)	
GWG, kg	15.77 ± 5.88	15.70 ± 5.59	15.08 ± 5.36	16.41 ± 6.91	0.095
GWG					
Adequate	312 (30.4)	201 (30.7)	42 (28.2)	69 (31.2)	0.705
Inadequate	84 (8.2)	52 (7.9)	10 (6.7)	22 (10.0)	
Excessive	629 (61.4)	402 (61.4)	97 (65.1)	130 (58.8)	

TABLE 3 The independent associations of prepregnant BMI and GWG on child BMI-z growth trajectory OR (95%CI).

	Boys		Girls	
	High-BMI-z trajectory	Low-BMI-z trajectory	High-BMI-z trajectory	Low-BMI-z trajectory
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Model 1[a]				
Prepregnant BMI category				
Adequate weight	1.00	1.00	1.00	1
Underweight	1.02 (0.58, 1.80)	0.97 (0.63, 1.50)	0.58 (0.30, 1.11)	**1.88 (1.26, 2.81)**[b]
Overweight	1.52 (0.86, 2.70)	0.78 (0.43, 1.39)	1.64 (0.93, 2.89)	0.99 (0.54, 1.82)
Obesity	0.75 (0.17, 3.34)	0.48 (0.11, 2.11)	0.71 (0.16, 3.22)	0.83 (0.23, 2.98)
Gestational weight gain				
Adequate	1	1	1	1
Inadequate	0.83 (0.35, 1.98)	1.56 (0.92, 2.66)	0.95 (0.44, 2.02)	1.16 (0.65, 2.06)
Excessive	**1.76 (1.14, 2.72)**	0.48 (0.11, 2.11)	1.07 (0.71, 1.61)	1.06 (0.75, 1.51)
Model 2				
Prepregnant BMI category				
Adequate weight	1.00	1.00	1.00	1
Underweight	1.10 (0.60, 2.00)	0.96 (0.61, 1.51)	0.63 (0.33, 1.23)	**1.85 (1.22, 2.79)**
Overweight	1.41 (0.76, 2.59)	0.84 (0.46, 1.54)	1.46 (0.80, 2.65)	0.94 (0.50, 1.76)
Obesity	0.39 (0.08, 1.84)	0.37 (0.08, 1.72)	0.57 (0.12, 2.72)	0.84 (0.23, 3.08)
Gestational weight gain				
Adequate	1.00	1.00	1.00	1
Inadequate	0.84 (0.35, 2.03)	1.54 (0.89, 2.69)	0.72 (0.33, 1.61)	1.28 (0.71, 2.32)
Excessive	**2.04 (1.29, 3.20)**	1.41 (0.99, 2.01)	1.18 (0.77, 1.80)	1.07 (0.75, 1.52)

[a]Model 1, Crude model; Model 2, Adjusted for household income, mother's education, age at pregnancy, type of delivery, parity, gestational age of delivery, birth weight, time of complementary foods introduction. [b]The bold data indicates the value of p less than 0.05.

trajectories were modestly associated with excessive GWG (28). However, the index used in this study to fit the growth trajectory of children is the raw BMI value, and the timeframe for the trajectory is 2–6 years old. Compared with the BMI trajectory, the BMI-z trajectory can better reflect the change in BMI values relative to their peers. Additionally, Montazeri et al. (39) found that excessive GWG was positively associated with the BMI trajectory of higher birth size and subsequent accelerated BMI gain, and inadequate GWG was associated with the BMI trajectory of lower birth size and slower BMI gain. However, our study did not observe a significant association between inadequate GWG and the low-BMI-z trajectory after adjustment. This may be due to the differences in the timeframe and classification of childhood growth trajectories. More in-depth studies are required to determine how inadequate GWG affects childhood growth trajectory.

Previous studies have reported positive associations between maternal prepregnant obesity and child high BMI growth trajectory (24, 40), which were consistent with the results of our study, though not statistically significant. Our study found that maternal prepregnant underweight predicted the increased risk for the low-BMI-z trajectory group for girls, which may be explained mainly by long-term changes in fetal endocrine and metabolic disorders (41).

There are several strengths in our study. First, multiple assessment points of BMI-z score were collected to identify the childhood growth trajectories with the LCGM approach, revealing the potential heterogeneity of growth trajectories in early childhood. Second, the study was conducted based on the Jiangsu Maternal and Child Health Management Information System to collect maternal and children's health data, which was electronically recorded with the standard quality control measures. Third, GWG was classified according to the standard of recommendation for weight gain during the pregnancy period (WS/T801-2022), which was based on the BMI of Chinese adults as the tangent point and more suitable for evaluating maternal weight status of Chinese women than the Institute of Medicine guidelines in 2009. Finally, a relatively large sample size was used in the study. It took comprehensive covariates into inclusion in evaluating the association between prepregnant BMI and GWG with childhood growth trajectories.

Nevertheless, several limitations should be mentioned as well. First, the retrospective cohort study was used in this study, and the credibility of the evidence is insufficient. Hence, more prospective studies are needed to corroborate the results of this study in the future. Second, the information on energy balance-related behavior was not collected and adjusted for in our study, which needs to be considered in the future.

5. Conclusion

The BMI-z trajectory from birth to 5 years of age was identified as three latent groups both for boys and girls with the approach of LCGM. Excessive GWG is associated with the increased risk for the high-BMI-z trajectory group for boys, prepregnancy underweight predicted the increased risk for the low-BMI-z trajectory group for girls. Pre-school age is the key window for the formation of trajectory patterns. Maternal weight should be managed precisely, and physical surveillance and intervention should be carried out for children at high risk of obesity, which can help to move the threshold of prevention and control of childhood overweight or obesity forward.

Data availbility statement

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

Author contributions

JS, YH, and LP designed and conceptualized the study. XG, YH, and PZ were responsible for the methodology. JX, YH, and JZ conducted the formal analysis. YD, JZ, and JX were the investigators. JX and JZ prepared the original draft of the manuscript. JS, XR, LZ, and YL reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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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.2023.1101158/full#supplementary-material

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Associations of serum concentrations of metal nutrients with postpartum anemia among pregnant Chinese women: A large retrospective cohort study

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Background and Aims: The association between serum concentrations of metal nutrients in pregnancy and postpartum anemia has not been widely studied. This study aimed to determine this association in a large retrospective cohort study.

Methods: We included 14,829 Chinese women with singleton pregnancies. Serum concentrations of metals before 28weeks of gestation, the occurrence of postpartum anemia and other potential covariates were obtained from their laboratory or medical records. Cox regression and restricted cubic spline regression models were used to explore the relationship between serum concentrations of metal nutrients in pregnancy and postpartum anemia.

Results: After adjustment for covariates, higher concentrations of iron (Fe), magnesium (Mg) and zinc (Zn) and lower concentrations of copper (Cu) were associated with a lower risk of postpartum anemia. Compared with those whose serum concentrations of metal nutrients were in the bottom quintile (Q1), the hazard ratios (HRs) of those whose serum concentrations of metal nutrients were in the top quintile (Q5) were 0.57 (95% confidence interval (CI): 0.50, 0.64) for Fe, 0.67 (95% CI: 0.60, 0.76) for Mg, 0.82 (95% CI: 0.73, 0.93) for Zn, and 1.44 (95% CI: 1.28, 1.63) for Cu. L-shaped curve relationships were found between increasing concentrations of Fe, Mg, and Zn and incidence of postpartum anemia. Higher serum concentrations of Cu were associated with an increased risk of postpartum anemia. Serum concentrations of Fe in Q5 were associated with a lower risk of postpartum anemia when they coincided with serum concentrations of Mg in Q5, Zn in Q5, or Cu in Q1.

Conclusion: Higher serum concentrations of Fe, Mg, and Zn, and lower serum concentrations of Cu were associated with a lower risk of postpartum anemia among pregnant women.

KEYWORDS
metal concentrations, postpartum anemia, pregnant women, Chinese, retrospective cohort study

Introduction

Postpartum anemia is a major and persistent public health problem worldwide. Its prevalence is high in developed countries (22–50%) and even higher in developing countries (50–80%) (1). Compared with women without postpartum anemia, those with postpartum anemia have higher risks of having depression (2, 3), fatigue and providing less responsive care for their babies (2). In addition, women with postpartum anemia due to acute blood loss have higher risks of sepsis (4) and mortality (5).

Oral iron (Fe), intravenous (IV) Fe and blood transfusion are common treatments for postpartum anemia (6). However, challenges remain in the use of these treatments and no optimal treatment has been identified. Up to 40% of women exhibit intolerance for oral Fe, in the form of adverse gastrointestinal effects (7). Compared with oral Fe, IV Fe is more effective in treating anemia (8–10), but Danish guidelines recommend against using IV Fe due to its having more severe side effects, a higher cost and there being a lack of sufficient evidence for its clinical efficacy (6). Compared with oral and IV Fe, blood transfusion is more expensive and puts women at higher risk of exposure to infectious pathogens. Given these treatment challenges, it is critical to identify interventions that can effectively and safely prevent postpartum anemia.

Fe is an essential nutrient for maintaining normal hemoglobin concentrations and Fe supplements are commonly used to prevent anemia (11). However, Fe overload or over supplementation can lead to increased adverse outcomes, such as gestational diabetes mellitus (GDM) (12). It is therefore crucial to determine optimal concentrations and supplemental doses of Fe to prevent postpartum anemia without causing adverse effects.

Deficiencies of several other metal nutrients, such as zinc (Zn), magnesium (Mg) and copper (Cu), may also be associated with anemia (13–15). In addition, deficiencies of these metal nutrients increase the risk of anemia in children, adolescents, adults and older adults (14, 16, 17). However, there has been little examination of associations between concentrations of metal nutrients during pregnancy and postpartum anemia, and some of these non-Fe metal nutrients (e.g., Zn and Cu) may interact with Fe metabolism and affect the development of anemia (13, 18, 19). Thus, the combined correction of these trace element deficiencies may represent a viable intervention for the prevention of anemia.

This retrospective cohort study aimed to explore the associations and dose–response relationships of maternal concentrations of seven metal nutrients during pregnancy (measured before 28 weeks of gestation) with the risk of postpartum anemia in Chinese women aged 18 to 45 years old. This study also investigated the potential combined influence of serum concentrations of Fe and other metal nutrients on the risk of postpartum anemia.

Material and Methods

Participants

This retrospective cohort study was carried out at a large obstetrics hospital in Foshan, Guangdong province, China. We reviewed the obstetric medical records from March 1, 2015 to July 31, 2018, of 16,930 women aged 18 to 45 years who had delivered their babies at the hospital and whose serum concentrations of metals (Fe, Mg, Cu, Zn, calcium [Ca], lead [Pb] and manganese [Mn]) were measured during pregnancy. Then, 2,101 women were excluded on the basis of their having (a) incomplete outcome data or exposure indicators (1,146 women); (b) multiple pregnancy; (c) a history of abnormal placental implantation (24 women) or placenta previa (147 women); (d) a baseline serum concentration of Fe < 6.5 μmol/l (246 women); or (e) serum concentrations of metals measured after 28 weeks of gestation (558 women). This yielded 14,829 women for inclusion in this study. The study protocol was approved by the ethics committee of the Affiliated Foshan Maternity and Child Healthcare Hospital, Southern Medical University. The Affiliated Foshan Maternity and Child Healthcare Hospital provided administrative permission for the research team to access and use the data.

Measurement of serum concentrations of metals

Serum concentrations of metals were measured during the women's' regular obstetric check-ups in the hospital. Only women whose serum concentrations of metals were measured before 28 weeks of gestation were included, as this ensured that only true and early associations between serum concentrations of metals in pregnancy and postpartum anemia were obtained. Blood samples were collected by nurses in the clinic and then transported to the laboratory within 1 h for measurement. Serum concentrations of metals were measured using the polarography method (AS-9000\u00B0C, AWSA, Wuhan, China), with a detection limit of less than or equal to 1×10^{-8} mol/l. The coefficient of variation and the relative error of the detection was less than or equal to 1% during daily quality control.

Postpartum anemia and other covariates

Two staff members (G.D.C and T.T.P) independently extracted outcome data from medical records. In this retrospective study, the outcomes of postpartum anemia were collected from medical records and based on the ICD-10 code of O99.001. The diagnosis of postpartum anemia was made by professional doctors according to the criteria of the concentration of hemoglobin in their peripheral blood was less than 110 g/l happened postpartum, but not necessarily happened at 1 week postpartum. Other covariates reviewed and extracted from medical records were age, body mass index (BMI) at delivery, gestational week of delivery, parity, delivery mode, occurrence of abnormal placental implantation, placenta previa, immediate postpartum hemorrhage, and intrapartum injury.

Statistical analysis

Continuous variables are reported as means ± standard deviations (SDs) or medians (interquartile ranges). Outcome variables (serum concentrations of metals) are reported as medians with interquartile ranges.

The women were divided into quintiles according to their serum concentrations of metals, with the bottom quintile (Q1) comprising those with the lowest serum concentrations of metals and the top quintile (Q5) comprising those with the highest serum concentrations of metals. Cox regression analyses were used to determine the associations between serum concentrations of metals and postpartum anemia. Follow-up time was calculated as the time between measurement of serum concentrations of metals and discharge after delivery. Two models were used in the analysis: a univariate model (Model 1) and a multivariate model (Model 2) adjusting for potential covariates (age, gestational week of delivery, BMI, parity, delivery mode, immediate postpartum hemorrhage and intrapartum injury). Those in Q1 were used as the reference group for most metals (Fe, Mg, Cu Zn, Ca and Mn). For inverse Cu and Pb, those in Q1 had the highest serum concentrations and those in Q5 had the lowest serum concentrations. Restricted cubic spline regression with five knots was performed to explore the dose–response associations between serum concentrations of metals and postpartum anemia. Likelihood ratio tests were used to test for nonlinearity of these associations. Analyses were performed using SPSS 20.0 software (Chicago, IL, USA) and R statistics software version 3.6.3.[1] Plots were also drawn using R 3.6.3 software. Results with a two-sided p value of less than 0.05 were considered statistically significant.

Results

This retrospective cohort study included 14,829 women with singleton pregnancies and who were aged 29.9 ± 4.80 years old. They had delivered their babies at a mean gestational age of 38.9 ± 1.76 weeks and had a mean parity of 1.41 ± 0.55. Over half of the women (55.1%) gave birth spontaneously and the remaining 44.9% delivered by caesarean section. Nearly one fifth (18.4%) of women had postpartum anemia. The women had median serum concentrations of 18.0 µmol/l, 1.28 mmol/l, 23.4 µmol/l, 90.1 µmol/l, 1.60 mmol/l, 34.0 µg/l and 0.81 µmol/l for Fe, Mg, Cu, Zn, Ca, Pb and Mn, respectively (Table 1).

As shown in Table 2, serum metal concentrations tended to be related by Spearman correlation analysis. Significant positive or negative correlations were observed between several (but not all) pairs of metals, while the correlations were weak or very weak ($r = -0.165 \sim 0.331$, all $p < 0.01$). A very strong positive correlation was observed between Zn and Mn ($r = 0.846$, $p < 0.001$).

As shown in Table 3, after adjusting for potential covariates in the Cox regression analyses, higher serum concentrations of Fe, Mg and Zn were associated with a lower risk of postpartum anemia, while a higher serum concentration of Cu was associated with a higher risk of postpartum anemia. Compared with the risk of postpartum anemia in the women whose serum concentrations of Fe were in Q1, the risk of postpartum anemia decreased by 27% in the women whose serum concentrations of Fe were in Q2 (hazard ratio [HR]: 0.73, 95% confidence interval [95% CI]: 0.65, 0.81), decreased by 35% in the women whose serum concentrations of Fe were in Q3 (HR: 0.65, 95% CI: 0.58, 0.73), decreased by 43% in the women whose serum concentrations of Fe were in Q4 (HR: 0.57, 95% CI: 0.51, 0.64), and decreased by 43% in the women whose serum concentrations of Fe were in Q5 (HR: 0.57, 95% CI: 0.50, 0.64). Similarly, higher serum concentrations of Mg were associated with decreases in the risk of postpartum anemia: 17, 33 and 33% for the women whose serum concentrations of Mg were in Q3 (HR: 0.83, 95% CI: 0.74, 0.93), Q4 (HR: 0.67, 95% CI: 0.60, 0.75) and Q5 (HR: 0.67, 95% CI: 0.60, 0.76), respectively. The women whose serum concentrations of Zn were in Q4 (HR: 0.85, 95% CI: 0.75, 0.96) and Q5 (HR: 0.82, 95% CI: 0.73, 0.93) had 15 and 18% lower risks of postpartum anemia than the women whose serum concentrations of Zn were in Q1. In contrast, compared with the women whose serum concentrations of Cu were in Q1, the women whose serum concentrations of Cu were in Q2, Q3, Q4 and Q5 had 1.15-, 1.22-, 1.31- and 1.41-fold greater risks of postpartum anemia, respectively. A small increased risk of postpartum anemia (HR:1.15, 95%CI: 1.01, 1.29) was found for women whose serum concentrations of Ca were in Q3. No significant associations were found between women's serum concentrations of Pb and Mn and their risk of postpartum anemia.

