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The association between dietary patterns and risk of miscarriage: a systematic review and meta-analysis

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Importance: The evidence on the association between diet and miscarriage risk is scant and conflicting.
Objective: To summarize the evidence on the association between periconceptual diet and miscarriage risk in healthy women of reproductive age.
Data Sources: Electronic databases were searched from inception to August 2022 without restriction of regions, publication types, or languages.
Study Selection and Synthesis: Experimental or observational studies were considered for inclusion. The population was healthy women of reproductive age. Exposure was periconception diet. Study quality was assessed using the modified Newcastle-Ottawa Scale. Summary effect sizes (odds ratio [OR] with 95% confidence interval [CI]) were calculated for each food category.
Main Outcomes: Miscarriage rate (as defined by primary studies).
Results: We included 20 studies (11 cohort and 9 case-control), of which 6 presented data suitable for meta-analysis (2 cohort and 4 case-control, n = 13,183 women). Our primary analyses suggest a reduction in miscarriage odds with high intake of the following food groups: fruit (OR, 0.39; 95% CI, 0.33–0.46), vegetables (OR, 0.59; 95% CI, 0.46–0.76), fruit and vegetables (OR, 0.63; 95% CI, 0.50–0.81), seafood (OR, 0.81; 95% CI, 0.71–0.92), dairy products (OR, 0.63; 95% CI, 0.54–0.73), eggs (OR, 0.81; 95% CI, 0.72–0.90), and cereal (grains) (OR, 0.67; 95% CI, 0.52–0.87). The evidence was uncertain for meat, red meat, white meat, fat and oil, and sugar substitutes. We did not find evidence of an association between adherence to predefined dietary patterns and miscarriage risk. However, a whole diet containing healthy foods as perceived by the trialists, or with a high Dietary Antioxidant Index score (OR, 0.43; 95% CI, 0.20–0.91) may be associated with a reduction in miscarriage risk. In contrast, a diet rich in processed food was demonstrated to be associated with increased miscarriage risk (OR, 1.97; 95% CI, 1.36–3.34).
Conclusion and Relevance: A diet abundant in fruit, vegetables, seafood, dairy, eggs, and grain may be associated with lower miscarriage odds. Further interventional studies are required to accurately assess the effectiveness of periconception dietary modifications on miscarriage risk.
PROSPERO registration: CRD42020218133 (Fertil Steril® 2023;120:333–57. ©2023 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Diet, dietary pattern, food, miscarriage, pregnancy loss

Miscarriage is common, affecting approximately 1 in 6 pregnancies (1). There are many known causes of miscarriage, including embryo aneuploidy and endometrial infection. Yet, nearly 50% of early pregnancy losses remain unexplained (2). In the absence of an identifiable cause, couples often turn to clinicians for guidance on ways to optimize their health and reduce the risk of further miscarriages. Although lifestyle choices are not usually considered to be a direct cause leading to pregnancy loss, there is a growing body of evidence attesting to the role of periconceptual health in determining obstetric and fetal outcomes (3). It is thought that this may be influenced by modifiable lifestyle choices such as diet, smoking, and alcohol intake (1, 4).

Nutrition is a lifestyle factor that consistently draws both academic and public interest. Reproduction demands a high level of energy expenditure, relying on the availability of specific nutrients, and nutritional imbalances

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have long been established to affect reproductive health. For example, the normal ovarian activity requires a minimum amount of body fat content, below which ovulation is unlikely to occur because of the dysregulation of the hypothalamic-pituitary-ovarian axis (5). Conversely, a state of overnutrition can be just as deleterious to reproductive health, with obesity contributing to menstrual irregularities, infertility, and miscarriage (6).

Between under- and overnutrition, there is a large spectrum of dietary patterns resulting in a variety of nutritional states. However, there is a paucity of evidence on the association between dietary choices and miscarriage. In addition, there are no consensuses or evidence-based guidelines outlining the dietary advice that should be given to couples who wish to minimize their risk of pregnancy loss. For this reason, advising women and their partners after a miscarriage remains a challenge for many clinicians. Couples often wish to know whether there are any specific food groups or dietary patterns that have been associated with increased miscarriage risk.

We conducted a systematic review and meta-analysis to summarize and appraise the existing evidence on periconceptual diet and miscarriage risk in healthy women of reproductive age.

MATERIALS AND METHOD

Registration

We registered this systematic review with PROSPERO (CRD42020218133) on December 3, 2020.

Search Strategy

We conducted comprehensive bibliographic searches according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (7). A specialist medical sciences librarian (Birmingham Women's Hospital, UK) was consulted to formulate an extensive search strategy to identify all studies that investigated the association between periconceptual dietary intake and miscarriage risk. The following electronic databases were searched from inception until August 3, 2022: PubMed, MEDLINE (Ovid MEDLINE®), EMBASE (Ovid), CINAHL Plus (EBSCOhost), and the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL). There was no restriction on language, publication year, or publication status (published, unpublished, in press, or in progress), but the search was limited to human subjects. The search used keywords and mapping to Medical Subject Headings (MeSH) terms where applicable. We conducted the search in 2 main steps. The first aimed to identify the relevant exposure and used the following keywords: diet* OR nutrition* OR food. The second search was to identify the relevant outcome using the following keywords: miscarriage* OR abortion* OR pregnancy loss* OR embryo loss*. Search tools such as Boolean operators (AND/OR), truncation, and searching using text were used to optimize results. Secondary hand searches and full-text screening were conducted in reference lists of all included studies and any relevant reviews on a similar topic. The investigators explored an alternative search strategy with more complex and expanded search terms using keywords and MeSH terms for common food groups and dietary patterns. However, this did not increase the recall or precision of the search and therefore the decision was made to keep the search simple yet comprehensive using the explosion of overarching and relevant MeSH terms.

Study Selection

Studies were selected in a 2-stage process using Covidence (8). Two independent reviewers (Y.C. and P.M., Y.C. and O.P., Y.C. and R.D.-S., or Y.C. and A.D.) evaluated the articles for eligibility. In stage one, the titles and abstracts were screened for eligibility. In stage 2, a full-text review was performed on all the articles that met the predefined inclusion criteria and the abstracts whose eligibility was uncertain. During this stage, secondary reference screening from review articles on a similar topic was also completed. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (A.C.). If insufficient information was available, respective investigators were contacted and given a minimum of 4 weeks before further information was deemed unavailable and classified as "awaiting classification". Google translate (9) was used to translate the full text of non-English articles into English to enable screening and data collection.