Restricted cubic spline regression was performed to investigate dose–response associations between serum concentrations of metals and postpartum anemia. The median concentrations of Fe, Mg, Cu, Zn, Ca and Mn in Q1 were used as the reference values for analyses of these species, while the median concentration of Pb in Q5 was assigned as the reference value for this species. As shown in Figure 1, an L-shaped curve association was observed between serum

TABLE 1 Characteristic of subjects.

	Total (N=14,829)
Age, years	29.9 ± 4.80
BMI, kg/cm^2	26.2 ± 3.11
Gestational week of delivery, weeks	38.9 ± 1.76
Parity, times	1.41 ± 0.55
Postpartum anemia, N (%)	
Yes	2,728 (18.4)
No	12,101 (81.6)
Delivery mode	
Natural birth	8,167 (55.1)
Caesarean section	6,662 (44.9)
Immediate postpartum hemorrhage	
Yes	220 (1.5)
No	14,609 (98.5)
Intrapartum injury	
Yes	148 (1.0)
No	14,659 (98.9)
Measurement time, gestational weeks	18.2 ± 3.51
Concentrations of metal, median (interquartile)	
Iron (Fe), µmol/L	18.0 (14.1, 22.0)
Magnesium (Mg), mmol/L	1.28 (1.20, 1.41)
Copper (Cu), µmol/L	23.4 (19.0, 27.6)
Zinc (Zn), µmol/L	90.1 (79.1, 108)
Calcium (Ca), mmol/L	1.60 (1.50, 1.72)
Lead (Pb), µg/L	34.0 (24.0, 45.9)
Manganese (Mn), µmol/L[a]	0.81 (0.73, 0.89)

[a]The sample size for Mn is: n = 4,915.

1 https://www.r-project.org/

TABLE 2 Spearman correlation between the serum metal concentrations.

Coefficients	Iron (Fe)	Magnesium (Mg)	Copper (Cu)	Zinc (Zn)	Calcium (Ca)	Lead (Pb)	Manganese (Mn)
Iron (Fe)	–	–	–	–	–	–	–
Magnesium (Mg)	−0.043***	–	–	–	–	–	–
Copper (Cu)	−0.035***	−0.134**	–	–	–	–	–
Zinc (Zn)	−0.039***	0.331***	−0.130***	–	–	–	–
Calcium (Ca)	0.027**	0.124***	0.156***	−0.165***	–	–	–
Lead (Pb)	0.002	0.010	0.030***	−0.103***	0.078***	–	–
Manganese (Mn)	0.007	−0.047**	−0.039**	0.846***	−0.007	−0.137***	–

**$p < 0.01$; ***$p < 0.001$.

TABLE 3 Cox regression analyses of quartile of metal concentrations and postpartum anemia.

Median (interquartile)	Quartile of metal concentrations								
	Q1	Q2		Q3		Q4		Q5	
	HR	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Fe, μmol/L	11.0 (9.60, 12.3)	15.0 (14.0, 16.0)		18.0 (17.2, 19.0)		21.0 (20.3, 22.0)		26.2 (24.7, 29.0)	
Model 1	1.00	0.73	(0.65, 0.81)***	0.66	(0.59, 0.73)***	0.58	(0.52, 0.65)***	0.58	(0.52, 0.66)***
Model 2	1.00	0.73	(0.65, 0.81)***	0.65	(0.58, 0.73)***	0.57	(0.51, 0.64)***	0.57	(0.50, 0.64)***
Mg,mmol/L	1.14 (1.11, 1.16)	1.22 (1.20, 1.24)		1.29 (1.27, 1.31)		1.38 (1.35, 1.42)		1.63 (1.53, 1.80)	
Model 1	1.00	0.96	(0.86, 1.07)	0.81	(0.72, 0.91)**	0.68	(0.60, 0.76)***	0.69	(0.62, 0.78)***
Model 2	1.00	0.96	(0.86, 1.08)	0.83	(0.74, 0.93)**	0.67	(0.60, 0.75)***	0.67	(0.60, 0.76)***
Cu, μmol/L	15.0 (12.9, 16.6)	19.9 (19.0, 20.8)		23.4 (22.5, 24.2)		26.7 (25.7, 27.6)		30.7 (29.7, 32.3)	
Model 1	1.00	1.13	(0.997, 1.27)	1.18	(1.04, 1.33)**	1.28	(1.14, 1.44)***	1.40	(1.24, 1.58)***
Model 2	1.00	1.15	(1.02, 1.30)*	1.22	(1.08, 1.38)**	1.31	(1.16, 1.48)***	1.44	(1.28, 1.63)***
Zn, μmol/L	72.1 (68.7, 74.9)	80.9 (79.1, 83.0)		90.2 (87.6, 93.4)		103.8 (100.0, 108.1)		123.7 (117.4, 134.1)	
Model 1	1.00	1.05	(0.93, 1.17)	0.91	(0.81, 1.03)	0.87	(0.77, 0.98)*	0.85	(0.75, 0.96)**
Model 2	1.00	1.06	(0.94, 1.19)	0.91	(0.81, 1.02)	0.85	(0.75, 0.96)**	0.82	(0.73, 0.93)**
Ca, mmol/L	1.33 (1.22, 1.42)	1.53 (1.51, 1.55)		1.60 (1.58, 1.62)		1.69 (1.66, 1.72)		1.84 (1.80, 1.90)	
Model 1	1.00	0.93	(0.82, 1.05)	1.11	(0.98, 1.25)	1.08	(0.97, 1.22)	1.05	(0.93, 1.18)
Model 2	1.00	0.95	(0.84, 1.08)	1.15	(1.01, 1.29)*	1.12	(0.995, 1.26)	1.06	(0.95, 1.20)
Pb, μg/L	17.0 (12.1, 20.4)	25.9 (24.0, 27.8)		34.0 (32.0, 36.0)		43.0 (40.6, 45.9)		57.0 (52.0, 66.0)	
Model 1	1.10 (0.97, 1.23)	1.00	(0.89, 1.28)	1.02	(0.90, 1.14)	0.95	(0.84, 1.07)	1.00	
Model 2	1.11 (0.99, 1.25)	1.02	(0.90, 1.14)	1.04	(0.92, 1.17)	0.98	(0.87, 1.10)	1.00	
Mn, μmol/L	0.64 (0.57, 0.68)	0.75 (0.73, 0.77)		0.81 (0.80, 0.83)		0.87 (0.86, 0.89)		0.97 (0.94, 1.02)	
Model 1	1.00	1.08	(0.87, 1.32)	1.13	(0.92, 1.39)	1.00	(0.81, 1.23)	1.05	(0.85, 1.30)
Model 2	1.00	1.08	(0.88, 1.33)	1.11	(0.90, 1.36)	0.99	(0.80, 1.23)	1.04	(0.84, 1.28)

Model 1: univariate model. Model 2: adjusted for age, BMI, parity, gestational week at delivery, parity, delivery mode, immediate postpartum hemorrhage, and intrapartum injury. *$p<0.05$; **$p<0.01$; ***$p<0.001$.

concentrations of Fe and postpartum anemia, with a significant nonlinearity ($p < 0.0001$). Increasing serum concentrations of Fe were associated with a lower risk of postpartum anemia up to a concentration of 18.4 μmol/l, with this protective association decreasing at serum concentrations of Fe greater than 22.0 μmol/l. Similar L-shaped curve associations were found between serum concentrations of Mg and Zn and the risk of postpartum anemia. The risk of postpartum anemia decreased rapidly as serum concentrations of Mg and Zn increased from 1.20 to 1.40 μmol/l and from 80 to 100 μmol/l, respectively, but thereafter decreased less rapidly. Significant nonlinearity was found for Mg ($p < 0.0001$) but not for Zn ($p = 0.162$). In contrast, the risk of postpartum anemia increased as serum concentrations of Cu increased (p for nonlinearity = 0.925). An inverse U-shaped association was observed between serum concentrations of Ca and the risk of postpartum anemia, with no significant nonlinearity detected ($p = 0.146$). No significant associations were observed between serum concentrations of Pb and Mn and the risk of postpartum anemia.

We observed that higher quintiles of Cu were associated with higher HR of postpartum anemia, whereas higher quintiles of Fe, Mg, and Zn were associated with lower HR of postpartum anemia (Table 3). We aimed to investigate potential protective associations of the combination of serum metal concentrations and postpartum anemia. To avoid the potential confounding influence of Cu, inverse Cu was introduced instead of Cu in the combination with other metals (Fe, Mg, and Zn). As shown in Table 4, compared with high serum concentrations of Fe alone, high serum concentrations of Mg, Zn and/or inverse Cu in combination with high serum concentrations of Fe were associated with a lower risk of postpartum anemia. HRs for postpartum anemia ranged from 0.31 to 0.37 when high serum concentrations of Mg, Zn or inverse Cu occurred in combination with a high serum concentration of Fe, compared with a HR of 0.51 for postpartum anemia when there was only a high serum concentration of Fe. HRs ranged from 0.21 to 0.23 when high serum concentrations of two of Mg, Zn and inverse Cu occurred in combination with high serum concentrations of Fe, compared with an HR of 0.46 when there was only a high serum concentration of Fe. The HR for postpartum anemia was 0.10 when high serum concentrations of Mg, Zn and inverse Cu occurred in combination with a high serum concentrations of Fe, compared with an HR of 0.44 for postpartum anemia when there was only a high serum concentration of Fe.

Discussion

In this large retrospective cohort study, higher serum concentrations of Fe, Mg and Zn and lower serum concentrations of Cu in pregnancy contributed to lower risk of postpartum anemia. The association of the risk of postpartum anemia with serum concentrations of Fe, Mg and Zn decreased rapidly as serum concentrations of Fe increased from 6.5 to 22.0 μmol/l, serum concentrations of Mg increased from 1.20 to 1.40 μmol/l and as serum concentrations of Zn increased from 80 to 100 μmol/l, but the curves soften with further increment. Increased serum concentrations of Cu had a linear association with an increased risk of postpartum anemia. Compared with high serum concentrations of Fe alone, the coexistence of high serum concentrations of Fe with high serum concentrations of Mg and Zn and with low serum concentrations of Cu was associated with a lower risk of postpartum anemia.

Fe is an essential micronutrient for maintaining hemoglobin concentrations, so adequate serum concentrations of Fe are needed to prevent anemia. Oral or IV Fe supplementation increases hemoglobin concentration and thus prevents and treats all forms of anemia (6, 8–10). However, Fe overload increases the level of oxidative stress in the human body (20) and increases the risk of developing other diseases during pregnancy, such as GDM (12) and preeclampsia (21). Moreover, long-term periconceptional Fe supplementation of more than 30 mg/d was associated with increased GDM risk in a large prospective cohort of pregnant Chinese women (12). Thus, there is a need to optimize the use of Fe supplements to prevent postpartum anemia while avoiding the risk of predisposing women to adverse outcomes and the development of other diseases. Further studies are thus needed on Fe supplementation and maintaining appropriate serum concentration of Fe. In the current study, we found that the risk of postpartum anemia was decreased in women with serum concentrations of Fe of 6.5 to 22.0 μmol/l. This result needs to be validated in future high-quality studies using comprehensive Fe indicators.

There have been fewer studies on the relationship between serum concentrations of Zn and anemia than on the relationship between serum concentrations of Fe anemia, especially during pregnancy; however, most studies have indicated that a certain serum concentration of Zn protects against anemia. A lower serum concentration of Zn was associated with risk of anemia and Fe deficiency low concentrations of hemoglobin during pregnancy in a study of 1,185 pregnant Chinese women (22). A study of pregnant women in rural Bangladesh also showed found an association between low serum concentrations of Zn and low concentrations of hemoglobin, despite minimal Fe deficiency (23). Higher plasma or serum concentrations of Zn have also been found to be associated with higher concentrations of hemoglobin in non-pregnant populations (16, 24, 25). In addition, Zn supplementation was found to improve anemia status in certain populations, such as infants (26). It was suggested that Zn plays a role in modulating Fe metabolism by regulating the expression of divalent metal-ion transporter-1 and ferroportin, thereby affecting Fe uptake and transcellular transport (18).

There have been a few low-quality studies on the association between serum concentrations of Mg and postpartum anemia. In a cross-sectional study of 180 pregnant Sudanese women, serum concentrations of Mg were positively associated with concentrations of hemoglobin, and women with anemia had significantly lower concentrations of Mg than women without anemia (27). In older Chinese individuals, serum concentrations of Mg were found to mediate the associations between diet and development of anemia (17). In another study of 2,849 Chinese adults, a higher intake Mg was found to be associated with a lower risk of anemia and this association was not modified by serum concentrations of ferritin (15). Thus, current evidence partly supports our observations that higher serum concentrations of Mg contribute to a lower risk of postpartum anemia. Higher serum concentrations of Mg in pregnancy may also prevent the occurrence of gestational hypertensive disorders such as pre-eclampsia, which make women prone to bleeding (28). Magnesium sulfate is commonly used in the treatment of these diseases, and the dose should be carefully controlled to prevent Mg poisoning (29). In this study, the risk of postpartum anemia was decreased in women with serum concentrations of Mg ranging from 1.20 to 1.40 μmol/l. These results serves as reference data that needs to be validated in future studies.

The association between serum concentrations of Cu and postpartum anemia appears more complex. Cu deficiency causes anemia and leads to lower plasma and brain concentrations of Fe in rats (30). In a cross-sectional study, serum concentrations of Cu and hemoglobin were found to have an negative association with anemia and the ratio of Cu to Fe was higher among pregnant women with anemia than among pregnant women without anemia (22). In children, higher serum concentrations of Cu were found among those with iron deficiency anemia who also exhibited decreased Fe absorption and deficient hematological parameters (19). It is possible that U-shaped associations between serum concentrations of Cu and postpartum anemia may exist as similar associations have been previously found for unexplained anemia (31) and new-onset hypertension (32). In the current study, high serum concentrations of Cu was independently and positively associated with the risk of postpartum anemia. This may be because the pregnant women in our study were less likely to be Cu deficient than those in other studies. Thus, there needs to be more examination on the risk of Cu overload

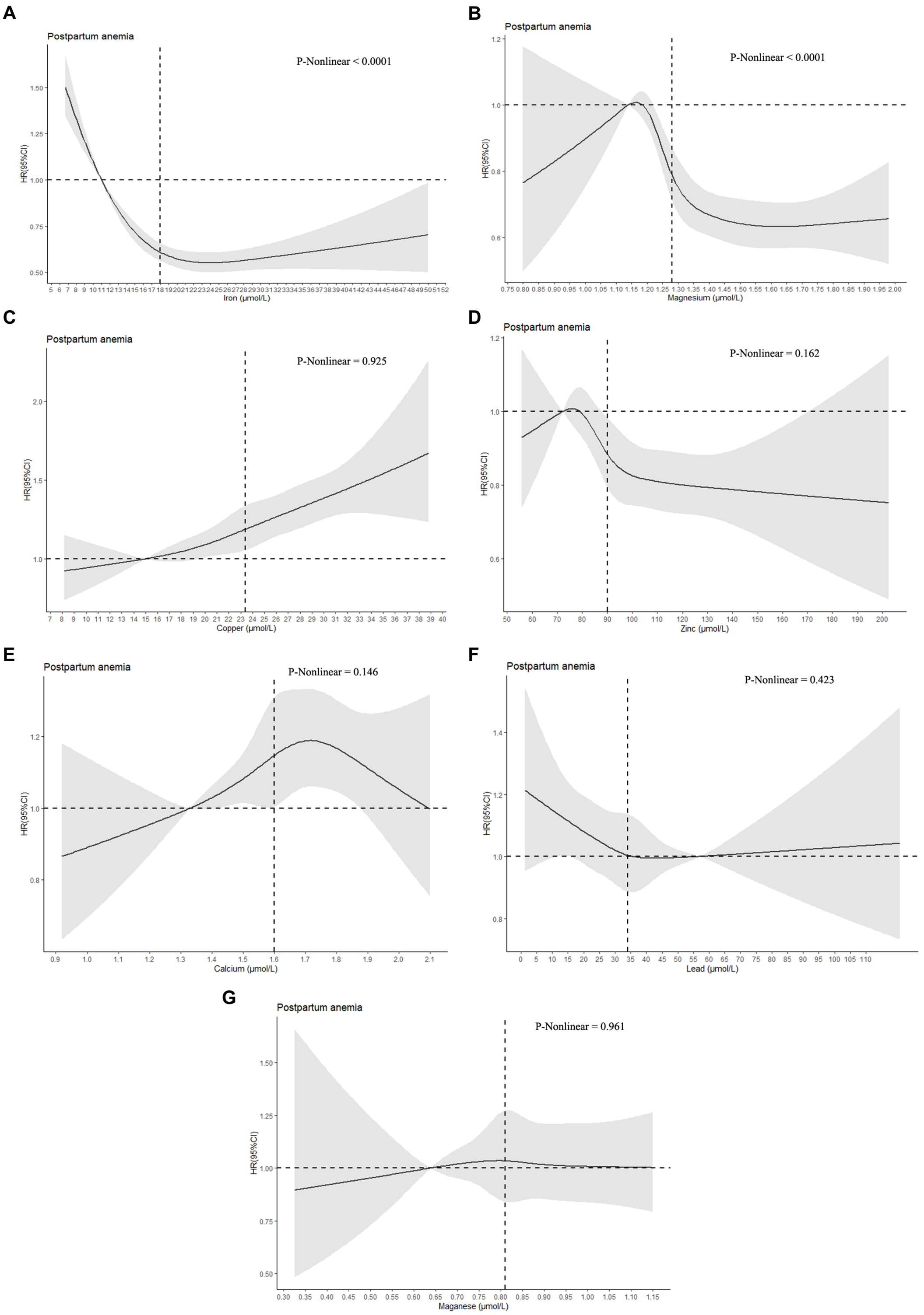

FIGURE 1
Dose–response associations between serum concentrations of metals and postpartum anemia. Analyses were performed by restricted cubic spline regressions (5knots). The median concentrations of iron, magnesium, copper, zinc, calcium, and magnanese in Q1 were used as the reference values (HR=1.00) for analyses of these species, while the median concentration of Pb in Q5 was assigned as the reference value (HR=1.00) for this species. The vertical lines represent the median metal concentrations. Parts **A-G** represent the dose-response associations of iron, magnesium, copper, zinc, calcium, lead, and magnanese with postpartum anemia.

during pregnancy and how this risk can be mitigated. Our results show that high serum concentrations of Cu should be avoided to prevent postpartum anemia in women.

We also found that a deficiency of Fe in combination with an imbalance in one or more other metal nutrients (Zn deficiency, Mg deficiency and/or Cu overload) was associated with a higher risk

TABLE 4 Cox regression analyses of combination of different metal concentrations and postpartum anemia.

Co-existence of bottom quintile groups of different metals	Bottom groups		Co-existence of top group of different division of metal combinations							
	N	Reference	5 division[a]		10 division[a]		15 division[a]		20 division[a]	
			N	HR (95%CI)	*N*	HR (95%CI)	*N*	HR (95%CI)	*N*	HR (95%CI)
Fe	n[b]	1.00	2,958	0.57 (0.50, 0.64)***	1,484	0.51 (0.44, 0.60)***	1,042	0.46 (0.39, 0.56)***	776	0.44 (0.36, 0.55)***
Fe + Mg	623	1.00	–	–	522	0.31 (0.24, 0.41)***	–	–	–	–
Fe + Zn	551	1.00	–	–	532	0.36 (0.27, 0.49)***	–	–	–	–
Fe + inverse Cu[c]	638	1.00	–	–	601	0.37 (0.29, 0.48)***	–	–	–	–
Fe + Mg + Zn	169	1.00	–	–	–	–	226	0.21 (0.13, 0.33)***	–	–
Fe + Mg + inverse Cu[c]	135	1.00	–	–	–	–	198	0.21 (0.13, 0.33)***	–	–
Fe + Zn + inverse Cu[c]	104	1.00	–	–	–	–	175	0.23 (0.13, 0.43)***	–	–
Fe + Mg + Zn + inverse Cu[c]	36	1.00	–	–	–	–	–	–	99	0.10 (0.04, 0.25)***

[a]Divisions means the groups of the numbers of separations of the serum Fe concentrations or the numbers of the groups of the combine calculation of different metals. [b]The sample in the bottom groups of different divisions of Fe were 2,961 for 5 division; 1,506 for 10 division; 989 for 15 division; and 747 for 20division. [c]For inverse Cu, subjects with the highest serum Cu concentrations were assigned as the bottom quintile group (Q1), while those with lowest serum Cu concentrations were in the top quintile group (Q5). Model 1: univariate model. Model 2: adjusted for age, BMI, parity, gestational week at delivery, parity, delivery mode, immediate postpartum hemorrhage, and intrapartum injury.

of postpartum anemia than a deficiency of Fe alone. Our results are supported by another study that found that adults with the lowest risk of anemia in were those who also had the highest intake of Mg and Fe. However, studies of the effects in pregnant women of multiple supplementations with Fe or Fe–folic acid (IFA) and/or multiple micronutrients (MM) have yielded inconsistent results. In a study of1,813 pregnant Vietnamese women, MM and IFA supplementation resulted in increased Fe stores but did not have an effect on anemia (33). In a study among pregnant women in rural Nepal, supplementation with IFA + Zn or IFA + Zn + MM did not provide additional benefits in improving maternal hematologic status compared with IFA supplementation alone (34). In a study of pregnant women in semirural Mexico, MM supplementation slightly reduced concentrations of hemoglobin compared with Fe supplementation (35). In a study among women with postpartum anemia who were treated with oral Fe supplements, Zn supplementation had a negative but transient influence on hematological status; however, this finding was not clinically significant (36).

The abovementioned findings may indicate that women with simultaneous deficiencies of Fe and other micronutrients may be less likely to be involved in randomized controlled trials (RCTs) with a relatively small sample size than women without simultaneous deficiencies of Fe and other micronutrients. Moreover, over-supplementation of several nutrients *via* MM may not provide obvious additional benefits for individuals who do not have existing deficiencies and may even have negative effects. In the current study, we identified that women with deficiencies in Fe and concomitant imbalances in other metal nutrient (a Zn deficiency, a Mg deficiency and/or a Cu overload) had a higher risk of postpartum anemia than those who were only deficient in Fe, which highlights the need to treat women with such multiple metal -nutrient deficiencies to prevent postpartum anemia. Large RCTs are needed to focus on these special populations and elaborate associations between metal nutrient imbalance and postpartum anemia.

Strength and limitations

This study had several strengths. First, serum concentrations of metals were measured during pregnancy before delivery, and the exclusion criteria meant that we included only women whose serum concentrations of metals were measured before 28 weeks of gestation. This helped to ensure the temporal sequence of events and avoid possible causal inversions. Second, the large sample size enabled us to divide the population into different groups and thus obtain more accurate results and narrower 95% CIs for HRs than would have been possible otherwise. Third, the use of restricted cubic spline regression and investigation of the simultaneous deficiency of Fe and several other metals provided comprehensive results on the associations of metal nutrients with postpartum anemia.

However, there were also several limitations to this study. First, the data were collected from a single obstetric center in Southern China. Although this center is the largest obstetric center in its city and covers a large population, there may have been selection bias, so further studies based on more representative populations are needed. Second, serum concentrations of metals were measured only once; no data for multiple time points were available. Thus, we were unable to explore the associations between serum metal concentrations over time and postpartum anemia. Third, data on dietary metal intake were not available in this study. Thus we were unable to examine the associations between dietary metal intake and postpartum anemia, which should be further investigated by high-quality studies in the future. Four, the use of oral iron supplements during pregnancy was not collected during the regular obstetric check-up, and we could not obtain related data and could not make up the missing of these data due to the retrospective design. Therefore, it was not included in the statistics and be adjusted for. However, the use of iron supplementation may have tended to underestimate rather than overestimate the associations found in our study. Finally, aside from serum concentrations of ferritin, transferrin, soluble transferrin receptor and hepcidin are also important indicators for measuring Fe metabolism status. Unfortunately, these were not measured during regular obstetric check-ups, meaning we were unable to explore more comprehensive associations between iron metabolism indicators and postpartum anemia, and possible interactions with other metals indicators.

Conclusion

In this large retrospective cohort study of Chinese women with singleton pregnancies, we found that higher serum concentrations of Fe, Mg and Zn before 28 weeks of gestation were associated with lower risk of postpartum anemia. The risk of postpartum anemia showed large and significant decreases as serum concentrations of Fe, Mg and Zn increased within a certain range and then the risk decreased as the serum concentrations of these species increased beyond this range. In contrast, serum concentrations of Cu were positively associated with an increased risk of postpartum anemia. Women who had high serum concentrations of Fe in combination with high serum concentrations of Mg and Zn and low serum concentrations of Cu exhibited a lower risk of postpartum anemia than women who only had high serum concentrations of Fe. Our study had emphasized the importance of addressing imbalances of multiple metal nutrients as a strategy to prevent postpartum anemia. More high-quality studies are needed to determine a comprehensive strategy for managing serum concentrations of metal nutrients during pregnancy to prevent postpartum anemia.

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 Affiliated Foshan Maternity and Child Healthcare Hospital, Southern Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

G-dC, H-lL, and Z-pL devised the idea and designed the study. G-dC, T-tP, P-sL, Z-xZ, X-yG, H-yW, D-xL, and D-zF contributed to the primary data collection. G-dC and T-tP re-examined the data and analysis the data. G-dC and T-tP wrote the original draft, which was revised by H-lL and Z-pL. H-lL and Z-pL supervised the study and administered the project. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Impact of parental lifestyle patterns in the preconception and pregnancy periods on childhood obesity

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Introduction: High prevalence of overweight and obesity already observed in preschool children suggests the involvement of early-life risk factors. Preconception period and pregnancy are crucial windows for the implementation of child obesity prevention interventions with parental lifestyle factors as relevant targets. So far, most studies have evaluated their role separately, with only a few having investigated their potential synergistic effect on childhood obesity. Our objective was to investigate parental lifestyle patterns in the preconception and pregnancy periods and their association with the risk of child overweight after 5years.

Materials and methods: We harmonized and interpreted results from four European mother-offspring cohorts participating in the EndObesity Consortium [EDEN, France; Elfe, France; Lifeways, Ireland; and Generation R, Netherlands] with data available for 1,900, 18,000, 1,100, and 9,500 families, respectively. Lifestyle factors were collected using questionnaires and included parental smoking, body mass index (BMI), gestational weight gain, diet, physical activity, and sedentary behavior. We applied principal component analyses to identify parental lifestyle patterns in preconception and pregnancy. Their association with risk of overweight (including obesity; OW-OB) and BMI z-scores between 5 and 12years were assessed using cohort-specific multivariable logistic and linear and regression models (adjusted for potential confounders including parental age, education level, employment status, geographic origin, parity, and household income).

Results: Among the various lifestyle patterns derived in all cohorts, the two explaining the most variance were characterized by (1) "high parental smoking, low maternal diet quality (and high maternal sedentary behavior in some cohorts)" and, (2) "high parental BMI and low gestational weight gain." Patterns characterized by high parental BMI, smoking, low diet quality or high sedentary lifestyle before or during pregnancy were associated with higher risk of OW-OB in children, and BMI *z*-score at any age, with consistent strengths of associations in the main cohorts, except for lifeways.

Conclusion: This project provides insight into how combined parental lifestyle factors in the preconception and pregnancy periods are associated with the future risk of child obesity. These findings are valuable to inform family-based and multi-behavioural child obesity prevention strategies in early life.

KEYWORDS

1,000days, parental lifestyle patterns, preconception, childhood obesity, parental diet, parental physical activity, parental smoking, parental BMI

1. Introduction

Childhood obesity is a major public health issue associated with short and long-term adverse consequences, such as psychological problems and lower educational attainment, and a higher risk for many harmful comorbidities later in life, such as type 2 diabetes mellitus, dyslipidemia, and coronary heart disease (1). Around 40 million children under 5 years are living with overweight or obesity worldwide (2). High prevalence of obesity in preschool children suggests the involvement of early-life risk factors. However, the multiple causes of childhood obesity are not fully understood. The first 1,000 days, from conception to two years of age, represent a unique window of opportunity to implement child obesity prevention strategies and increase future health benefits (2).

Several systematic reviews have synthesized the results of observational studies linking suboptimal maternal lifestyle factors in preconception and during pregnancy with the risk of childhood obesity (3–5). Recent evidence showed that the preconception period is a key determinant of pregnancy success and next generation health (6, 7). Such maternal lifestyle factors in the preconception period can directly influence oocyte quality, embryonic, and placental development in the very first weeks of pregnancy, thus predisposing to a higher risk of childhood obesity and its related comorbidities (8). During pregnancy, unfavorable maternal lifestyle and health factors could also lead to abnormal fetal development and predispose to childhood obesity (3, 5). Maternal overweight, obesity, excessive gestational weight gain (GWG), unhealthy diet, smoking, and sedentary behaviours are the most prevalent adverse lifestyle factors before and during pregnancy (3, 5, 7). A recent meta-analysis, including more than 162,000 mother–children pairs from 37 cohort studies in high-income countries, reported that maternal overweight at conception and excessive GWG were independently associated with the risk of overweight and obesity during childhood and adolescence (9). Other associations between low maternal diet quality during pregnancy and overweight or obesity in children have been reported; however, results are inconsistent (10, 11).

So far, most studies have evaluated the effects of early-life maternal factors separately, with only a few having used patterning approaches to investigate their combined and potentially synergistic effect on childhood obesity. Furthermore, paternal lifestyle factors during the first 1,000 days have scarcely been considered, despite their likely influence on both the mother's and the child's lifestyle. Clustering of parental risk factors is a major public health concern, because they not only have individual effects on childhood obesity risk, but also interact with each other, which can further increase the risk of childhood obesity. There has been a consensus that family-based interventions, targeting the two generations, i.e., parents and their children, tend to be more effective (12). Lastly, strategies to prevent childhood obesity should start as early as possible, before birth and even in the preconception period; based on the scientific evidence of the life course epidemiology, developmental programming around the time of conception, and parental predisposition to adopt healthier behaviors for the future child (7).

In this context, our aim was to identify parental-based lifestyle patterns in the preconception and pregnancy periods and to assess their association with childhood overweight and obesity between 5 and 12 years. To this end, we have performed cohort-specific analyses in four European cohorts implementing a harmonized data and analysis approach.

2. Methods

2.1. Study population

This project involves four mother—offspring cohort studies across 3 European countries within the EndObesity consortium, which was established in 2020 with an overarching aim to develop, implement and evaluate innovative, multi-disciplinary strategies for prevention of childhood overweight by targeting family-based lifestyle factors in the 1,000 days. These cohorts/longitudinal follow-ups include the study on the pre- and early postnatal determinants of child health and development (EDEN; recruitment of ≈1,900 pregnant women from 27 January 2003 to 6 March 2006); the French national birth cohort (Elfe; recruitment of ≈18,000 children in 4 waves in 2011) in France; the Lifeways Cross-Generation Cohort Study (Lifeways; recruitment of ≈1,100 participants from 2 October 2001 to 4 April 2003) in Ireland; and The Generation R Study (Generation R; recruitment of ≈9,500 participants pregnant women with an expected delivery date between 1 April 2002 and 31 January 2006) in the Netherlands.

Briefly, the EDEN mother–child study is a prospective cohort that was designed to evaluate the early, pre-, and post-natal

Abbreviations: AR, adiposity rebound; BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; DII®, Dietary Inflammatory Index; E-DII™, energy-adjusted DII; FFQ, food-frequency questionnaire; GWG, gestational weight gain; OW-OB, overweight and obesity; PCA, principal component analyses.

determinants of child health and development. Study participation was proposed to all women visiting the prenatal clinic before 24 weeks' gestation. Between 2003 and 2006, 2002 (53%) pregnant women 18 to 45 years old were recruited in two centers: Nancy and Poitiers hospitals (13) and 89.2% of fathers agreed to participate. Children have been followed-up for up to 12 years, by visits to research centres and questionnaires mailed to parents. The ELFE study is a French national longitudinal birth cohort with more than 18,000 children included at birth (14). Recruitment took place on 25 selected days during four periods in 2011. Participation in the cohort was proposed to women who gave birth in 349 maternity hospitals randomly selected among the 544 public and private maternity hospitals in metropolitan France. Among eligible mothers, 51% agreed to participate ($N = 18,040$), and a sub-sample of 5,600 fathers have also participated. Children will be followed-up until 20 years of age by questionnaires mailed to parents or telephone interviews and visit to doctors at 2, 4 and 12 yrs.