Type of studies. We planned to include both observational and interventional studies investigating the impact of different dietary patterns on reproductive outcomes in healthy women of reproductive age. We included studies reported as full text, those published as abstract only, and unpublished data. If sufficient evidence was identified, we planned to explore whether a cause-effect relationship may exist. To reduce the potential for reverse causation, we excluded designs such as cross-sectional studies where the temporal sequence of association is unclear. In addition, studies of descriptive or ecological design, case series or reports, personal opinion-based articles, or publications without original data such as reviews were also excluded.

Types of participants. The population of interest was healthy women of reproductive age who had at least one pregnancy outcome.

Types of interventions or exposure. The intervention or exposure of interest was diet, assessed as intake of specific food categories or the whole diet. We used the term "index pregnancy" to refer to the pregnancy on which information was collected. We aimed to only include studies with low or no risk of reverse causation where the collected information reflected the periconceptual dietary intake of the index pregnancy. We excluded studies evaluating the effects of calorie-restrictive or weight-reducing diets, micronutrient deficiency, or supplementation with minerals or vitamins. To avoid confounding, we excluded studies evaluating the effects of a dietary pattern that targeted a specific disease. This is because such interventions may influence miscarriage risk through disease control. Examples include coeliac disease and gluten-free diet; diabetes and low glycemic-index diet; phenylketonuria and low phenylalanine diet; and chronic kidney disease and low protein diet.

Type of outcome measures. The primary outcomes of interest were miscarriage or recurrent miscarriage. Miscarriage was defined as one or more spontaneous pregnancy losses before viability. We did not set a stringent upper gestational age limit to define viability but accepted the limit set by each included study. Recurrent miscarriage was defined as 2 or more spontaneous pregnancy losses before viability (10).

Data Extraction Process

Two reviewers (Y.C. and P.M.) independently extracted data from the eligible studies into a template designed specifically for this review. Differences were resolved by consensus or arbitration by a third reviewer (A.C.). We extracted the following study characteristics and outcome data, if available: study information data (the first investigator's name, publication year, country, objective, study design); participants (number, population demographics); exposure (type, duration, frequency, dosage of the assessed diet, dietary data collection and reporting method); confounders (list of confounders considered and adjusted for in the study design or during the analysis); and outcomes (relevant study findings and conclusions).

Quality Assessment

The quality of included studies was evaluated using a modified Newcastle-Ottawa Scale (NOS) for quality assessment of observational studies (11). Two independent reviewers (Y.C. and P.M.) conducted the assessment as recommended by the Cochrane Collaboration (12).

The NOS assessment is composed of 8 parameters covering 3 broad categories: selection of participants; comparability of groups; outcome assessment (for cohort studies) or exposure ascertainment (for case-control studies). We adapted these parameters to this review, as outlined in Supplemental Table 1 (available online). We classified the overall quality of each study according to the total score assigned to it: high quality or low risk of bias (score 7–9); moderate quality or moderate risk of bias (score 4–6); and low quality or high risk of bias (score 0–3).

Data Synthesis and Analysis

We planned to summarize the effect sizes using odds ratios (OR) and 95% confidence intervals (CI). Data analyses were performed using Stata statistical software (Release 17, TX, USA). A fixed-effect model was used to estimate the summary effect and CI, based on the assumption that all studies in the analysis shared a common effect size.

Food categories. Dietary data were grouped according to food categories to facilitate evidence synthesis and interpretation. The categorization was based on the Eatwell Guide produced by Public Health England (13) (Supplemental Material 1, available online). Both unadjusted and adjusted data were extracted. However, where available, the adjusted estimate was selected for the analysis. If more than one adjusted effect measure was reported, we selected the effect estimate that had been adjusted for the most confounders. Where studies provided data comparing multiple exposure categories, we selected the effect estimate with the largest sample size and compared the lowest vs. the highest intake group. Where data were reported on several food items within a single food category, the item deemed by reviewer consensus to most typically represent the food category was selected for the meta-analysis. Table 1 outlines the dietary exposure assessment and reporting methods (14–33). Supplemental Table 2 summarizes the comparison groups from each primary studies that were selected in the final meta-analysis.

Whole diet. We grouped data on participants' whole diet into 2 broad categories of dietary pattern analysis: a priori and a posteriori. The a priori method was dietary score or index driven, typically evaluating adherence to a whole diet according to a predefined dietary pattern or scoring system (e.g., adherence to the Mediterranean diet). The a posteriori method was data driven. This approach used statistical methods to derive eating behavior patterns that may be associated with an outcome of interest. If enough studies were available, we planned to categorize and meta-analyze dietary patterns based on the presence of similar constituent foods, regardless of the terminology used to identify the dietary pattern. For example, Mediterranean-type diet, alternative Mediterranean diet, and Mediterranean diet index would be classified and analyzed under the same category. We planned to contact study investigators to verify key study characteristics and obtain missing information including numerical data. If this approach was not successful, we planned to describe the study's findings in the narrative synthesis only.

Subgroup and sensitivity analyses. Because of the low number of included studies, subgroup analysis to explore heterogeneity was limited to the classification of national income status. We used the World Bank classification (34) to categorize each study into low-, middle-, or high-income groups. Based on the existing evidence suggesting socioeconomic status at the individual or country level influences dietary choice and quality (35–38), we hypothesized that the subgroup analysis by national income would reduce estimation error and strengthen the accuracy of the effect estimates by narrowing the 95% CI. Planned subgroup analyses of dose-response, duration of the exposure, and history of recurrent miscarriages were not possible because of an insufficient number of studies. Further subgroup analyses based on the type or length of dietary assessment were considered but not deemed useful because of the limited number of studies.

We planned to perform sensitivity analyses to assess whether our conclusions would have differed if eligibility for the meta-analyses had been restricted to studies at low risk of bias. In addition, we aimed to explore whether statistical heterogeneity may be a result of different risks of bias. We conducted repeat meta-analyses after the exclusion of the following: studies without confounder adjustment and

TABLE 1

Characteristics of the included studies.