The Lifeways Cross-Generation Cohort Study is a prospective family study which aimed to document health status, diet, and lifestyle in the family members and establish patterns and links across generations (15). Mothers ($n = 1,124$) were initially recruited by a midwife during their first antenatal visit in two maternity hospitals in the Republic of Ireland between 2001 and 2003. The participating mothers' partners (biological father) were also directly contacted by the Lifeways research team at recruitment (participant mothers having given their contact details at their booking visit) and invited to participate ($n = 333$ agreed). Longitudinal follow-up was conducted with linkage data to hospital and general practice records and examination of children when aged on average 5 and 9 years.

Generation R Study is a population based prospective cohort study from early pregnancy onwards in Rotterdam, the Netherlands (16). Among participants, 9,978 mothers were enrolled in the study, of whom 91% ($n = 8,800$) were between early pregnancy and until birth. Maternal data has been collected repeatedly during pregnancy by physical examinations, biological samples and questionnaires. Fathers were invited to participate and 71% ($n = 6,347$) agreed. The fathers were assessed once during the first prenatal visit to the research center using physical examinations and questionnaires. At the ages of 5 and 9 years all children were invited to the research center for detailed cardiometabolic data collection by physical examination, biological samples and questionnaires. Repeated measurements of child growth from birth until the age of 13 were used for the calculations of adiposity peak and rebound. The study design for each cohort has been described in detail elsewhere (13–16). We retained one out of each twin pair in the Elfe and Lifeways cohorts involving twin births on a random basis. Twins in Generation R were excluded from analyses ($n = 106$) because the percentage of missing data was higher in this group and imputation was questionable due to the inherent specificities of this population. The characteristics of each study and numbers of participants included for the current analysis are summarized in Table 1.

2.2. Ethics statement

All studies have been approved by the local ethics review committees and written informed consents were obtained from all families (Supplementary Table S1).

2.3. Candidate variables for parental-based lifestyle

We selected candidates for parental-based lifestyle factors in preconception and pregnancy possibly associated with childhood overweight from an extensive literature search and priori hypotheses. The literature search included observational and interventional studies, as well as systematic reviews and meta-analyses (3–5). We did a first work to organize the different factors identified from the literature search, according to the period of interest and following the level of evidence, from the lowest possible early markers to the highest probable early markers of obesity in preconception and during pregnancy. Our classification was based on how different reviews (3–5) have graded the level of evidence according to the number of studies reporting an association between the factor and risk of obesity in children. Then, we compared this list to the available information in the EndObesity cohorts. We conducted a data inventory to identify available variables within each cohort. Preference was given to the use of variables harmonized between the four cohorts from previous work conducted as part of either the H2020 LifeCycle (17) or the ERA-Net HDHL APLHABET (18) projects. The LifeCycle project is a Horizon 2020-funded international project, which has developed a harmonized set of variables (including those describing lifestyle) in a Europe-wide network of cohort studies started in early life. Protocols for LifeCycle harmonization are available in free access (19). The ALPHABET project is a European consortium composed of seven longitudinal birth cohort studies, the food frequency questionnaires of which were harmonized, then DASH and DII scores derived following a common methodology. All the harmonized variables for parental-based lifestyle used in our project are described in Supplementary Table S2 and Supplementary Text 1.

In preconception, we retained the following factors: maternal pre-pregnancy and paternal body mass index [BMI = weight (kg)/height(m^2)], smoking before pregnancy (No, <10 cig/day defined as low smoking, ≥10 cig/day defined as high smoking), and dietary quality and inflammatory potential (Supplementary Table S2). We selected BMI as a marker of an obesogenic lifestyle by considering that it was related to other lifestyle factors. During pregnancy, we used similar information including maternal pre-pregnancy BMI, paternal BMI, smoking during pregnancy (No, <10 cig/day, ≥10 cig/day), diet, and additionally included maternal GWG (calculated as measured weight at the end of pregnancy (third trimester in Generation R) minus weight at conception as reported by mothers) and information on physical activity level when available (Supplementary Table S2). If pre-pregnancy weight was not available, we used early pregnancy weight closest to conception, limited to 1st trimester (<12 weeks). Data were collected using self-administered health and lifestyle questionnaires at inclusion or at birth, face-to-face interviews or information collected in medical records.

2.4. Dietary scores

The usual diet of women was assessed using validated semi-quantitative food frequency questionnaires (FFQs) completed during pregnancy or at birth. The FFQs were based on different periods: the maternal diet during the year before pregnancy in EDEN, at early trimester (12–16 weeks of gestation) in Lifeways, over the three

TABLE 1 Characteristics of the cohort populations.

	EDEN* (N=1981)	Elfe* (N=17,904)	Generation R* (N=8,765)	Lifeways* (N=932)
Maternal characteristics				
Age (years)	29.5 ± 4.9	30.2 ± 5.1	30.3 ± 5.3	29.6 ± 5.9
Born abroad	4.1 (79)	13.7 (2327)	34.3 (2897)	NA**
Low	7.5 (144)	8.5 (1524)	11.0 (901)	18.8 (171)
Medium	39 (745)	34.9 (6240)	46.0 (3753)	31.3 (285)
High	53.5 (1021)	56.6 (10136)	43.0 (3508)	49.9 (454)
Employed/self-employed	76.3 (1461)	78.8 (14016)	72.9 (4772)	67.2 (620)
Primiparous	44.6 (848)	45.9 (8110)	56.0 (4810)	45.9 (421)
Pre-pregnancy smoking (Yes)	36.1 (688)	41.9 (7392)	39.1 (2822)	52.3 (404)
Underweight	8.6 (162)	7.9 (1385)	4.4 (320)	2.9 (22)
Normal	65.1 (1226)	64.9 (11431)	67.0 (4826)	69.4 (532)
Overweight	17.6 (332)	17.2 (3038)	19.4 (1399)	19.6 (150)
Obese	8.7 (164)	10 (1764)	9.1 (658)	8.2 (63)
Pre-pregnancy E-DII	0.5 ± 1.7	NA	NA	NA
Pre-pregnancy DASH	24 ± 4.3	NA	NA	NA
Maternal GWG (kg)	13.4 ± 4.8	13.2 ± 5.5	10.3 ± 5.0	NA
Pregnancy smoking	27.1 (520)	19.9 (3514)	18.0 (1290)	21.6 (192)
Pregnancy E-DII	0.92 ± 1.7	NA	−0.3 ± 1.1	0.43 ± 1.8
Pregnancy DASH	23.9 ± 4.3	24.0 ± 4.4	24.0 ± 4.6	23.7 ± 4.6
Paternal characteristics				
Age (years)	32.00 ± 5.9	33.3 ± 6.2	33.4 ± 6.0	32.1 ± 6.2
Born abroad	7.3 (138)	15.1 (2475)	35.6 (2785)	NA**
Low	10 (191)	8.7 (1184)	8.2 (423)	31.8 (261)
Medium	46.3 (885)	40.3 (5513)	41.2 (2115)	26.9 (221)
High	43.7 (835)	51 (6966)	50.6 (2602)	41.3 (339)
Employed/self-employed	91.1 (1709)	90.1 (15769)	91.3 (4356)	99.1 (751)
Pre-pregnancy smoking (Yes)	43.9 (740)	NA	NA	52.2 (129)
Underweight	1.1 (19)	0.8 (94)	1.0 (59)	1.1 (3)
Normal	54.2 (966)	55 (6855)	49.3 (3046)	33.3 (89)
Overweight	36.2 (645)	36.1 (4500)	41.0 (2534)	49.8 (133)
Obese	8.6 (153)	8.1 (1004)	8.7 (539)	15.7 (42)
Pregnancy smoking	40.2 (697)	35.2 (4407)	44.8 (3282)	32.5 (89)
Pregnancy E-DII	NA	NA	NA	1.5 ± 1.7
Household income				
1st quartile (lowest)	16.7 (318)	14 (2145)	20.1 (1306)[a]	62.9 (531)[d]
2nd quartile	29.7 (564)	21 (3207)	25.0 (1621)[b]	37.1 (313)[e]
3rd quartile	26.3 (500)	33 (5047)	54.9 (3563)[c]	NA
4th quartile (highest)	27.2 (517)	31.9 (4875)	NA	NA

Values are means ± SD for continuous variables and % (*n*) for categorical variables. BMI, body mass index; DASH, dietary approach to stop hypertension; E-DII, energy-adjusted dietary inflammatory index; GWG, gestational weight gain. *Data characteristics based on the selection of the population before imputation of the lifestyle factors: EDEN *N* = 1981 (with at least one factor in the maternal model in preconception); Elfe *N* = 17,904 (with at least one factor in the family model in pregnancy); Gen-R *N* = 8,765 (with at least one factor in the parental pregnancy model), Lifeways *N* = 932 (with at least one factor in the parental pregnancy model). **Maternal birth outside Ireland was an exclusion criterion in Lifeways. [a]Value for category (<1,200 or 1,200 euro).
[b]Value for category (1200–2,200 euro).
[c]Value for category (>2,200 euro).
[d]<600£/week.
[e]≥600£/week.

preceding months in Generation R (thereby covering dietary intake in the first trimester of pregnancy), or for the last three months of pregnancy in EDEN and Elfe. FFQs comprised a variety of items in each cohort, along with their frequencies of consumption and portion sizes, thus allowing us to assess the daily intake of each item (g/d). The micronutrient, macronutrient and total energy intake were also calculated at the individual level. Description of the methodology to assess the dietary data was published in detail elsewhere (10, 20–23). A sub-sample of 998 fathers completed a short FFQ based on diet in the months before the beginning of their partner's pregnancy in the Elfe study (23), while in Lifeways, 333 fathers also completed a similar FFQ providing information on their habitual diet for the last year from after booking visit when mothers were recruited (10).

Diet quality was assessed by degree of adherence to the dietary approach to stop hypertension (DASH) score, while the dietary inflammatory potential was determined using the energy-adjusted dietary inflammatory index (E-DII) (18). We collectively decided to use established *a priori* scores such as the DASH (18) and the E-DII (24) rather than create *a posteriori (data-driven)* dietary patterns that would possibly be cohort-dependent. In brief, the DASH score measured the consumption of eight food components based on cohort-quintile rankings for an overall score ranking from 8 to 40 points with a higher score characterizing a higher diet quality (18). The E-DII score measured the intake of food parameters with a pro- or anti-inflammatory potential. All the food parameter-specific E-DII scores are summed to obtain the overall E-DII score with a positive score indicating a more proinflammatory diet, whereas a negative score indicating a more anti-inflammatory diet (24). For EDEN, Lifeways and Generation R, these two scores were for maternal diet generated using a harmonised procedure (described in Supplementary Text 1) within the ERA-Net HDHL ALPHABET project (18, 25). In Elfe, the maternal DASH score was created following a similar methodology among mothers, but was not available for fathers; we thus used the food groups that were coherent with those constituting the DASH score (such as fruit, vegetables, meat), and for which we had at least 50% of consumers. For paternal diet, E-DII was available in Lifeways only.

2.5. Physical activity data

Physical activity data were available in the EDEN, Elfe and Lifeways cohorts. In EDEN, women completed an adapted French version of the Baecke questionnaire, validated measure of habitual physical activity for adults (26, 27). This questionnaire was administered at the 24–28 weeks pregnancy visit and refers to the frequency of physical activities during the first trimester of pregnancy. In Elfe, 15,544 women completed the self-administered Pregnancy Physical Activity Questionnaire, specifically designed and validated to assess physical activities among pregnant women (28, 29). Respondents were asked to report the time spent participating in 32 activities during the last three months of pregnancy. The different questionnaires reported information on occupational, sports, leisure-time activity, household/caregiving and sedentary activities (see Supplementary Text 1). In Lifeways, at recruitment during their first antenatal visit mothers were given a questionnaire with sections relating to general health, lifestyle and social characteristics to complete and return by email. The mothers' participating partner (biological father) also returned the baseline self-completed questionnaire. The questions relating to physical activity have been used in the Irish National Surveys of Lifestyle Attitudes and Nutrition 1998, 2002, 2007 (30–32). Respondents were asked "considering a 7 day period (a week), how many times on average do you do the following kinds of exercise (mild, moderate and strenuous, with examples provided for each) for more than 20 min during your free/leisure time?"

2.6. Outcomes

Child BMI was assessed using weight and height measurements collected from the clinical examinations, the child's health booklet or assessed by parents between 5 and 12 years. We considered two or three age ranges depending on each cohort, which corresponded either to the clinical examinations in the study or to key points in the child's development. In each cohort, we used the International Obesity Task Force (IOTF) references and cut-offs to assess BMI *z*-score and risk of overweight, obesity and thinness, taking child sex and age into account (33). We investigated the risk of child overweight and obesity (OW-OB) by combining the categories of overweight/obesity vs. thin/normal BMI (the equivalent of <25 kg/m^2).

We considered as secondary outcome the age at adiposity rebound AR (available in EDEN, Elfe and Generation R); the timing of AR, independent of BMI itself, being a relevant predictor of obesity in later childhood and adulthood (34).

2.7. Covariates

Important covariates were identified and harmonized for subsequent analyses. These include maternal and paternal age (in years), education level according to the International Standard Classification of Education (low [no education; early childhood; pre-primary; primary; lower secondary or second stage of basic education]/medium [Upper secondary, Post-secondary non-tertiary]/high [Short cycle tertiary, Bachelor, Masters, Doctoral or equivalent]), employment status ((self)employed/not employed: unemployed, housewife, student, inactive/other); geographical origin (born outside the cohort country or not); maternal parity (primiparous/multiparous); and total yearly household income categorized into quartiles in EDEN and Elfe, based on national distribution of household yearly income (low/medium-low/medium-high/high). The household's total net income per week (take-home family weekly income from all sources including social benefits) was categorized as <600 or ≥600 £/week in Lifeways. In the Generation R cohort, household income data were categorized as follows: ≤1,200, 1,201–2,200, >2,200 €/month. These data were originally collected by questionnaires (interviewer- or self-administered) or abstracted from birth medical records. Data are expressed in different units and categories in different studies, thus we used harmonized data for downstream analysis.

2.8. Statistical analyses

2.8.1. Principal component analysis

We derived "lifestyle patterns" using principal component analysis (PCA) (35). PCA is both a global and an integrated method to synthetize the information contained in a large number of correlated factors into a smaller number of independent dimensions (or "components"). Their number was selected considering eigenvalues >1.0, the scree plot, and their interpretability. To interpret the results and provide a label for a given pattern, we considered the variables most strongly related to that pattern, and those for which the absolute value of the factor loading (which is the correlation of each standardized variable with the given lifestyle pattern) was >0.30. An individual score for each lifestyle pattern was calculated by summing the observed standardized values of each variable weighted according to the PCA factor loadings. Because PCA is sensitive to outliers, we also checked results by excluding some extreme values, when necessary (i.e., for maternal BMI). Analyses were conducted within each cohort separately with the maximum of available variables per cohort: we considered that at least 4 variables were requested for a given period (preconception and pregnancy) to compute the PCAs. Due to insufficient available information related to preconception in the Lifeways cohort, we did not consider this cohort for this period. PCAs were performed using imputation with the missMDA R package (36). This package can be used to perform single imputation to complete data involving continuous, categorical and mixed variables (i.e., data with different types of variables). As it is based on a principal component method, imputation considers both similarities between individuals and correlations between variables. We used the regularized iterative PCA algorithm for imputation of the missing values using the values predicted by iterative PCA until convergence. When using imputation, we selected individuals with information on at least one variable to be included in the PCA. PCAs were run at each period separately and in two steps: first including maternal variables only and, second, using both maternal and paternal variables.

2.9. Regression models

We assessed the associations of the identified maternal or parental lifestyle patterns at each period, with the risk of child OW-OB between 5 and 12 years of age using multivariable logistic regression models. Based on literature and identification of available information in the different studies, the following set of *a priori* covariates was adjusted for: maternal and paternal age, education level, employment status, geographic origin, family household income and maternal parity. Secondly, we studied the associations between the identified lifestyle patterns, included in the same model, with both the child's BMI *z*-score and age at AR (when available) using multivariable linear regressions (adjusted for the same confounders desribed above, and for child sex when the outcome is age at AR). We checked that there was no collinearity between all covariates by using the variance inflation factor (considering the threshold of collinearity when variance inflation factor, VIF > 3). Confounders were imputed using the "MICE" R package that imputes incomplete multivariate data by chained equations. We generated 20 imputed datasets, using logistic regression, multinomial logit model, and predictive mean matching for categorical and quantitative variables (37) (see Supplementary Tables S3–S6). Finally, as a sensitivity analysis, we re-ran all the analyses restricted to complete cases, and results were consistent (data not shown). Specific estimates were obtained for each cohort. Analyses were performed using R studio (for PCA and imputation), and SAS or R studio (for regression models). Statistical significance was defined as p-values <0.05, two-tailed.