First investigator, year, country, and income status	The main aim of the study	Study characteristics Direction Design	Total no. of women	Population characteristics Overview Inclusion/exclusion criteria	Exposure Food groups/whole diet Diet details	Exposure assessment Method Validation (Yes/No) Reporting Comparison groups	Outcome (definition)	Confounders Adjustment (Yes/No) Details	Analysis Point estimate Method	Risk of bias	Meta-analysis (Yes/No) Food categories
Axmon 2000 (14) Sweden HIC	To evaluate the association between high intake of fish contaminated with persistent organochlorine compounds, and miscarriage and stillbirth risk	Retrospective Cohort	438	Fishermen's wives cohort Women who were wives of fishermen, living on the Swedish coast who were born in 1945 or later with information on the first planned pregnancy	Food categories Fatty fish	1-item FFQ No frequency per month 2 groups (based on consumption frequency)	Miscarriage and Stillbirth (miscarriage pregnancy loss <28 wk, stillbirth >28 wk)	Yes (analysis adjustment) Heavy lifting (smoking, coffee consumption, education, employment status, working hours, shift work, heavy lifting, and paternal age were considered but not used for the final multivariate model analysis because no significant difference was found in the effect estimate)	OR and 95% CI Logistic regression	7	No
Gaskins (15) 2014 USA HIC	To evaluate the association between prepregnancy adherence to well-known dietary patterns (aMED, FD, aHEI-2010) and miscarriage risk	Prospective Cohort	11,072	Nurses' Health Study II (NHS II) Longitudinal survey of female nurses aged 24–44 y, between 1992 and 2009. Women aged $\leq$40 y, at least 1 pregnancy during 1992–2009, no history of pregnancy loss in 1991, no history of infertility, first eligible pregnancies, married women not using oral contraception, pregnancies in years closest to a diet assessment excluded those with missing data (on diet, gestational age, year of pregnancy, diagnosis of diabetes, cardiovascular disease, cancer before pregnancy)	Whole diet Alternate Mediterranean diet (aMED), FD, alternate Healthy Eating Index 2010 (aHEI-2010)	131-item FFQ Yes Adherence score to dietary pattern 4 groups (based on adherence scoring)	Miscarriage (<20 wk)	Yes (analysis adjustment) Age, total energy intake, BMI, smoking status, physical activity, history of infertility, year, marital status, race, nulliparity	RR and 95% CI Log-binomial regression	9	No
Hsiao 2019 (16) USA HIC	To evaluate the association between prepregnancy adherence to AHEI-P and miscarriage risk	Prospective Cohort	132	ISIS study Healthy, nulliparous couples with no known fertility problems who were planning their first pregnancy. Women aged 18–39 y, 1 male partner only	Whole diet Alternative Healthy Eating Index for Pregnancy (aHEI-P)	3 $\times$ 24 h dietary recalls, using Nutrition Data System for research software No Adherence score to dietary pattern 3 groups (based on adherence scoring)	Fetal loss (loss of confirmed clinical pregnancy, upper gestational cut-off not specified)	Yes (analysis adjustment) Age, energy, BMI, male partner education, male partner smoking status, male partner's AHEI-P score (caffeine and alcohol consumption were considered but not used for final multivariate model analysis because no significant difference was found in the results)	HR and 95% CI Cox proportional hazards regression	9	No
Kalla 2022 (17) Algeria LMIC	To evaluate the association between demographic, diet, and lifestyle risk factors, and miscarriage risk	Prospective Cohort	786	Pregnant women in Eastern Algeria receiving care in the recruiting health care centers between 2011 and 2015 Excluded those with incomplete periodic survey data	Food categories Fruit and vegetables, meat, fish, eggs, dairy products, cereals, sweets, soft drinks	8-item FFQ No General frequency or quantity level 3 groups (based on consumption level)	Miscarriage (<24 wk)	Yes (analysis adjustment) Age, BMI	OR and 95% CI Multivariate logistic regression	6	Yes Fruit and vegetables, meat, seafood, dairy products, eggs, cereal

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TABLE 1

Continued.

First investigator, year, country, and income status	The main aim of the study	Study characteristics Direction Design	Total no. of women	Population characteristics Overview Inclusion/exclusion criteria	Exposure Food groups/whole diet Diet details	Exposure assessment Method Validation (Yes/No) Reporting Comparison groups	Outcome (definition)	Confounders Adjustment (Yes/No) Details	Analysis Point estimate Method	Risk of bias	Meta-analysis (Yes/No) Food categories
Laursen 2022 (18) Denmark HIC	To evaluate the association between adherence to DDGI, HNFI, and first trimester miscarriage risk	Prospective Cohort	3,043	SnartForældre.dk Soon Parents (SF) study Internet-based longitudinal cohort study of Danish couples trying to conceive. Nonpregnant women aged 18–49 y, in a relationship with a male partner, not using contraception or fertility treatment	Whole diet DDGI, HNFI	220-item FFQ Yes Adherence score to dietary pattern 4 groups (based on adherence scoring)	Miscarriage (≤12 wk)	Yes (analysis adjustment) Age, education, gravidity, BMI, BMI-adjusted waist circumference, activity MET-h/wk, physical activity, alcohol, smoking, pat age	HR and 95% CI Cox proportional hazards regression	8	No
Madzorera 2020 (19) Tanzania LMIC	To evaluate the association between antenatal adherence to WDDS, PDQS, and birth outcomes	Prospective Cohort	7,553	Women recruited into the parent double-blind, randomized, placebo-controlled study, evaluating the effect of multivitamin supplements on birth outcomes between August 2001 and July 2004 Women aged 18–45 y, who attended antenatal clinics in Dar es Salaam, Tanzania. HIV negative, 12–27 wk of gestation at enrollment based on the last menstrual period, intended to stay in the city for 1 y after delivery	Whole diet WDDS, PDQS	Multiple 24-h dietary recalls (at recruitment and monthly thereafter) No Adherence score to dietary index 5 groups (based on adherence scoring)	Miscarriage (<28 wk)	Yes (analysis adjustment) Marital status, trial group assignment, parity, height, BMI, anemia, energy intake (age, marital status, history of fetal loss, parity, maternal height, household income, wealth characteristics, wealth index, season, long rains, harvest, short rains were considered but not used for final multivariate analysis)	RR and 95% CI Log-binomial regression	8	No
Salas-huetos 2022 (20) USA HIC	To evaluate the association between a couple's intake of omega-3 fatty acids and omega-3-rich foods and ART outcomes and semen quality	Prospective Cohort	229	EARTH study A prospective cohort study of couples with subfertility between 2007 and 2020. Women aged 18–45 y, men aged 18–55 y, receiving ART with autologous gametes	Food categories Nuts, fish	131-item FFQ Yes Servings per day 4 groups (based on consumption level)	Clinical pregnancy loss (loss of any clinical pregnancy, upper gestational cut-off not specified)	Yes (analysis adjustment) Age, BMI, smoking status, education, dietary patterns, total energy intake, male partner diet	Marginal effect probability and 95% CI Multivariable generalized linear mixed models with binomial distribution and random intercepts	9	No
Setti 2022 (21) Brazil UMIC	To evaluate the association between maternal lifestyle factors and ART outcomes	Prospective Cohort	752	Women receiving ART with ICSI at recruiting hospitals Women aged 18–40 y, premenopausal women with regular menstrual cycles, BMI 17.5–30, normal pelvic structure on USS, first ICSI cycle using fresh sperm and fresh embryo transfer on day 5, male partner ≥18 y without abnormal examination findings	Food categories Refined sugar, artificial sweeteners, fruits, legumes and vegetables, milk and dairy, fish, poultry, and red meat	8-item FFQ No Adherence to specified frequency per week 3 groups (based on consumption level)	Miscarriage (<20 wk)	Yes (analysis adjustment) Maternal age, BMI, number of retrieved oocytes	OR and 95% CI Multivariate general linear models	8	Yes Fruit, vegetables, red meat, white meat, seafood, dairy products, sugar substitutes

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TABLE 1

Continued.

First investigator, year, country, and income status	The main aim of the study	Study characteristics Direction Design	Total no. of women	Population characteristics Overview Inclusion/exclusion criteria	Exposure Food groups/whole diet Diet details	Exposure assessment Method Validation (Yes/No) Reporting Comparison groups	Outcome (definition)	Confounders Adjustment (Yes/No) Details	Analysis Point estimate Method	Risk of bias	Meta-analysis (Yes/No) Food categories
Wesselink 2021 (22) USA HIC	To evaluate the association between preconception maternal seafood intake and misc risk	Prospective Cohort	3,821	Women trying to conceive and conceived during the 12-mo follow-up	Food categories Fatty seafood, lean seafood	2-item FFQ No Grams per day 3 groups (based on consumption level)	Miscarriage (not specified)	Yes (analysis adjustment) Other dietary variables	HR and 95% CI Cox proportional hazards regression	6	No
Wesselink 2022 (23) USA, Canada, Denmark HIC	To evaluate the association between protein-rich foods and miscarriage risk	Prospective Cohort	7,199 (PRESTO 4,246 and SF 2,953)	PRESTO study and SnartForældre.dk Soon Parents (SF) study PRESTO: prospective preconception online study. Nonpregnant women aged 21–45 y, attempting to conceive and succeeded within 12 mo of recruitment SF: internet-based longitudinal cohort study of Danish couples trying to conceive and succeeding within 12 mo of recruitment. Nonpregnant women aged 18–45 y, in a relationship with a male partner, not using contraception or fertility treatment	Food categories Red meat, poultry, processed meat, seafood, eggs, plant-based proteins (nuts, seeds, legumes, soy), dairy (milk, cheese, yogurt)	37-item FFQ (PRESTO) | 53-item (SF) Yes Grams per week Not categorized into groups but linear association as g/wk analyzed	Miscarriage (<20 wk)	Yes (analysis adjustment) Both: total energy intake, age, education, household income, prepregnancy BMI, physical activity, smoking, alcohol, multivitamin or folic acid intake, parity, individual components of diet quality scores, caffeine intake PRESTO only: race/ethnicity	HR and 95% CI Cox proportional hazards regression	9	No
Zhang 2019 (24) China UMIC	To evaluate the association between maternal nutrition and health outcomes in mothers and children	Prospective Cohort	200	Pregnant women who received care at the recruiting hospital	Food categories Diet rich in seasonal fruit, seasonal fresh juice, vegetables, calcium and protein-rich source from milk products	Food questionnaire Yes Adherence to diet rich in specified food groups 2 groups (based on adherence level)	Poor pregnancy outcome (miscarriages, postpregnancy complications, premature birth with birth weight less than 2.5 kg)	No	No point estimation Fisher's exact test	5	No
Ahmadi 2017 (25) Iran LMIC	To evaluate the association between maternal nutrient deficiency and miscarriage risk	Retrospective Case-control	662	Healthy pregnant women who received care at the recruiting hospitals Women aged 18–35 y, singleton pregnancy. naturally conceived, no history of chronic diseases (i.e., diabetes, hypertension, cardiovascular diseases, thyroid dysfunction), no parental or close family history of congenital or karyotypic abnormalities, no vaginal bleeding in the first trimester for the control group, no fetal malformations in the index pregnancy, no smoking	Food categories Vegetables, fruits, bread and cereals, meat and beans, dairy products, fats and oils	168-item FFQ Yes Frequency of specified portion per day 3 groups (based on consumption level)	Miscarriage (<14 wk)	Yes (control matching) Age (others considered but not adjusted)	OR and 95% CI Logistic regression	7	Yes Fruit, vegetables, meat, dairy products, cereal, fat and oil
Amini 2017 (26) Iran LMIC	To evaluate the association between food intake, BMI, and miscarriage risk	Retrospective Case-control	166	Healthy pregnant women who received care at the recruiting hospitals Women aged 18–40 y	Food categories Rice, pasta, bread, cereals, milk, yogurt, yogurt-based drink, ice cream, cheese, dairy products, fish and seafood, red meat and chicken, beans, eggs, meat, fruit, vegetable, fat in food, simple sugars, soft drinks, fast food	46-item FFQ Yes Frequency of specified portion per day 4 groups (based on consumption level)	Miscarriage (<20 wk)	Yes (control matching and analysis adjustment) Social class, education, (control matching) age (analysis adjustment)	No point estimation ANCOVA	8	No

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TABLE 1

Continued.