3. Results

3.1. Descriptive results

Parental characteristics of the samples included in the analyses are presented in Table 1. On average, across cohorts, mothers, and fathers were 30 and 33 years old. The prevalence of parental obesity varied between 8.2 and 10% for mothers; and 8.1 and 15.7% for fathers. From 50 to 57% of mothers had a high education level in the French cohorts and Lifeways, whereas it was 43% in Generation R. Overall, 36 to 42% of women smoked before pregnancy in EDEN and Elfe, 39% in Generation R and 52% in Lifeways. This percentage decreases during pregnancy to 27% in EDEN, 20% in Elfe, 18% in Generation R and 22% in Lifeways. The percentage of paternal smoking before pregnancy was 44% in EDEN and 52% in Lifeways.

3.2. Preconception parental lifestyle patterns and associations with child risk of overweight and BMI *z*-score

We identified various maternal and parental lifestyle patterns in preconception (Table 2). Consistent patterns were identified in EDEN and Generation R, the first one being characterized by "parental smoking and low maternal diet quality." As expected, the DASH and the E-DII scores were associated with opposite factor loadings to this pattern since they are negatively correlated. Low diet quality was used to label patterns characterized by high DASH and low E-DII scores. The second pattern was labelled "high parental BMI and low smoking." A third pattern was characterized by "high parental smoking, BMI, and high maternal diet quality." Consistent patterns were identified when only maternal factors were included in the PCAs (Table 2). In Elfe, three other patterns were characterized by "low paternal diet quality," "high parental BMI, maternal smoking and low paternal consumption of vegetables," "high paternal BMI, paternal consumption of vegetables and low maternal smoking." Factor loadings of the parental lifestyle patterns in the preconception period are presented in Supplementary Table S7. We reported that the parental lifestyle pattern characterized by a high parental BMI and low smoking was positively associated with child risk of OW-OB at 5 years in both EDEN and Generation R (OR [95% CI] = 1.59 [1.33;1.89], and 1.63 [1.52;1.74] respectively, per 1 standard-deviation (SD) increase in the score) (Table 3). Consistent findings were observed at later ages (until 12 years) regarding risk of OW-OB, higher child BMI *z*-score (Supplementary Table S8), and with a similar maternal lifestyle pattern (Supplementary Table S9). The pattern characterized by high parental smoking, BMI and high maternal diet quality was also associated with higher risk of OW-OB at 5 years in EDEN and Generation R (OR = 1.37 [1.11;170], and 1.34 [1.25;1.44] respectively, per 1 SD increase), and higher child BMI *z*-score (p-values < 0.05). In Elfe, the pattern with high parental BMI, maternal smoking, and low paternal consumption of vegetables was positively associated with the risk of OW-OB (OR = 1.34 [1.01; 1.79]). Finally, an increase of score in the pattern characterized by high parental smoking, and low maternal diet quality was associated with higher risk of OW-OB at 5 and 9 years in Generation R (OR = 1.13 [1.07; 1.19] at 5 years) (Table 3).

3.3. Pregnancy parental lifestyle patterns and associations with child risk of overweight and BMI *z*-score

Regarding the pregnancy period (Table 2), a first pattern was consistent with the one described in preconception with "parental smoking and low maternal diet quality" as common characteristics

TABLE 2 Summary of PCA results in preconception and pregnancy.

	EDEN	Elfe[a]	Gen R	Lifeways
Preconception period				
Family patterns in preconception	N = 1981 Parental smoking and low maternal diet quality (32.9%) High parental BMI and low smoking (20.4%) High parental smoking, BMI, and high maternal diet quality (17.8%)	N = 917 Low paternal diet quality (21.1%) High parental BMI, maternal smoking and low paternal consumption of vegetables (18%) High paternal BMI, consumption of vegetables and low maternal smoking (15.1%)	N = 8,352 High parental smoking and low maternal diet quality (31.8%) High parental BMI and low smoking (19.7%) High parental smoking, high paternal BMI and high maternal diet quality (16.9%)	NA
Maternal lifestyle patterns in pre-conception	N = 1981 High smoking and diet inflammatory potential & low DASH (43.8%) High BMI and rather low smoking (25.3%)	NA	N = 8,156 High smoking, diet inflammatory potential & low DASH (42.1%) High BMI, and low smoking (25.6%)	NA
Pregnancy period				
Family patterns in pregnancy	N = 1962 High parental smoking, low maternal diet quality and low leisure PA (20.2%) Low parental BMI and high GWG (13.6%) Parental smoking, low GWG and low maternal work PA (11.3%)	N = 17,904 High parental smoking, low maternal diet quality and maternal sedentary (16.3%) Low parental BMI and high GWG (13.4%) High maternal physical activity (12.8%) High GWG, maternal sedentary and occupational PA (10.6%)	N = 8,765 High parental smoking, low maternal diet quality (27.2%) Low parental BMI, high GWG (18.9%)	N = 932 High parental smoking, inflammatory diet, low maternal DASH, and rather low paternal PA (25.2%)
Maternal lifestyle patterns in pregnancy	N = 1925 Low smoking, high diet quality and leisure PA (23.5%) Low BMI and high GWG (15.9%) Smoking and high sport PA (13.1%)	N = 17,879 High BMI, smoking, low diet quality, high household PA and sedentary (17.4%) High diet quality, and high PA (15.9%) Low BMI, high GWG, smoking, high PA (15.6%)	N = 8,546 High BMI, smoking, low diet quality (34.7%) Low BMI and high GWG, and smoking (24.3%)	N = 931 Smoking, and low diet quality (35.4%) Low BMI and high PA (21.1%)

Lifestyle pattern labels and proportion of variance explained (%). PA, physical activity. Results are presented with imputation for all cohorts. [a]Elfe results on complete cases for the preconception period. Contrary low diet quality = low DASH and high E-DII scores.

between all cohorts. A second one was essentially defined by weight status as "low parental BMI and high GWG" in EDEN, Elfe and Generation R. Of note, a great coherence was observed when only maternal factors were included (Table 2).

In generation R, we observed a positive association between the lifestyle pattern with "high parental smoking, low maternal diet quality" and the risk of OW-OB, while the parental lifestyle pattern characterized by a low parental BMI and high GWG was negatively associated with risk of OW-OB and child BMI z-score in EDEN, Elfe and Generation R (Table 4 and Supplementary Table S10). We also found that another pattern characterized by parental smoking, low maternal diet quality and maternal sedentary behaviour was positively associated with a higher risk of OW-OB in Elfe (OR [95% CI] = 1.31 [1.23; 1.40]), and higher child BMI z-score at 5 years. In Elfe, the one SD score increase on the pattern labeled "high GWG, sedentary and occupational PA" was also associated with higher risk of OW-OB (OR = 1.17 [1.09; 1.26]), and higher child BMI z-score. Associations were consistent at later ages. No significant associations were reported in Lifeways and effect sizes were smaller than in the other cohorts. Consistent findings were observed with maternal lifestyle patterns (Supplementary Table S11).

3.4. Associations with age at adiposity rebound (AR)

The associations of parental lifestyle patterns with age at AR are documented in Table 5. Results for the associations with maternal lifestyle patterns are shown in Supplementary Tables S9, S11.

In preconception, we found that a parental lifestyle pattern defined by high parental BMI and low smoking was associated with an earlier age at AR in EDEN and Generation R [β (95% CI) = −82.5 (−106.1; −58.9) in days, per 1 SD increase in the score] and [β = −114.7 (−126.0; −103.4)], respectively. Similar findings were found with the maternal lifestyle pattern also characterized by a

TABLE 3 Associations of preconception family lifestyle patterns with child risk of overweight between 5 and 12years.

IOTF overweight/obesity adjusted OR [95% CI]										
EDEN				Elfe				Gen R		
	5.5years (*N* =1,143)	8years (*N* =737)	12years (*N* =706)		5years (*N* =638)	7years (*N* =493)	9years (*N* =352)		5years (*N* =5,778)	9years (*N* =4,926)
"Parental smoking and low maternal diet quality"	1.12 [0.94–1.35]	0.90 [0.74–1.09]	1.21 [1.00–1.47]*	"Low paternal diet quality"	1.06 [0.77–1.46]	1.10 [0.78–1.56]	0.82 [0.53–1.27]	"High parental smoking, and low maternal diet quality"	1.13 [1.07–1.19]*	1.17 [1.10–1.24]*
"High parental BMI and low smoking"	1.59 [1.33–1.89]*	1.64 [1.35–2.01]*	1.57 [1.28–1.92]*	"High parental BMI, maternal smoking and low paternal consumption of vegetables"	1.34 [1.01–1.79]*	1.84 [1.34–2.53]*	1.88 [1.28–2.76]*	"High parental BMI and low smoking"	1.63 [1.52–1.74]*	1.69 [1.57–1.82]*
"High parental smoking, BMI and high maternal diet quality"	1.37 [1.11–1.70]*	1.54 [1.21–1.97]*	1.44 [1.12–1.85]*	"High paternal BMI, high consumption of vegetables and low maternal smoking"	1.78 [1.31–2.44]*	1.37 [0.99–1.90]	1.51 [1.04–2.19]*	"High parental smoking, high paternal BMI, and high maternal diet quality"	1.34 [1.25–1.44]*	1.36 [1.26–1.47]*

Lifeways study is not included because of the lack of information on behaviors during the pre-conception period. Models are adjusted for parental age, born abroad or not, parental education, parental employment status, parity, household income. Results are presented using imputed lifestyle patterns (except for Elfe). *Significant associations $p < 0.05$. **IOTF overweight/obesity vs. underweight/normal BMI (reference). OR values of logistic regression and 95% CIs for 1 SD increase in lifestyle pattern score.

high BMI and low smoking (Supplementary Table S9). We observed that a pattern with "high parental smoking, and low maternal diet quality" was associated with decreased age at AR in Generation R [$\beta = -20.8$ (-30.1; -11.6)]. Finally, patterns with "high parental smoking, BMI and high maternal diet quality" in EDEN and Generation R or "high parental BMI, high paternal consumption of vegetables and low maternal smoking" in Elfe were associated with an earlier age at AR (Table 5).

In pregnancy, a parental lifestyle pattern defined by low parental BMI and high GWG was associated with later age at AR in all cohorts. In Generation R, a pattern with high parental smoking, low maternal diet quality was also associated with earlier age at AR. In Elfe, a pattern combining high parental smoking, low maternal diet quality and maternal sedentary lifestyle, was associated with reduced age at AR [β (95% CI) = -41.3 (-49.4; -33.1)] (Table 5); inversely, a pattern with higher maternal physical activity was associated with later age at AR. Lastly, a pattern defined by high GWG, sedentary lifestyle and occupational PA in Elfe was associated with an earlier age at AR [β (95% CI) = -24.5 (-33.4; -15.5]. Maternal patterns characterized by factors such as high BMI, smoking, low diet quality, high household PA and sedentary lifestyle were associated with an earlier age at AR (Supplementary Table S11).

4. Discussion

In this large collaborative project with harmonized participant data across four European cohorts, we identified various parental lifestyle patterns in the preconception period and during pregnancy with great consistency between countries. The two patterns explaining the most variance in pregnancy were characterized by "high parental smoking, low maternal diet quality and high maternal sedentary behavior" and by "high parental BMI and low gestational weight gain." Overall, we found that lifestyle patterns characterized by high parental BMI, smoking, low diet quality or high sedentary lifestyle were positively associated with risk of OW-OB and child BMI z-score in children aged between 5 and 12 years. Although parental BMI was included in most of the patterns associated with the risk of obesity in children, it is noteworthy that a pattern independent of BMI and characterized by high parental smoking and low maternal diet quality in preconception, was associated with higher OW-OB in both the Generation R and EDEN cohorts. In Elfe, two other patterns of multiple behaviors in pregnancy, i.e., "parental smoking, low maternal diet quality and high maternal sedentary behavior" and "high GWG, sedentary behavior and occupational physical activity" were also associated with higher risk of OW-OB and higher child BMI z-score.

TABLE 4 Associations of pregnancy family lifestyle patterns with child risk of overweight between 5 and 12years.

IOTF overweight/obesity adjusted OR [95% CI]**													
EDEN				Elfe				Gen R			Lifeways		
	5.5years (*N*=1,143)	8years (*N*=737)	12years (*N*=706)		5years (*N*=9,335)	7years (*N*=3,826)	9years (*N*=3,339)		5years (*N*=6,117)	9years (*N*=5,227)		5years (*N*=534)	9years (*N*=289)
"High parental smoking, low maternal diet quality and low leisure PA"	1.20 [1.00–1.44]	1.11 [0.90–1.36]	1.14 [0.95–1.39]	"High parental smoking, low maternal diet quality and maternal sedentary"	1.31 [1.23–1.40]*	1.34 [1.21–1.48]*	1.32 [1.19–1.47]*	"High parental smoking, low maternal diet quality"	1.12 [1.06–1.18]*	1.14 [1.08–1.21]*	"High maternal and paternal smoking & inflammatory diet, low maternal DASH diet, low paternal PA"	1.06 [0.92–1.23]	1.04 [0.85–1.27]
"Low parental BMI and high GWG"	0.70 [0.58–0.83]*	0.67 [0.54–0.81]*	0.76 [0.62–0.93]*	"Low parental BMI and high GWG"	0.83 [0.78–0.88]*	0.71 [0.65–0.78]*	0.73 [0.66–0.80]*	"Low parental BMI, high GWG"	0.75 [0.71–0.79]*	0.71 [0.67–0.76]*			
"Parental smoking, low GWG and low maternal work PA"	1.01 [0.82–1.26]	0.80 [0.62–1.01]	1.14 [0.91–1.44]	"High maternal physical activity"	0.95 [0.89–1.02]	1.00 [0.90–1.10]	0.93 [0.83–1.04]						
				"High GWG, sedentary and occupational PA"	1.17 [1.09–1.26]*	1.25 [1.12–1.39]*	1.23 [1.10–1.38]*						

Models are adjusted for parental age, born abroad or not, parental education, parental employment status, parity, household income. For Lifeways, models were not adjusted for paternal employment status (almost all cases reported being employed/self-employed) and on country of birth (maternal birth outside Ireland was an exclusion criterion). *Significant associations $p < 0.05$. **IOTF overweight/obesity vs. underweight/normal BMI (reference). OR values of logistic regression and 95% CIs for 1 SD increase in lifestyle pattern score.

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TABLE 5 Associations of preconception and pregnancy family lifestyle patterns with age at adiposity rebound.

Age at adiposity rebound (days) adjusted β [95% CI]					
Preconception family patterns					
EDEN (*N*=1,415)		**Elfe (*N* =649)**		**Gen R (*N* =5,922)**	
"Parental smoking and low maternal diet quality"	−8.6 [−29.0; 11.7]	"Low paternal diet quality"	4.9 [−28.6; 38.4]	"High parental smoking, and low maternal diet quality"	−20.8 [−30.1; −11.6]*
"High parental BMI and low smoking"	−82.5 [−106.1; −58.9]*	"High parental BMI, maternal smoking and low paternal consumption of vegetables"	−105.5 [−139.7; −71.3]*	"High parental BMI and low smoking"	−114.7 [−126.0; −103.4]*
"High parental smoking, BMI, and high maternal diet quality"	−53.2 [−78.2; −28.1]*	"High paternal BMI, high consumption of vegetables and low maternal smoking"	−54.4 [−86.9; −22.0]*	"High parental smoking, high paternal BMI and high maternal diet quality"	−69.9 [−81.7; −58.1]*
Pregnancy family patterns					
EDEN (*N*=1,415)		**Elfe (*N* =7,767)**		**Gen R (*N* =6,299)**	
"High parental smoking, low maternal diet quality and low leisure PA"	−14.3 [−35.2; 6.7]	"High parental smoking, low maternal diet quality and maternal sedentary"	−41.3 [−49.4; −33.1]*	"High parental smoking, low maternal diet quality"	−19.7 [−29.1; −10.4]*
"Low parental BMI and high GWG"	65.8 [42.8; 88.9]*	"Low parental BMI and high GWG"	52.0 [43.5; 59.8]*	"Low parental BMI, high GWG"	64.0 [53.2; 74.8]*
"Parental smoking, low GWG and low maternal work PA"	−5.6 [−31.8; 20.7]	"High maternal physical activity"	9.6 [1.6; 17.7]*		
		"High GWG, sedentary and occupation PA"	−24.4 [−33.4; −15.5]*		

Models are adjusted for parental age, born abroad or not, parental education, parental employment status, parity, household income and child sex. Results are presented using imputed lifestyle patterns (excepted for Elfe for the preconception period). *Significant associations $p < 0.05$. β values of linear regression and 95% CIs for 1 SD increase in lifestyle pattern score.

Finally, it is also interesting to note that the observation of early AR was higher with suboptimal parental lifestyle patterns. The results of our study, which is, to the best of our knowledge, the first to simultaneously analyze child OW-OB risk and age at AR in relation to parental lifestyle patterns in the preconception and pregnancy periods, represent a novel and significant contribution to the knowledge base regarding family-based and multi-behavioral child obesity prevention strategies from early life onwards.

4.1. Interpretation

Obesity is a multifactorial disease and its etiology includes complex interactions between several factors (38). On a population level, it is estimated that up to 50% of childhood OW-OB could be attributed to modifiable family-centered early-life risk factors (39, 40). Family lifestyle factors are often correlated and co-vary, and may contribute synergistically to obesity development (38). The lifestyle pattern approach used in our study allowed us to account for the potential covariation and correlations between lifestyle factors, thus providing more holistic and integrated information for public health prevention. Growing evidence suggests the potential for multiple-behavior interventions to have a greater impact on public health than single-behavior interventions (41). Additionally, success in changing one or more lifestyle behaviors of the mother may also increase confidence or self-efficacy to improve correlated lifestyle behaviors of the father, and vice versa (41).

Recent scientific evidence has highlighted the need to include fathers in lifestyle and health interventions spanning the first 1,000 days. Paternal factors, including BMI and smoking, have been associated with fertility, imprinting of genes during spermatogenesis, embryonic, and future child development (42). Partners play a role in supporting future mothers, thus contributing to successful behavioural changes at the family level (43, 44). One study reported that the smoking status of a pregnant smoker's partner influences her chances of quitting (44, 45). Other results showed that fathers may influence family food practices, and what is consumed within families is the product of interactions and negotiations between family members (46). Pregnancy is also an important time when parents, who play the role of health promoters, role models and educators in their offspring life, may be more susceptible, to make better lifestyle choices to positively impact their future baby's health and influence their future behaviors (47). Parents are an integral target of interventions, given their influence in supporting and managing their children's energy balance-related behaviors (43, 48).

Most studies have evaluated the effects of parental factors separately, with only few having studied the combined effect of these factors in the first 1,000 days (12, 49, 50). The Millennium Cohort Study investigated the dynamic relation between underlying family lifestyle (especially parental weight and smoking status, exclusive breastfeeding duration; and child behaviors between birth and 7 years) and childhood obesity until 7 years. They found that the proportion of variance in childhood weight status explained by underlying family lifestyle increases from 7.0% at age 3 to 11.3% by the age of 7 years, suggesting that improvements to the family lifestyle could substantially reduce the risk of childhood obesity (12). Another recent study of 114 mother–father–child triads evaluated the independent contributions of body composition, physical activity and sedentary time of both parents in pregnancy on growth trajectories of their offspring until 1 year of age (49). They reported a positive association between maternal GWG and paternal sedentary time and weight trajectories in girls, while there was a negative association with maternal moderate-to-vigorous PA (49). These results are in line with our observations regarding the association between lifestyle patterns characterized by high parental BMI or sedentary behaviors from preconception onwards and the risk of childhood obesity.

Regarding parental BMI, it is difficult to disentangle the relative contribution of environmental and genetic factors in the observed associations with offspring BMI or obesity risk. A systematic review found BMI heritability estimates from twin studies that ranged from 0.47 to 0.90 (51). Using a Mendelian randomisation approach, another recent study reported a low causal intrauterine effect of greater maternal BMI on later offspring adiposity and highlighted the importance of genetic transmission (52). Therefore, genetic inheritance could have a preponderant role in our results. However, recent evidence reports that the obesity epidemic cannot be solely explained by sudden changes in our genetic background, but is also attributed to the environment, energy balance-related behaviors or modifiable factors involved in programming including family lifestyle in the first 1,000 days (53, 54). In this context, parental lifestyle factors, including diet, physical activity or smoking are relevant behaviors to target. Moreover, the more lifestyle factors adopted during one pregnancy are optimal, the healthier are behaviors in subsequent pregnancies.

4.2. Strengths and limitations

To our knowledge, this is the largest multi-country study to evaluate the overall parental lifestyle patterns in preconception and during pregnancy to date. We aimed to reduce extraneous heterogeneity by harmonizing data across included studies, using information on several parental lifestyle factors in preconception and pregnancy: weight, smoking status, diet, and physical activity. We acknowledge that this harmonized approach can lead to some oversimplification in definitions and a subsequent loss of information for certain variables; and that more precise analyses could be carried out within each cohort using the initial non-harmonized variables. Besides, some information was missing, such as physical activity in Generation R, or was insufficient in the preconception period as in Lifeways. Nevertheless, this harmonized approach allowed us to report consistent findings across cohorts, in a greater number of children, thus reinforcing robustness of our conclusions. The use of multiple imputation techniques limited selection bias due to missing data in the lifestyle variables and confounders.

However, our findings should be interpreted with caution. Diet measures were based on FFQs with different degree of detail (number of food items, response categories, etc.) which could result in discrepancies in estimated intakes and diet scores. The fact that we have differences in the measurement of some lifestyle factors could explain why they are less frequently reported in the associations, and that BMI, which is more accurately measured, is an important factor in the patterns. Additionally, self-reported information on diet and physical activities are memory based and subject to well-known reporting and social desirability biases, that can introduce random error and information bias. However, FFQ is a validated tool, which limits such potential bias. Notwithstanding the fact that we performed our analyses using data from three different European countries with potential for differences in dietary intake, BMI, smoking status, and sociodemographic characteristics, the results of our study samples can mainly be generalized to women in high-income countries. However, it is worth noting that we found similar associations in EDEN, including mainly French pregnant women and Generation R, with a large proportion of children ethnicities other than Dutch (44%) (16). We focused on the family lifestyle patterns in the preconception and pregnancy period, however, family practices in the early childhood period influence the child development as well (4). Further research is warranted to investigate how the dynamic path of lifestyle changes throughout pregnancy until early childhood may have synergistic influences. Finally, a large difference in the prevalence of childhood obesity between advantaged and disadvantaged families is reported in the literature (12). We adjusted our analyses for some socioeconomic characteristics, however further research should be conducted to investigate the social determinants of the identified family lifestyle patterns, with a specific focus on socio-economic inequalities, migration history and geographic origin.

5. Conclusion

Among the various lifestyle patterns identified in the four European cohorts, the two explaining the most variance in pregnancy were characterized by "high parental smoking, low maternal diet quality or high maternal sedentary behavior" and, by "high parental BMI and low GWG." The observed associations between the identified parental lifestyle patterns and the child's risk of obesity from the age of 5 years underlines the importance of family and multi-behavioral approaches. Our findings represent a significant contribution to the knowledge regarding the importance of parental lifestyle factors from preconception. A better understanding of their social determinants will help increase the effectiveness of future childhood obesity prevention strategies in early life.

Data availability statement

Datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Bicêtre Hospital for the EDEN study, Ethics committee (Comité de Protection des Personnes), the national committee on information concerning health research (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le domaine de la Santé), and the data protection authority (Commission Nationale de l'Informatique et des Libertés) for

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Author contributions

ML, RG, BH, and SL: conceptualization. ML, MG, MT, AD, JH, BL-G, and BH: data curation. ML, MS, AO'D, AA, BH, and SL: formal analysis. CP, RG, and BH: funding acquisition and resources. CP, RG, BH, and SL: investigation. ML, CP, RG, BH, and SL: methodology. CP, RG, CK, and BH: project administration. ML: software. BH and SL: supervision and validation. ML, BH, and SL: visualization and writing – original draft preparation. ML, MS, AO'D, AA, MT, MG, AD, JH, BL-G, CK, M-AC, CP, RG, BH, and SL: writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

JH owns controlling interest in Connecting Health Innovations, a company that has licensed the right to his invention of the dietary inflammatory index from the University of South Carolina to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings.

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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1166981/full#supplementary-material

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Vitamin D intake and determinants of vitamin D status during pregnancy in The Norwegian Mother, Father and Child Cohort Study

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Background: Norwegian data on vitamin D status among pregnant women indicate a moderate to high prevalence of insufficient vitamin D status (25-hydroxyvitamin D (25OHD) concentrations ≤50 nmol/L). There is a lack of population-based research on vitamin D intake and determinants of 25OHD in pregnant women from northern latitudes. The aims of this study were (1) to evaluate total vitamin D intake from both diet and supplements, (2) to investigate determinants of vitamin D status, and (3) to investigate the predicted response in vitamin D status by total vitamin D intake, in pregnant Norwegian women.

Methods: In total, 2,960 pregnant women from The Norwegian Environmental Biobank, a sub-study within The Norwegian Mother, Father and Child Cohort Study (MoBa), were included. Total vitamin D intake was estimated from a food frequency questionnaire in gestational week 22. Concentrations of plasma 25OHD was analyzed by automated chemiluminescent microparticle immunoassay method in gestational week 18. Candidate determinant variables of 25OHD were chosen using stepwise backward selection and investigated using multivariable linear regression. Predicted 25OHD by total vitamin D intake, overall and stratified by season and pre-pregnancy BMI, was explored using restricted cubic splines in an adjusted linear regression.

Results: Overall, about 61% of the women had a total vitamin D intake below the recommended intake. The main contributors to total vitamin D intake were vitamin D supplements, fish, and fortified margarine. Higher 25OHD concentrations were associated with (in descending order of the beta estimates) summer season, use of solarium, higher vitamin D intake from supplements, origin from high income country, lower pre-pregnancy BMI, higher age, higher vitamin D intake from foods, no smoking during pregnancy, higher education and energy intake. During October–May, a vitamin D intake according to the recommended intake was predicted to reach sufficient 25OHD concentrations >50 nmol/L.

Conclusion: The findings from this study highlight the importance of the vitamin D intake, as one of few modifiable determinants, to reach sufficient 25OHD concentrations during months when dermal synthesis of vitamin D is absent.

KEYWORDS

determinants, vitamin D intake, 25-hydroxyvitamin D, pregnancy, The Norwegian Mother, Father and Child Cohort Study (MoBa)

1. Introduction

The importance of vitamin D throughout life is widely acknowledged, although it is likely that some of its biological functions have not yet been discovered. Vitamin D is obtained from dermal synthesis induced by solar exposure and intake from foods and supplements (1, 2). After endogenous synthesis or absorption, vitamin D is hydroxylated in a two-step process, formation of: (1) the biomarker 25-hydroxyvitamin D (25OHD) and (2) the biologically active metabolite 1,25-dihydroxyvitamin D (1,25OH2D) (3). The main role of 1,25OH2D is to ensure adequate concentrations of calcium and phosphate in plasma (3, 4). However, in early pregnancy, the vitamin D metabolism change and maternal concentrations of 1,25OH2D rise, provided that maternal concentration of 25OHD is sufficient (5, 6). The reason for the alterations in vitamin D metabolism is not entirely clear (6, 7). Besides skeletal health (8), vitamin D has also been studied for its potential associations with a range of detrimental maternal and neonatal outcomes, including preeclampsia, gestational diabetes, and low birth weight (9, 10). For these associations, the evidence of causality is insufficient.

Despite the many potential health effects, recommended concentrations of the biomarker 25OHD are based on the role of 1,25OH2D for skeletal health (11–13). In the Nordic Nutrition Recommendations 2012 (NNR 2012), a 25OHD concentration >50 nmol/L define sufficiency, 30–50 nmol/L define insufficiency, and < 30 nmol/L define deficiency, in both pregnant and non-pregnant individuals (13). To achieve concentrations of 25OHD >50 nmol/L, the NNR 2012 set the average requirement (AR) and the recommended intake (RI) of vitamin D for adults, including pregnant women, to 7.5 μg/day and 10 μg/day, respectively. An intake of 20 μg/day is recommended for those with little or no sun exposure, or who are older than 75 years of age. In Norway, the adult population is recommended to supplement with 10 μg/day of vitamin D if sun exposure and the intake of vitamin D rich foods are low (14, 15). Pregnant women in Norway are given the advice to supplement with vitamin D if fatty fish consumption is less than 2–3 times/week (16). Fish and eggs are some of the foods that naturally contain vitamin D, while margarine, butter, and some fat-reduced milk are fortified with vitamin D in Norway (15).

No study has previously investigated a broad spectrum of determinants of vitamin D status, also including the vitamin D intake from foods and supplements in a pregnant Norwegian population. As dermal synthesis of vitamin D can only occur from late spring (April–May) to early autumn (August–September) in the Nordic countries (17), sufficient vitamin D intake is important to maintain adequate vitamin D status during the rest of the year. Due to increased calcium requirements during pregnancy, and possible negative effects of insufficient vitamin D status on maternal and neonatal outcomes, the importance of vitamin D sufficiency during pregnancy is highlighted. Thus, there is a need to increase the understanding of how vitamin D intake and other determinants contribute to 25OHD in pregnant women living in Nordic countries. The aims of this study were (1) to evaluate total vitamin D intake from both diet and supplements, (2) to investigate determinants of vitamin D status, and (3) to investigate the predicted response in vitamin D status by total vitamin D intake, in pregnant Norwegian women.

2. Materials and methods

2.1. Study population

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (18). Participants were recruited from all over Norway from 1999 to 2008, and 41% of the invited women consented to participate. The cohort now includes approximately 114,500 children, 95,200 mothers and 75,200 fathers. MoBa data are linked to information from the Medical Birth Registry of Norway, a national health registry containing information about all births in Norway (19). The Norwegian Environmental Biobank is a sub-study within MoBa (20), established with the aim of biomonitoring nutrients and environmental contaminants in MoBa participants. Eligibility of participants in the Norwegian Environmental Biobank required available genetic data, available data from the three questionnaires during pregnancy and the first three postnatal questionnaires, the fathers' questionnaire (21), and available maternal plasma, urine, and whole blood samples. In total, 2,999 women from MoBa were included in the Norwegian Environmental Biobank. Of these 2,988 had the biomarker 25OHD analyzed in pregnancy and were thus eligible for inclusion in the current study. Further, 28 participants (0.9%) with implausible reported daily energy intake below 1,076 kcal (4.5 MJ) or above 4,780 kcal (20 MJ) were excluded from the analyses. These cut-points are used in MoBa to exclude food frequency questionnaires (FFQs) of poor quality and are based on results from the validation study (22). Thus, the final analytic sample consisted of 2,960 pregnant women.

MoBa is conducted according to the guidelines laid down in the declaration of Helsinki and written informed consent was obtained from all participants. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. MoBa is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (REC 2019/770–12172). The current study is based on version 12 of the quality-assured data files released for research in January 2019 (23).

2.2. Assessment of dietary intake and vitamin D supplement use

The women's habitual food consumption and supplement use since becoming pregnant was assessed by a semi-quantitative FFQ including 255 food items answered in gestational week 22 (22, 24, 25). Intake frequency of each item in the FFQ ranged from never to more than eight times a day. Portion size was only specified for liquids, bread, and fruit, while standard Norwegian portion sizes for women were used for all other food items (26). Food intake (g/day) and energy intake (kcal/day) was estimated based on the given intake frequency and portion size. At the time of data collection, the following foods were fortified with vitamin D: margarine and butter (8.0 µg/100 g), fat-reduced milk (0.4 µg/100 g), and lactose free milk (0.4 µg/100 g). In the current study, all foods containing vitamin D were aggregated into eight food groups: fish, margarine, butter, milk, yoghurt, eggs, cheese, and mixed dishes/products containing milk, margarine, butter, and/or egg. The women's intake of these foods (g/day), as well as their contribution to the daily vitamin D intake (µg/day) were calculated. The women's intake of vitamin D from supplements was also calculated, based on the frequency and amount of supplement intake reported in the FFQ. The FFQ listed 13 commonly used cod liver oil/fish oil, vitamin, and mineral supplements followed by six open-ended spaces where respondents were instructed to record the name and manufacturer of supplement(s) used but not listed. For each supplement there were nine options for frequency, ranging from never to daily, and for dose there were three options for liquid supplements and four options for tablets/capsules. For nutrient calculation of the dietary supplements, a database containing the nutrient value of more than 1,000 different food supplements was constructed and continuously updated (24, 27).

The estimated vitamin D intake from foods and supplements has previously been validated in a sub-group of 119 women using a weighed food diary and biomarkers. The results showed fair agreement between reported vitamin D intake and 25OHD with Spearman's rank correlation coefficient (0.32–0.45, $p < 0.01$) and <5% classified into opposing quintiles of vitamin D intake and 25OHD (24, 25).