First investigator, year, country, and income status	The main aim of the study	Study characteristics Direction Design	Total no. of women	Population characteristics Overview Inclusion/exclusion criteria	Exposure Food groups/whole diet Diet details	Exposure assessment Method Validation (Yes/No) Reporting Comparison groups	Outcome (definition)	Confounders Adjustment (Yes/No) Details	Analysis Point estimate Method	Risk of bias	Meta-analysis (Yes/No) Food categories
Di Cintio 2001 (27) Italy HIC	To evaluate the association between dietary habits and miscarriage risk	Retrospective Case-control	2,681	Healthy pregnant women who received care at the recruiting hospitals	Food categories Milk, meat, liver, ham, fish, eggs, cheese, carrots, green vegetables, fruit, butter, oil, margarine	10-item FFQ No (tested for reproducibility) Frequency of specified portion per week 2–3 groups (based on consumption level)	Miscarriage (<12 wk)	Yes (analysis adjustment) Age, BMI, marital status, education, n of previous miscarriages, prepregnancy coffee, and alcohol intake	OR and 95% CI Unconditional multiple logistic regression	7	Yes Fruit, vegetables, meat, red meat, seafood, dairy products, eggs, fat and oil
Maconochie 2007 (28) UK HIC	To evaluate the association between biological, behavioral, and lifestyle risk factors and miscarriage risk	Retrospective Case-control	6,442	National Women's Health study Women randomly sampled from the UK electoral register in 2001, aged <55 y, with information on the most recent pregnancy and participated in all relevant stages of the survey. Last pregnancy conceived after January 1, 1980, at the time of recruitment	Food categories Red meat, white meat, fish, eggs, fresh fruit and vegetables, dairy products, soya products, sugar substitutes, chocolate	13-item FFQ No Adherence to specified frequency per day or week 2–5 groups (based on consumption level)	Miscarriage (<13 wk)	Yes (analysis adjustment) Year of conception, age, pregnancy order, miscarriage history, live birth history, nausea, fertility treatment, relationship status	OR and 95% CI Logistic regression	6	Yes Fruit and vegetables, red meat, white meat, seafood, dairy products, eggs, sugar substitute
Vahid 2017 (30) Iran LMIC	To evaluate the association between adherence to DII, serum concentration of inflammatory markers, and miscarriage risk	Retrospective Case-control	135	Women with a history of recurrent miscarriages (≥3 miscarriages) who received care at recruiting infertility and miscarriage specialist center Women aged 20–45 y, maximum of 6 mo since the last miscarriage, and no supplements containing folic acid consumed in the last 6 mo. Excluded ectopic pregnancy, termination of pregnancy, medical history including malignancy, chromosomal abnormalities, impaired renal, hepatic, endocrine, immune, or gastrointestinal functions, user of alcohol, smoke, recreational drug use	Whole diet DII	168-item FFQ Yes Adherence score to dietary index 2 groups (based on adherence scoring)	Miscarriage (<20 wk)	Yes (control matching and analysis adjustment) Age, BMI, education, occupation	OR and 95% CI Logistic regression	8	No
Vahid 2021 (29) Iran LMIC	To evaluate the association between adherence to Index of Nutritional Quality, DAI, and miscarriage risk	Retrospective Case-control	135	Women with a history of recurrent miscarriages (≥3 miscarriages) who received care at recruiting infertility and miscarriage specialist center Women aged 20–45 y, maximum of 6 mo since the last miscarriage, and no supplements containing folic acid consumed in the last 6 mo. Excluded ectopic pregnancy, termination of pregnancy, medical history including malignancy, chromosomal abnormalities, impaired renal, hepatic, endocrine, immune, or gastrointestinal functions, user of alcohol, smoke, recreational drug use	Whole diet DAI	168-item FFQ Yes Adherence score to dietary index 2 groups (based on adherence scoring)	Miscarriage (<20 wk)	Yes (control matching and analysis adjustment) Age, BMI, education, occupation	OR and 95% CI Logistic regression	8	No

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TABLE 1

Continued.

First investigator, year, country, and income status	The main aim of the study	Study characteristics Direction Design	Total no. of women	Population characteristics Overview Inclusion/exclusion criteria	Exposure Food groups/whole diet Diet details	Exposure assessment Method Validation (Yes/No) Reporting Comparison groups	Outcome (definition)	Confounders Adjustment (Yes/No) Details	Analysis Point estimate Method	Risk of bias	Meta-analysis (Yes/No) Food categories
Xu 2014 (31) China UMIC	To evaluate the association between biological, behavioral, environmental factors, and miscarriage risk	Retrospective Case-control	1,860	Women who received pregnancy care at the recruiting hospitals	Food categories Fresh fruit and vegetables	1-item FFQ No Adherence to specified frequency per week 2 groups (based on adherence level)	Miscarriage (<13 wk)	Yes (control matching and analysis adjustment) Age, miscarriage history, previous induced abortion, vitamin supplementation, frequency of night shift, frequency of staying up late, regular physical exercise, smoking, alcohol	OR and 95% CI Logistic regression	7	Yes Fruit and vegetables
Yan 2019 (32) China UMIC	To identify and evaluate the association between dietary patterns and adverse pregnancy outcomes	Retrospective Case-control	15,980	Women recruited to Survey the status and risk factors of birth defects in Shaanxi Province study Healthy women of childbearing age, recruited by multistage stratified random sampling from Shaanxi province. Excluded women with poor memory for dietary recall, medical disease including diabetes during pregnancy, heart, liver, kidney problems, mental illness, or poor cognition	Whole diet Vegetarian dietary pattern balanced dietary pattern, traditional dietary pattern, processed dietary pattern	102-item FFQ No (but tested for reproducibility) Adherence score to dietary pattern 3 groups (based on adherence scoring)	Miscarriage (<28 wk or fetal weight <1000 g)	Yes (analysis adjustment) Age, residence (urban vs. rural), education, monthly household expenditure, regional classification, partner's residence (urban vs. rural)	OR and 95% CI Factor analysis and logistic regression	5	No
Zhang (33) 2011 China UMIC	To evaluate the association between environmental, behavioral factors, and miscarriage risk	Retrospective Case-control	552	Women who received pregnancy care at the recruiting hospitals	Food categories Fried food	1-item food preference questionnaire No Preference for food group 2 groups (based on preference level)	Miscarriage (<12 wk)	No	OR and 95% CI Logistic regression	5	No

Studies are presented by study design (cohort followed by case-control), then in alphabetical order of the first investigator.

aHEI-2010 = alternate Healthy Eating Index 2010; AHEI-P = alternative Healthy Eating Index for Pregnancy; aMED = alternate Mediterranean diet; ANCOVA = analysis of covariance; ART = assisted reproductive therapy; BMI = body mass index; DAI = Dietary Antioxidant Index; DDGI = Danish Dietary Guidelines Index; DII = Dietary Inflammatory Index; FD = Fertility Diet; FFQ = food frequency questionnaire; HIC = high-income country; HNFI = Healthy Nordic Food Index; HR = hazards ratio; ICSI = intracytoplasmic sperm injection; LMIC = lower middle-income country; OR = odds ratio; PDQS = Prime Diet Quality Score; PRESTO = Pregnancy Study Online; RR = risk ratio; SF = SnartForældre.dk Soon Parents; UMIC = upper middle-income country; USS = ultrasound scan; WDDS = Women's Dietary Diversity Score.

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studies with a moderate or high risk of bias (a total score of ≤6 after NOS assessment).

RESULTS

Search Results

The study selection process is detailed in Supplemental Figure 1 (available online). The systematic search, last updated on August 3, 2022, identified 16,601 articles that were imported into Covidence (8). After removing duplicate records, 11,745 titles and abstracts were screened, of which 11,463 articles were excluded. We retrieved the full texts of the remaining 282 records for detailed evaluation. We additionally identified 6 articles for full-text assessment from the reference list of relevant studies and reviews. After a detailed evaluation of full texts, we included 20 studies (14–33) in the qualitative synthesis, of which 6 studies (17, 21, 25, 27, 28, 31) presented data suitable for meta-analysis.

We excluded 262 articles after consideration of the full text; the detailed list of reasons for the exclusions is outlined in Supplemental Figure 1. We attempted to contact with the investigators of 32 articles to obtain additional study details and data (Supplemental Table 3). To date, we received responses for 6 publications (15, 18, 19, 26, 39, 40).

Included Studies

The characteristics of the included studies are detailed in Table 1.

Study design and setting. All 20 included studies were observational in design: 11 were cohort (14–24) and 9 were case-control studies (25–33). Ten of 11 cohort studies were prospective (15–24). All the case-control studies were retrospective in nature. Nineteen studies were published as full articles and one as a conference abstract (22). Our searches did not identify any experimental studies. There was a broad geographical representation with the included studies including 5 continents. Further details of the study characteristics, including country of origin, income status, and publication date, are displayed in Table 1.

Participants. We included a total of 63,838 women in this review, of whom 13,183 were deemed suitable for meta-analysis. The studies' sample sizes ranged from 135 to 11,072 women. Most participants were selected from a general population of healthy women, with 2 studies evaluating participants from a population with a history of recurrent miscarriages (29, 30). Four studies restricted participant selection based on the method of conception: natural (16, 25) or assisted conception (20, 21). For the remaining studies, the method of conception method was not a criterion for participant selection.

Dietary exposure assessment and reporting. The period of dietary exposure varied across the studies. Eighteen studies (15–32) investigated the dietary intake specifically concerning the index pregnancy; 7 studies focused on the preconception period (15, 16, 18, 20–23); 3 studies investigated periconception dietary habits (26, 28, 31); and 5 studies evaluated diet during the index pregnancy (22, 24, 29, 32, 37). The periconception period assessed by the studies ranged from 1–4 years before conception to the second trimester of the index pregnancy. The remaining 3 studies evaluated the dietary pattern at the time of recruitment (25, 29, 30), once the pregnancy outcome has been established, which was assumed to reflect the usual dietary intake.

Dietary exposures were assessed by a food frequency questionnaire (FFQ) (14, 15, 17, 18, 250–33) or multiple 24-hour recalls (16, 19). The number of items for the FFQ ranged from 1 to 220. All of the studies included in the meta-analysis used FFQs. Nine studies used validated questionnaires (15, 18, 20, 23–26, 29, 30) and 2 studies (27, 32) tested the questionnaires for their reproducibility. Thirteen studies (14, 17, 20–28, 31, 33) evaluated the association between food categories and miscarriage risk and 7 studies (15, 16, 18, 19, 29, 30, 32) evaluated the association between a whole diet and miscarriage risk.

There was no consistency in how the dietary intake for each food category was reported across the studies. Ten of 13 studies (14, 17, 20–22, 25–28, 31) that evaluated individual food categories reported the dietary exposure as ranked groups of consumption portions or frequencies per defined period (day, week, or month). Two studies (24, 33) reported a general adherence or preference to a diet rich in the food categories of interest. The remaining study (23) did not categorize consumption amounts into ranked groups but instead analyzed if a linear association existed with no intake as the reference. Details on exposure assessment and reporting methods for individual studies are summarized in Table 1.

Miscarriage definition. All studies defined miscarriage as the loss of pregnancy before viability. Sixteen studies used gestational age to define the limits of viability (14, 25, 17–19, 21, 23, 25–33). The gestational threshold ranged from 12 to 28 weeks of pregnancy. The remaining 4 studies did not specify the definition used for the limits of viability (16, 20, 22, 24).

Risk of bias across studies. Fourteen of the included studies (14–16, 18–21, 23, 25–27, 29–31) were considered to be at low risk of bias. The remaining 6 publications (17, 22, 24, 28, 32, 33) were judged to be at moderate risk of bias. This was mainly because of a lack of data on whether the FFQs were validated to minimize recall bias or whether the analyzed groups were comparable in baseline demographics such as age and body mass index (Supplemental Table 4).

Food categories. Thirteen studies (n = 25,788) (14, 17, 20–28, 31, 33) evaluated the association between the intake of individual food categories and miscarriage risk. Six studies (n = 13,183) presented data suitable for meta-analysis (17, 21, 25, 27, 28, 31). All the studies included in the meta-analysis presented results controlled for confounding at the sampling stage with matched control selection or adjustment during the analysis stage.

Fruit. Five studies reported on the association between fruit intake and miscarriage risk (21, 24–27), of which 3 presented data suitable for meta-analysis (21, 25, 27). One was a prospective cohort (21) and 2 were case-control in design (25, 27). All the studies were deemed to be of high quality. Compared with low fruit intake, high intake of fruit was associated with a 61% reduction in miscarriage odds (OR, 0.39; 95% CI, 0.33–0.46, $I^2 = 90.2\%$, 3 studies, 3,168 women; Fig. 1). Subgroup analysis by national income status did not change our conclusions (Supplemental Fig. 2).

Two studies evaluating fruit intake were excluded from the quantitative synthesis for the following reasons: the first study by Amini et al. (26) (retrospective case-control, n = 166 women) did not provide an effect estimate but instead compared the mean daily portion. The investigators concluded that there was a significant difference in fruit consumption between the control group who had a live birth of a healthy baby and the case group who miscarried (2.21 vs. 1.95 daily portions, $P<.001$), therefore supporting the primary analysis findings that higher fruit intake may be associated with reduced miscarriage odds. The second study by Zhang et al. (24) (prospective cohort, n = 200 women) was excluded for 2 reasons: first, an effect estimate was not presented, and second, miscarriage risk was reported as part of a composite outcome measure. The investigators evaluated the association between a diet rich in seasonal fruit and a "good" pregnancy outcome, defined as live birth with fetal birth weight ≥2.5 kg; and a composite of "poor" outcomes, including miscarriage or premature birth with fetal weight <2.5 kg. It is unclear whether the analysis was adjusted for confounders, but the overall quality was judged as high. The investigators reported that there was a difference in the consumption of fruit between good and poor pregnancy outcome groups (68% vs. 27%; $P<.0001$), therefore also corroborating the aforementioned findings and suggesting that a diet rich in seasonal fruit may be associated with good pregnancy outcomes.

Vegetables. The same 5 studies (21, 24–27) that reported on fruit intake also reported on the vegetables intake and miscarriage risk. The 3 studies from the fruit analysis also contributed to the vegetable intake analysis. Compared with low vegetable intake, high intake of vegetables was associated with a 41% reduction in miscarriage odds (OR, 0.59; 95% CI, 0.46–0.76, $I^2 = 0.0\%$, 3 studies, 2,903 women; Fig. 1). Subgroup analysis by national income status did not change our conclusions (Supplemental Fig. 2).