2.3. Assessment of vitamin D status in plasma

The blood samples were collected in gestational week 18 (mean 18.5, SD 1.3) in connection with the routine ultrasound examination, offered to all pregnant women in Norway (20). Samples were analyzed at the National Institute for Health and Welfare in Helsinki, Finland. Plasma concentrations of 25OHD were analyzed in 2015 using the high through-put automated chemiluminescent microparticle immunoassay method (Architect ci8200 system, Abbott Laboratories, Abbott Park, IL, United States). Both 25OHD2 and 25OHD3 are measured and the sum is reported. The laboratory regularly partake in the Vitamin D External Quality Assessment Scheme and met the performance target set by the advisory panel (28). Coefficient of variation of control samples (Biorad Liquid Assayed Multiqual lot 45,680 high and low level) were 3.7–5.5%.

2.4. Other variables

Maternal age at time of delivery, parity, and country of origin was obtained from the Medical Birth Registry of Norway. Information about education, pre-pregnant weight, height, smoking habits, and use of solarium was obtained from questionnaires, answered around gestational weeks 15 and 30. In gestational weeks 15, participants were also asked about use of vitamin D containing supplements (yes or no) by weekly intervals prior to conception, and in the first trimester.

2.5. Statistical analysis

Dietary intake and supplement use during the first half of pregnancy were described by categories of 25OHD, based on the reference values (<30 nmol/L, 30–49.9 nmol/L, 50–75 nmol/L, >75 nmol/L) in NNR 2012 (13) and National Academy of Medicine (Institute of Medicine) (12). Statistical difference in study population characteristics between the categories of 25OHD were assessed by Kruskal Wallis test.

The candidate determinant variables of vitamin D status were selected based on biological plausibility and included: season at blood sampling (two seasons; June–September, October–May), vitamin D intake from foods (<2.5, 2.5–4.9, 5.0–7.49, ≥7.5 µg/day), supplemental vitamin D intake (none, 0.1–4.9, 5.0–9.9, 10.0–14.9, ≥15.0 µg/day), energy intake (kcal/day), use of solarium during pregnancy (no, 1–5, ≥6 times), country of origin (Norway, other high income country, low/middle income country), education (<13, 13–16, >16 years), pre-pregnancy BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m^2), age (<25, 25–34, >34 years), smoking during pregnancy (yes, no), and parity (nulliparous, multiparous). The variables were checked for multicollinearity using Spearman correlation matrix, and all correlation coefficients were below 0.4. Variables were selected using stepwise backward selection (29) and $p < 0.2$ as cut-off for inclusion. Bootstrap subsampling was used to investigate and quantify the stability of selected variables (30). One hundred resamples were drawn and variable selection was repeated in each of the resamples. Variables included in >50% of the resamples were selected in the final model (30). No variable was excluded after the stability check. Results are presented as a full sample and stratified by season, as season is the main source of vitamin D and that there is a large seasonal variation in 25OHD concentrations in the Nordic countries (17), and pre-pregnancy BMI. The estimates of the determinants of 25OHD concentration in pregnancy were investigated using multivariable linear regression analysis.

The association between the total vitamin D intake and continuous 25OHD, in all women and stratified by season and pre-pregnancy BMI, was explored using restricted cubic splines. Three splines were modeled for the total vitamin D intake, positioned at percentiles 10, 50, and 90 (31). Models were adjusted for country of origin, age, and smoking during pregnancy. The models in all women and stratified by season were additionally adjusted for pre-pregnancy BMI. The overall associations between total vitamin D intake and 25OHD were performed by testing the coefficients of all spline transformations equal to zero. Non-linearity was examined by testing the coefficients of the second spline transformation equal to zero. The associations between use of vitamin D containing supplements before and during pregnancy and maternal concentrations of 25OHD were analyzed by Kruskal Wallis test.

Stata version 16 was used for all statistical analyses (Stata Corporation, College Station, Texas). Significance was accepted at $p < 0.05$.

3. Results

3.1. Study population

Of the 2,960 participants, 72% had a high education (≥13 years) and 5.9% reported smoking during pregnancy (Table 1). Only 4.8% were born in a high-income country other than Norway, and 1.4% were born in a low or middle-income country. There were differences between vitamin D categories with regard to the characteristics of the study population in terms of, e.g., age, education, country of origin, and pre-pregnancy BMI. About 80% of the participants reported use of vitamin D supplement in pregnancy. Around 44% of all women had a total vitamin D intake below AR at 7.5 μg/day and 61% had an intake below RI at 10 μg/day (13). Median (25^{th}–75^{th} percentiles) 25OHD concentration was 51 (38–64) nmol/L.

3.2. Vitamin D from foods and supplements

Overall, the median vitamin D intake from foods was 3.1 μg/day, and the total vitamin D intake (from foods and supplements combined) was 8.3 μg/day (Table 2). Thus, the main contributor to vitamin D intake in pregnancy was vitamin D supplements (66%, Figure 1). The main food sources of vitamin D were fish and fortified margarine.

3.3. Determinants of vitamin D status

There was a difference in vitamin D intake from both foods and supplements between categories of 25OHD concentration, but no differences were observed for intake of energy or other nutrients (Table 2). Among the major food sources of vitamin D, there was a difference. In the consumption of margarine, but not fish or butter, between categories of 25OHD.

In a multivariable linear regression, determinants of 25OHD concentrations in pregnancy were (in descending order of the beta estimates) summer season, use of solarium, higher vitamin D intake from supplements, origin from high income country, lower pre-pregnancy BMI, higher age, higher vitamin D intake from foods, no smoking during pregnancy, higher education and energy intake (Table 3). Together, these variables explained 21% of the variation in 25OHD. During June to September, total vitamin D intake explained 1% of the variation in 25OHD, whereas during October to May, it was 7% (Table 3). Stratified by pre-pregnancy BMI, the total vitamin D intake explained 5% of the variation in 25OHD in women with pre-pregnancy BMI <25 kg/m^2, whereas in women with pre-pregnancy BMI ≥25 kg/m^2, it was 3% (Supplementary Table S1).

3.4. Total vitamin D intake and 25OHD

In the full sample of women, total vitamin D intake >5 μg/day was sufficient to reach predicted 25OHD >50 nmol/L (p-overall: <0.001, p non-linearity: <0.001, Figure 2). The effect of vitamin D intake on 25OHD seemed to level off at reported intakes >15 μg/day.

When total vitamin D intake was stratified by season of blood sampling, women who were sampled during June to September had a predicted 25OHD >50 nmol/L even at very low intakes (p-overall: 0.001, p non-linearity: 0.003, Figure 3A). However, during October to May, a total vitamin D intake ≥10 μg/day was required to reach predicted 25OHD >50 nmol/L (p-overall: <0.001, p non-linearity: 0.023, Figure 3B).

When total vitamin D intake was stratified by pre-pregnancy BMI, women with BMI <25 kg/m^2 had predicted 25OHD >50 nmol/L at vitamin D intakes ≥5 μg/day (p-overall: <0.001, p non-linearity: 0.004, Supplementary Figure S1A). Women with BMI ≥25 kg/m^2 required a vitamin D intake ≥15 μg/day to reach a predicted sufficient 25OHD (p-overall: <0.001, p non-linearity: 0.043, Supplementary Figure S1B).

There was a difference in 25OHD concentrations depending on duration and timing of vitamin D supplement use during pregnancy (Supplementary Table S2). Women who reported any use of vitamin D supplement, either before and/or in early pregnancy, or in mid pregnancy, or both, had a higher 25OHD compared to women who reported no use of vitamin D supplement either before or during pregnancy. Women who reported use of vitamin D supplement both before and/or in early pregnancy and in mid pregnancy had a higher 25OHD compared to those who started to take a supplement in mid pregnancy.

4. Discussion

There is a lack of studies investigating the contribution of vitamin D intake and other determinants of 25OHD in pregnant Nordic women. In this study of 2,960 participants, about 61% had a total vitamin D intake below the RI and about 44% had an intake below the AR. The main contributors to the vitamin D intake were vitamin D supplements, fish, and fortified margarine. The most important determinants of vitamin D status were (in descending order of the beta estimates) season, solarium use, vitamin D intake from supplements, country of origin, pre-pregnancy BMI, age, vitamin D intake from foods, and smoking during pregnancy. During October to May, a vitamin D intake according to the RI was predicted to ensure sufficient 25OHD concentration.

The results from this study emphasize the important contribution of vitamin D supplements to reach RI of vitamin D and as a determinant of 25OHD. More than half of the women in our study had a total vitamin D intake below the RI, and supplements were the main contributor to the total vitamin D intake. Vitamin D intake from foods and supplements in our study was somewhat lower compared to other studies of pregnant women in Norway, Sweden, and Finland (33–36). In Sweden and Finland, more foods are fortified with vitamin D and with higher amounts than in Norway, which might partly explain the differences. A study on pregnant women in Norway found the vitamin D intake from foods and supplements was 4.9 and 5.6 μg/day, respectively (34). The intake from foods was

TABLE 1 Study population characteristics by category of vitamin D status (25OHD) during pregnancy.

		Vitamin D status (25OHD) nmol/L				
	All	<30	30–50	>50–75	>75	*p*-value[b]
	% (*N*)	% (*N*)	% (*N*)	% (*N*)	% (*N*)	
Women	100 (2960)	10.9 (323)	37.4 (1106)	40.9 (1211)	10.8 (320)	
Age (years)						0.026
<25	8.0 (238)	17.6 (42)	37.0 (88)	39.1 (93)	6.3 (15)	
25–34	75.6 (2237)	10.3 (230)	37.7 (844)	41.1 (920)	10.9 (243)	
>34	16.4 (485)	10.5 (51)	35.9 (174)	40.8 (198)	12.8 (62)	
Education (years)						0.003
<13	25.8 (764)	13.9 (106)	37.7 (288)	40.4 (309)	8.0 (61)	
13–16	46.9 (1388)	9.9 (137)	35.7 (496)	42.9 (595)	11.5 (160)	
>16	25.2 (745)	9.3 (69)	39.6 (295)	39.1 (291)	12.1 (90)	
Missing	2.1 (63)	17.5 (11)	42.9 (27)	25.4 (16)	14.3 (9)	
Country of origin[a]						<0.001
Norway	92.0 (2723)	10.4 (283)	37.0 (1007)	41.5 (1129)	11.2 (304)	
Other high-income country	4.8 (141)	14.9 (21)	41.8 (59)	34.8 (49)	8.5 (12)	
Low/middle-income country	1.4 (42)	33.3 (14)	38.1 (16)	26.1 (11)	2.4 (1)	
Missing	1.8 (54)	9.3 (5)	44.4 (24)	40.7 (22)	5.6 (3)	
Pre-pregnancy BMI (kg/m^2)						<0.001
<18.5	2.7 (79)	12.7 (10)	21.5 (17)	51.9 (41)	13.9 (11)	
18.5–24.9	63.7 (1886)	8.7 (164)	36.1 (680)	42.4 (800)	12.8 (242)	
25–29.9	24.1 (712)	13.3 (95)	39.2 (279)	40.2 (286)	7.3 (52)	
≥30	7.7 (229)	19.7 (45)	48.5 (111)	27.9 (64)	3.9 (9)	
Missing	1.8 (54)	16.7 (9)	35.2 (19)	37.0 (20)	11.1 (6)	
Parity						0.020
Nulliparous	51.3 (1519)	9.6 (146)	36.4 (553)	43.3 (657)	10.7 (163)	
Multiparous	48.7 (1441)	12.3 (177)	38.4 (553)	38.4 (554)	10.9 (157)	
Season of blood sampling						<0.001
June–September	30.2 (893)	3.2 (29)	22.4 (200)	53.8 (480)	20.6 (184)	
October–May	69.8 (2086)	14.1 (294)	43.4 (906)	35.0 (731)	6.5 (136)	
Solarium in pregnancy (times)						<0.001
No	86.5 (2569)	11.8 (304)	38.7 (994)	38.9 (1000)	9.6 (247)	
1–5	11.5 (343)	4.7 (16)	29.2 (100)	49.3 (169)	16.3 (56)	
≥6	2.0 (59)	3.4 (2)	16.9 (10)	54.2 (32)	23.7 (14)	
Vitamin D supplement use (≥0.1 μg/day)						<0.001
Yes	80.4 (2379)	9.0 (214)	35.9 (854)	43.2 (1028)	11.9 (283)	
No	9.0 (266)	18.0 (48)	41.0 (109)	35.0 (93)	6.0 (16)	
Missing	10.6 (315)	19.4 (61)	45.4 (143)	28.6 (90)	6.6 (21)	

25OHD, 25-hydroxyvitamin D; BMI, Body Mass Index.
[a]Based on the Global Burden of Disease super regions classification system (32).
[b]Statistical difference between the categories of 25OHD were assessed by Kruskal Wallis test.

higher compared to our study. However, the supplemental intake was similar to our study, along with a similar prevalence (59%) of a vitamin D intake below RI. Different dietary assessment methods might explain the differences in vitamin D intakes. Our results also show that women who reported any use of vitamin D supplement had a higher 25OHD compared to women who reported no use of vitamin D supplement, further highlighting the importance of vitamin D supplements during pregnancy.

The nationwide diet survey Norkost 3 from 2010–2011 found, in both women and men, that the major food sources contributing with

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TABLE 2 Dietary intake and supplement use by categories of vitamin D status during pregnancy.

	Vitamin D status (25OHD) nmol/L					
	All	<30	30–50	>50–75	>75	*p*-value[a]
Women, *N*	2960	323	1106	1211	320	
Reported energy intake, kcal/day	2204 (1876, 2610)	2186 (1914, 2598)	2201 (1866, 2592)	2214 (1877, 2639)	2182 (1898, 2606)	0.854
Total vitamin D intake, µg/day[b]	8.3 (5.2, 13.1)	6.2 (3.7, 8.9)	7.8 (4.8, 11.6)	9.1 (5.5, 14.3)	10.5 (6.4, 17.1)	<0.001
Supplemental vitamin D intake, µg/day	5.0 (2.2, 9.8)	2.6 (0.9, 5.6)	4.3 (1.5, 7.9)	5.4 (2.6, 10.0)	7.2 (2.6, 13.6)	<0.001
Supplemental vitamin D intake, µg/day (users only)[c]	5.2 (2.6, 10.0)	4.0 (2.1, 6.3)	5.0 (2.6, 8.6)	6.3 (2.6, 11.4)	7.5 (3.2, 14.1)	<0.001
Vitamin D intake from food, µg/day	3.1 (2.1, 4.4)	2.9 (1.9, 4.0)	3.1 (2.1, 4.3)	3.2 (2.2, 4.5)	3.4 (2.2, 4.4)	<0.001
Vitamin D from fish, µg/day	1.1 (0.6, 1.8)	1.1 (0.6, 1.7)	1.1 (0.6, 1.7)	1.2 (0.6, 1.8)	1.1 (0.7, 1.8)	0.094
Vitamin D from margarine, µg/day	0.6 (0.1, 1,7)	0.2 (0.0, 1.4)	0.5 (0.1, 1.7)	0.8 (0.1, 1.7)	0.6 (0.0, 1.7)	0.038
Vitamin D from butter, µg/day	0.03 (0.00, 0.11)	0.02 (0.00, 0.12)	0.03 (0.00, 0.11)	0.02 (0.00, 0.11)	0.03 (0.00, 0.12)	0.888
Vitamin D from milk, µg/day	0.002 (0.00, 0.06)	0.002 (0.000, 0.026)	0.002 (0.000, 0.058)	0.002 (0.000, 0.055)	0.002 (0.002, 0.116)	0.133
Vitamin D from yoghurt, µg/day	0.025 (0.007, 0.075)	0.025 (0.012, 0.075)	0.025 (0.007, 0.053)	0.025 (0.007, 0.075)	0.025 (0.007, 0.075)	0.491
Vitamin D from eggs, µg/day	0.11 (0.05, 0.11)	0.11 (0.05, 0.11)	0.11 (0.05, 0.11)	0.11 (0.05, 0.01)	0.11 (0.05, 0.15)	0.370
Vitamin D from cheese, µg/day	0.008 (0.002, 0.016)	0.007 (0.002, 0.015)	0.007 (0.002, 0.015)	0.010 (0.002, 0.017)	0.011 (0.003, 0.018)	0.006
Vitamin D from mixed dishes and products, µg/day[d]	0.2 (0.2, 0.3)	0.2 (0.2, 0.4)	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.2 (0.16, 0.3)	0.390
Nutrient intake, g/day						
Protein	83 (72. 97)	82 (70. 97)	83 (71. 96)	84 (73. 98)	85 (73. 97)	0.178
Added sugar	51 (35, 74)	52 (37, 80)	51 (35, 73)	52 (36, 75)	48 (33, 69)	0.174
Fiber	29 (24, 36)	30 (24, 36)	29 (24, 36)	29 (24, 36)	29 (24, 36)	0.905
Food intake, g/day						
Fish	36 (23, 50)	36 (22, 50)	37 (23, 52)	36 (22, 50)	34 (23, 49)	0.328
Milk	288 (87, 428)	228 (82, 415)	313 (85, 428)	267 (87, 430)	400 (142, 477)	0.045
Yoghurt	32 (12, 89)	25 (12, 88)	32 (12, 85)	35 (12, 102)	37 (12, 103)	0.069
Margarine	13 (1, 24)	10 (1, 21)	13 (1, 24)	15 (2, 25)	14 (1, 25)	0.011
Butter	0.05 (0.0, 0.6)	0.05 (0.0, 0.6)	0.05 (0.0, 0.6)	0.05 (0.0, 0.5)	0.05 (0.0, 0.6)	0.805
Eggs	8 (4, 8)	8 (4, 8)	8 (4, 8)	8 (4, 8)	8 (4, 11)	0.370
Cheese	18 (9, 33)	18 (9, 36)	18 (9, 32)	18 (9, 32)	19 (9, 34)	0.509
Fruit and vegetables	389 (265, 546)	395 (264, 559)	384 (256, 538)	388 (269, 542)	402 (284, 561)	0.330

Values are provided as median (25th, 75th percentiles). 25OHD, 25-hydroxyvitamin D.
[a]Statistical difference between the categories of 25OHD were assessed by Kruskal Wallis test.
[b]Dietary and supplemental vitamin D intake.
[c]All; *N* = 2,379, <30 nmol/L; *N* = 214, 30–50 nmol/L; *N* = 854, >50–75 nmol/L; *N* = 1,028, >75 nmol/L; *N* = 283.
[d]Including milk, fortified margarine and butter, and/or egg.

vitamin D were fish (40%), followed by fortified margarine and butter (30%), eggs (17%), cakes (6%), and milk (4%), estimated by repeated 24-h recalls (37). The contribution from fish and margarine was similar to the results from our study, while the contribution of vitamin D from eggs was higher. However, Norkost 3 included both women and men and a wider age range, and the results are therefore not fully comparable.