Two studies (24, 26) were excluded from the quantitative synthesis for the same reasons as described for the fruit analysis. Amini et al. (26) concluded that there was a notable difference in the mean daily intake of vegetables between those who did or did not miscarry (1.31 vs. 1.12 daily portions, $P<.001$). Zhang et al. (24) concluded that there was a substantial difference between good and poor pregnancy outcome groups, in the proportion of women that consume vegetables rich diet (45% vs. 11%; $P<.0001$). Both of these studies support the findings of the meta-analysis and suggest that higher vegetable intake may be associated with reduced miscarriage odds or good pregnancy outcomes.

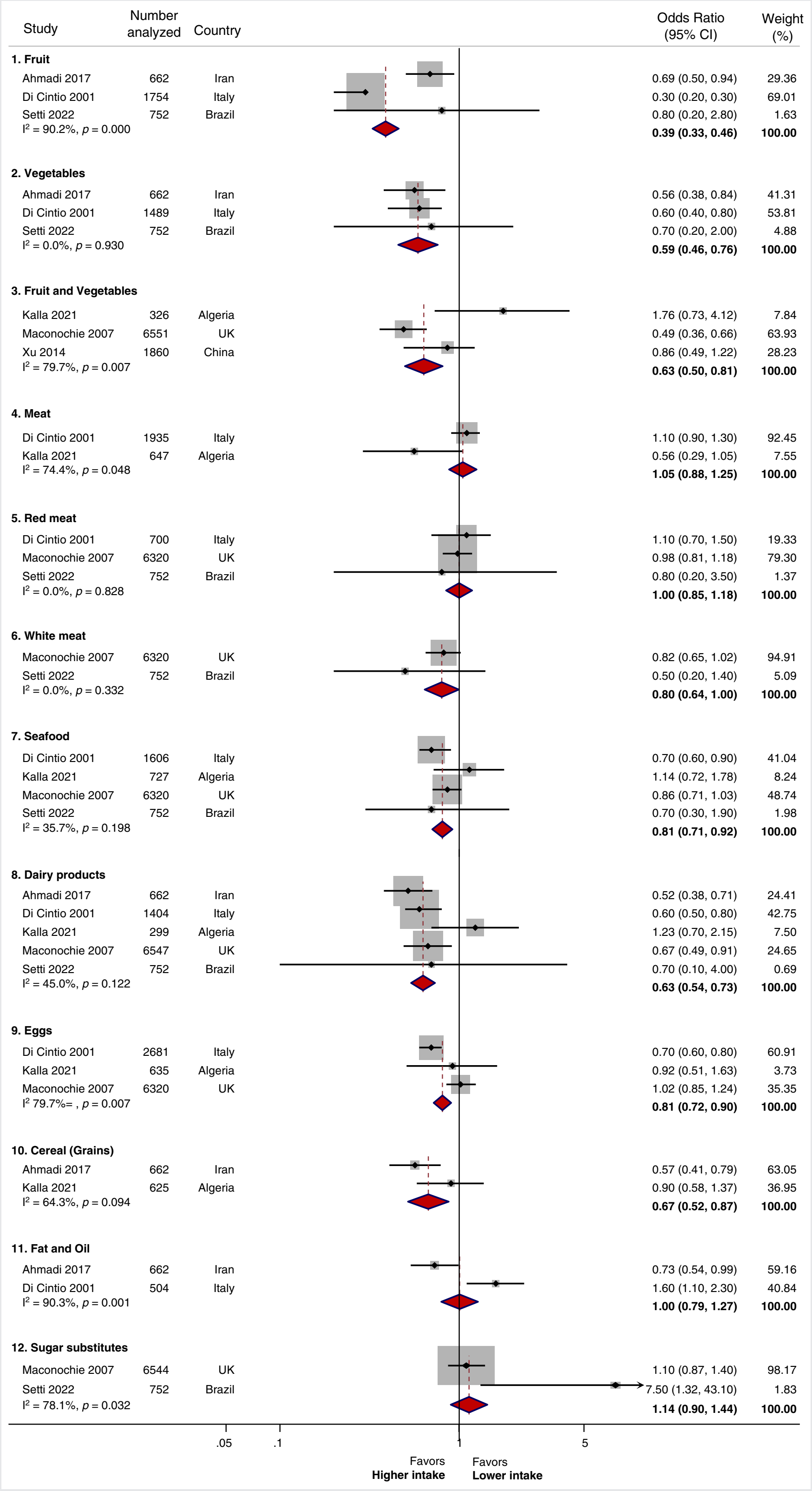
Fruit and vegetables. Three studies reported on the effect of combined intake of fruit and vegetables on miscarriage rates, all of which were suitable for meta-analysis (17, 28, 31). One was a prospective cohort (17) and 2 were case-control (28, 31) in design. One study was deemed to be of high quality (31), whereas the rest were judged to be of moderate quality (17, 28). Higher fruit and vegetable intake was associated with lower miscarriage odds (OR, 0.63; 95% CI, 0.50–0.81, $I^2 = 79.7\%$, 3 studies, 8,737 women; Fig. 1). The subgroup analysis according to income showed that higher vs. lower fruit and vegetable intake may be associated with a 51% reduction in miscarriage odds in high-income settings (OR, 0.49; 95% CI, 0.36–0.66, $I^2 = 0\%$, 1 study, 6,551 women; Supplemental Fig. 2). For the middle-income group, the level of within-group heterogeneity fell but the association became uncertain (OR, 1.00; 95% CI, 0.67–1.50, $I^2 = 51.4\%$, 2 studies, 2,186 women; Supplemental Fig. 2).

Meat. Four studies evaluated the association between meat intake and miscarriage risk (17, 25–27), of which 2 were included in the meta-analysis (17, 27). One was a prospective cohort (17) and one was case-control (27) in design. One study was deemed to be of high quality (27), whereas the other was judged to be of moderate quality (17). We are uncertain whether higher meat intake is associated with higher miscarriage odds (OR, 1.05; 95% CI, 0.88–1.25, $I^2 = 74.4\%$, 2 studies, 2,582 women; Fig. 1). Subgroup analyses did not change our conclusions, and the effect estimate remained imprecise with overlapping 95% CI. For the middle-income group, in contrast to the primary analysis, the effect suggested by the point estimate was noted to have reversed (OR, 0.56; 95% CI, 0.29–1.07, $I^2 = 0\%$, 1 study, 647 women; Supplemental Fig. 2)

The study by Amini et al. (26) was excluded from the quantitative synthesis for the reason stated previously in the fruit and vegetable analyses. Corroborating the meta-analysis findings, the investigators concluded that there was no substantial difference in the mean daily consumption of meat between women who had a healthy live birth and those who experienced miscarriage (1.65 vs. 2.40 daily portions, $P=.085$). The study by Ahmadi et al. (25) (case-control, n = 662 women) was deemed unsuitable for quantitative synthesis as the evaluated exposure was a combination of 2 dissimilar food categories. The study investigated the association between the combined intake of meat and beans, and miscarriage odds. Age was adjusted for as a confounder during the sampling stage, with matched control selection, but it is unclear whether further confounder adjustment was undertaken in the analysis stage. The overall study quality was assessed to be high. The study did not provide an effect estimate but concluded that there was a difference in the consumption of meat and beans between women who did or did not experience miscarriage and suggested that higher consumption of meat and beans may be associated with reduced miscarriage risk ($P=.004$).