We were able to explain 21% of the variation in 25OHD during pregnancy by both lifestyle factors and non-modifiable factors. The determinants with largest effect on the beta estimates were (in descending order) season at blood sampling, solarium use, vitamin D intake from supplements, country of origin, pre-pregnancy BMI, age, vitamin D intake from foods, smoking during pregnancy, education, and energy intake. A multi-ethnic study in Oslo, Norway,

TABLE 3 Determinants of vitamin D status (25OHD, nmol/L) in pregnancy.

	Vitamin D status (25OHD) nmol/L					
	All *N* =2,476		June–September *N* =738		October–May *N* =1,738	
	Beta	*p*-value	Beta	*p*-value	Beta	*p*-value
Season of blood sampling						
June–September	Ref					
October–May	−14.13	<0.001				
Vitamin D intake from foods (μg/day)						
<2.5	Ref		Ref		Ref	
2.5–4.9	2.00	0.010	0.34	0.831	2.56	0.003
5.0–7.49	3.43	0.003	2.80	0.221	3.58	0.008
≥7.5	5.25	0.009	3.87	0.366	5.62	0.013
Supplemental vitamin D intake (μg/day)						
None	Ref		Ref		Ref	
0.1–4.9	3.86	0.010	3.36	0.148	4.12	0.003
5.0–9.9	6.02	<0.001	4.23	0.080	6.64	<0.001
10.0–14.9	10.23	<0.001	6.70	0.018	11.71	<0.001
≥15.0	13.34	<0.001	7.10	0.010	15.82	<0.001
Energy intake (kcal/day)	−0.002	0.004	−0.002	0.146	−0.002	0.023
Use of solarium in pregnancy (times)						
No	Ref		Ref		Ref	
1–5	6.03	<0.001	4.43	0.039	6.70	<0.001
≥ 6	13.37	<0.001	6.23	0.243	15.48	<0.001
Country of origin						
Norway	Ref		Ref		Ref	
Other high-income country	−2.18	0.179	−2.37	0.500	−2.05	0.255
Low/middle-income country	−10.53	0.001	−18.91	<0.001	−4.83	0.204
Education (years)						
<13	Ref		Ref		Ref	
13–16	1.89	0.029	3.02	0.085	1.51	0.129
>16	0.53	0.598	2.09	0.304	−0.17	0.883
Pre-pregnancy BMI (kg/m^2)						
<24.9	Ref		Ref		Ref	
25–29.9	−4.83	<0.001	−5.34	0.001	−4.77	<0.001
≥30	−9.62	<0.001	−11.08	<0.001	−8.61	<0.001
Age (years)						
<25	Ref		Ref		Ref	
25–34	3.84	0.003	4.35	0.079	3.28	0.030
>34	5.75	<0.001	6.14	0.044	5.59	0.002
Smoking in pregnancy						
No	Ref		Ref		Ref	
Yes	−3.20	0.044	−4.63	0.095	−2.51	0.204
Parity						
Nulliparous	Ref		Ref		Ref	
Multiparous	0.26	0.720	2.74	0.057	−0.65	0.432

Results are shown for all women and stratified by season at blood sampling.
25OHD, 25-hydroxyvitamin D; BMI, Body Mass Index; Ref, reference category.

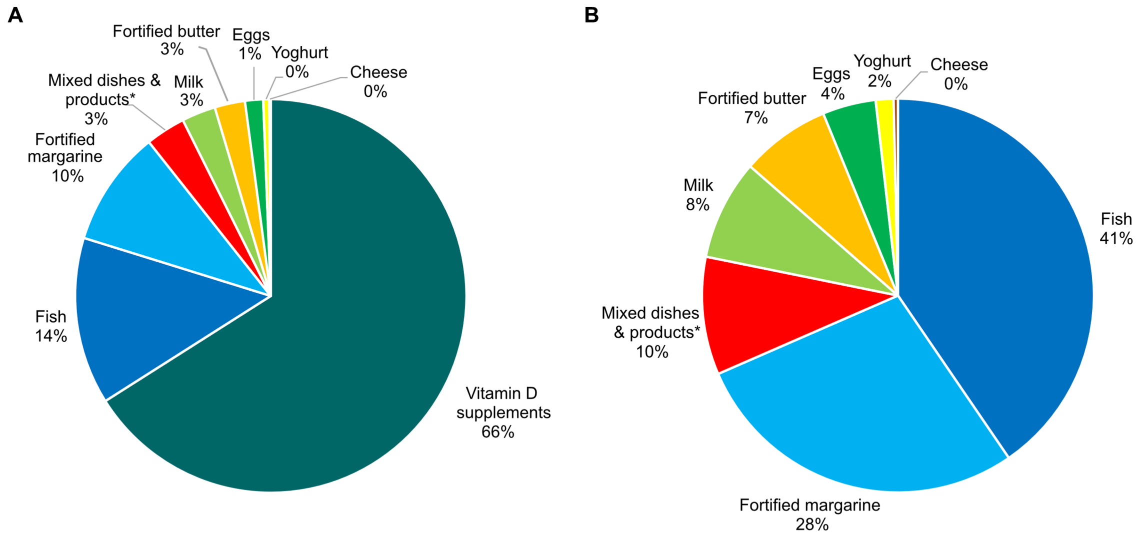

FIGURE 1
Sources contributing to the vitamin D intake in pregnancy in the Norwegian Environmental Biobank (N=2,960), with **(A)** and without **(B)** contribution from vitamin D supplements. *Including milk, fortified margarine and butter, and/or egg.

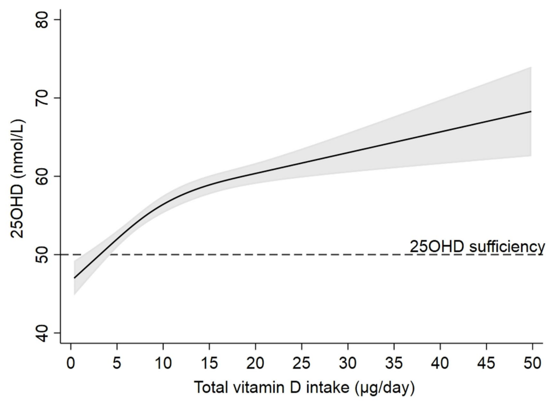

FIGURE 2
Predictions of 25-hydroxyvitamin D (solid black line) and 95% CI (grey area) by total vitamin D intake after estimating a linear regression model (N=2,645) using restricted cubic splines, adjusted for country of origin, pre-pregnancy BMI, age, and smoking during pregnancy. Knots were placed at 3.5, 8.3, and 19.5μg/day. Dotted black line corresponds to 25OHD sufficiency (50 nmol/L).

found 46% of the variation in 25OHD concentrations in gestational week 15 being explained by country of origin, season of blood sampling, and supplemental vitamin D intake ≥10 μg (38). In gestational week 28, the degree of explanation was lower (38) and similar to the results in our study. Other studies from Nordic countries have also found vitamin D intake from foods (33, 39) and supplements (33, 39) or total vitamin D intake (40), season (33, 39), ethnicity (40), age (39), BMI (39), smoking during pregnancy, solarium use, and outdoor physical activity (39) as determinants of 25OHD in pregnancy. Latitude and sunlight exposure are some factors known to affect the 25OHD concentration (41). These variables were not available though. However, solarium use might possibly also reflect other behaviors related to sun exposure, such as clothing habits and preference of sun or shade. This might have affected the effect estimates related to solarium use.

Pre-pregnancy BMI has previously been identified as a determinant of 25OHD in pregnancy, in some (39, 42), but not all (38) univariate models. Pre-pregnancy BMI modified the predicted response in 25OHD by total vitamin D intake. In addition, vitamin D intake from foods was not a significant determinant of 25OHD in women with pre-pregnancy BMI ≥25 kg/m^2. These findings may indicate a lower response in 25OHD in women with BMI ≥25 kg/m^2 by vitamin D intake or it might be due to reporting bias. Even though the causality is not fully understood, there is a negative association between 25OHD concentrations and body fat (43), possibly by sequestering of vitamin D in adipose tissue (44).

We also investigated the effect of the total vitamin D intake on 25OHD and found a plateau effect in intakes >15 μg/day. Possible explanations for this could be falsely overreporting of high vitamin D intakes, lack of data in this high intake category, or that the dose–response effect may be weaker at high 25OHD concentrations.

Using an immunoassay method and unstandardized values, almost half of the women in our study was classified as having either insufficient or deficient concentrations of 25OHD. Another study on pregnant women in Norway found that the prevalence of 25OHD <50 nmol/L was 47% and 25OHD <30 nmol/L was observed in 11% (45). A study on pregnant women in Denmark found that 10% had 25OHD <25 nmol/L and 42% had 25OHD <50 nmol/L (39). In pregnant women living in Sweden, 10% had 25OHD concentrations <30 nmol/L and 25% had 25OHD <50 nmol/L (40). Differences in vitamin D status have been found between ethnic groups (38, 46), at different latitudes (34), and by season (40, 47), which can explain differences in 25OHD concentrations between studies in Nordic populations, along with differences between laboratories and 25OHD assay methods (48).

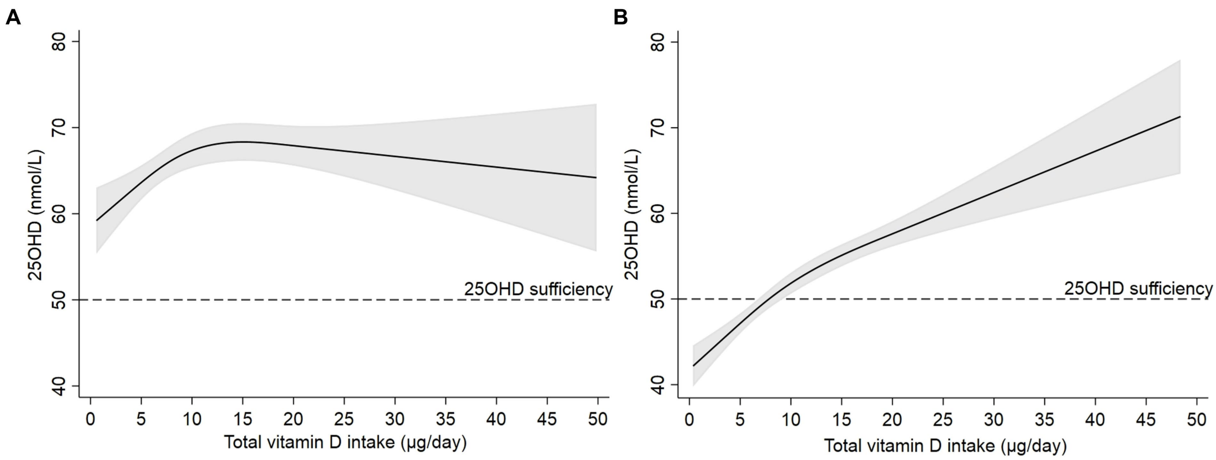

FIGURE 3
Predictions of 25-hydroxyvitamin D (solid black line) and 95% CI (grey area) by total vitamin D intake after estimating a linear regression model using restricted cubic splines in women blood sampling during **(A)** June to September (*N*=796) and **(B)** October to May (*N*=1,849). Models were adjusted for country of origin, pre-pregnancy BMI, age, and smoking during pregnancy. Knots were placed at 3.5, 8.3, and 19.5 μg/day. Dotted black line corresponds to 25OHD sufficiency (50 nmol/L).

We excluded 28 women (0.9%) due to implausibly low or high energy intake. Median (25th–75th percentile) 25OHD concentration of the excluded women were 47 (32–54) nmol/L and median pre-pregnancy BMI were 23.3 (21.0–25.9) kg/m^2. As so few were excluded, it has likely not impacted our results.

4.1. Strengths and limitations of the study

The main strength of our study is the availability of numerous potential determinants of vitamin D in a relatively large study population. In addition, questionnaires provided information both prospectively and retrospectively during pregnancy. The FFQ can be considered a suitable dietary assessment method in this study since only few foods contain significant amounts of vitamin D making food diaries less suitable and since the FFQ provides a fair estimation of the habitual diet over a specific period (49).

Some limitations should be considered in the interpretation of the results. Some studies have observed underestimation of 25OHD using Abbott Architect chemiluminescence immunoassays compared with liquid chromatography tandem mass spectrometry (50, 51), also in a pregnant population (52). Standardization of 25OHD was not possible as there was no plasma left for such analysis. If the assay method underestimated the 25OHD concentrations in our study, it would potentially lead to biased estimates of insufficiencies and deficiencies. Thus, the prevalence of vitamin D insufficiency and deficiency should be interpreted with caution. Further, some important variables were not available to us in the investigation of determinants of 25OHD, such as recent travels to southern latitudes and portion sizes. The participants included in the Norwegian Environmental Biobank were women with good compliance in MoBa. Thus, selection bias may be present and might negatively affect the representativeness and the external validity of the results. In addition, the lack of variation in country of origin in the study population limits the interpretation of the vitamin D intake and status in ethnic minorities. Other limitations related to the FFQ used in MoBa have previously been described (22, 25).

4.2. Implications

This study provides a thorough investigation of the vitamin D intake and other determinants of vitamin D status in pregnant women living in Norway. The contribution of the determinants is likely relevant to pregnant women also in other northern regions on corresponding latitudes. In addition, the response in 25OHD by total vitamin D intake might differ by season and pre-pregnancy BMI. Future studies should aim to investigate how vitamin D intake and status can be safely increased on a population level.

5. Conclusion

The results emphasize the importance of vitamin D from supplements, fish, and fortified margarine contributing to the total vitamin D intake. The most important determinants of vitamin D status were season, solarium use, vitamin D intake from supplements, country of origin, pre-pregnancy BMI, age, vitamin D intake from foods, and smoking during pregnancy. Our study indicates a seasonal variation in vitamin D status during pregnancy, and a dose–response in 25OHD by total vitamin D intake during October to May. These findings highlight the importance of the vitamin D intake, as one of few modifiable determinants, to reach sufficient 25OHD concentrations, during months when dermal synthesis of vitamin D is absent.

Data availability statement

Data from MoBa used in this study are owned and managed by a third-party organization, the national health register holders in Norway (Norwegian Institute of Public Health). Researchers who want access to data sets from MoBa for replication should apply to www.helsedata.no/en. Access to data sets requires approval from The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

Ethics statement

The studies involving human participants were reviewed and approved by The Regional Committees for Medical and Health Research Ethics in Norway. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HA initiated the study. HA, LB, AA, EP, AB, LL, HM, and AW planned the study and were involved in interpretation of the results and writing of the final manuscript. HA and AB are responsible for data protection and access. AA conducted the statistical analyses and wrote the first version of the manuscript. HA, LB, and EP assisted with the statistical analyses. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1111004/full#supplementary-material

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