Red meat. Four studies investigated the association between red meat intake and miscarriage odds (21, 23, 27, 28), of which 3 presented data suitable for meta-analysis (21, 27, 28). One was a prospective cohort (21) and the remaining 2 were case-control (27, 28) in design. Two studies (21, 27) were deemed to be high quality and the remaining study (28) was of moderate quality. We are uncertain whether red meat intake is associated with miscarriage odds (OR, 1.00;

FIGURE 1



The association between food group and miscarriage risk in healthy women of reproductive age.

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95% CI, 0.85–1.18, $I^2 = 0.0\%$, 3 studies, 7,772 women; Fig. 1). Subgroup analyses did not change our conclusions (Supplemental Fig. 2).

The study by Wesselink et al. (23) (prospective cohort, n = 7,199 women) presented its effect estimate as a hazard ratio (HR). It was not possible to calculate the corresponding OR from the available data and therefore the study was excluded from the meta-analysis. In this study, the investigators evaluated the association between protein-rich food sources and miscarriage risk using the data from 2 separate web-based cohorts (Pregnancy Online Study; PRESTO from the United States and Canada, and SnartForaeldre.dk; SF from Denmark). The study quality was judged to be high and the analysis was adjusted for multiple confounders. First, the investigators fitted restricted cubic splines to assess the shape of association between red meat intake and miscarriage risk, which was interpreted as being relatively linear. Then, the effect of increasing one type of protein-rich food at the expense of another on miscarriage risk was estimated. For the PRESTO cohort, replacing 100 g of seafood per week with 100 g of red meat was associated with increased miscarriage risk (HR, 1.10; 95% CI, 1.00–1.20). In contrast, the miscarriage risk fell in the SF cohort (HR, 0.89; 95% CI, 0.82–0.98). Overall, the study findings remain uncertain and there was insufficient evidence to determine whether there is an association between red meat intake and miscarriage risk.

White meat. Three studies reported on the association between white meat intake and miscarriage risk (21, 23, 28), of which 2 presented data suitable for meta-analysis (21, 28). One was a prospective cohort study (26), deemed to be of high quality, and the other was a case-control study (28), deemed to be of moderate quality. We are uncertain whether white meat intake is associated with miscarriage odds (OR, 0.80; 95% CI, 0.64–1.00, $I^2 = 0.0\%$, 2 studies, 7,072 women; Fig. 1). The direction of the estimate indicated that higher intake may be associated with reduced odds of miscarriage. However, with the upper CI touching 1, we could not be confident of its association. After the subgroup analyses, the evidence remained uncertain with consistency in the direction of estimates.

The study by Wesselink et al. (23) was excluded from the quantitative synthesis for the same reason described in the red meat analysis. Restricted cubic splines analysis indicated the association between white meat intake and miscarriage risk to be relatively linear. For the PRESTO cohort, it was uncertain whether increasing white meat consumption at the expense of other protein-rich food sources is associated with miscarriage risk. For the SF cohort, replacing 100 g of seafood per week with 100 g of white meat was associated with a marginal reduction in miscarriage risk (HR, 0.91; 95% CI, 0.83–0.99). Overall, the evidence remains uncertain on the association between white meat intake and miscarriage risk.

Seafood. Nine studies reported on the effect of seafood intake on miscarriage risk (14, 17, 20–23, 26–28), of which 4 presented data suitable for meta-analysis (17, 21, 27, 28). Two were prospective cohorts (17, 21) and the remaining 2 were case-control (27, 28) in design. Two studies were deemed to be of high quality (26, 32) and 2 of moderate quality (17, 28). Compared with low intake, high intake of seafood was associated with 19% reduction in miscarriage odds (OR, 0.81; 95% CI, 0.71–0.92, $I^2 = 35.7\%$, 4 studies, 9,405 women; Fig. 1). For the high-income setting, subgroup analysis did not change our conclusions despite the increase in within-group heterogeneity (OR, 0.78; 95% CI, 0.68–0.90, $I^2 = 53.5\%$, 2 studies, 7,926 women; Supplemental Fig. 2). For the middle-income setting, within-group heterogeneity was imperceptible but the evidence of association became uncertain (OR, 1.04; 95% CI, 0.69–1.56), $I^2 = 0.0\%$, 2 studies, 1,479 women; Supplemental Fig. 2).

Five studies (14, 20, 22, 23, 26) evaluating seafood intake were excluded from the quantitative synthesis. The first study by Amini et al. (26) was excluded for the same reason described for the fruit, vegetables, and meat analyses. The investigators concluded that there was no difference in the mean daily consumption of seafood including fish between women who had live birth and women who miscarried (0.15 vs. 0.41 daily portions, $P = .064$). The second study by Wesselink et al. (23) was excluded for the same reason as stated for the red and white meat analyses. Restricted cubic splines analysis suggested the association between seafood intake and miscarriage risk to be linear. For the PRESTO cohort, increasing seafood consumption by 100 g per week at the expense of 100 g of eggs was associated with a slight reduction in miscarriage risk (HR, 0.89; 95% CI, 0.80–0.98). For the SF cohort, it was uncertain whether increasing seafood consumption at the expense of other protein-rich food sources is associated with miscarriage risk. The third study by the same investigator (22) (prospective cohort, n = 3,821 women) was excluded as the effect estimate was presented as a HR. In this study, the investigators evaluated the association between preconception seafood intake and miscarriage risk. Seafood was grouped into 2 categories before the analysis: fatty or lean. The report states that adjustment for potential confounders was performed during the analysis, although the list of covariates was not explicitly specified. The overall quality was assessed to be moderate. Its findings were uncertain of whether a higher intake of fatty seafood may be associated with an increase in miscarriage risk (HR, 1.53; 95% CI, 0.91–2.57). It was also unclear whether a higher intake of lean seafood may be associated with a reduction in miscarriage risk (HR, 0.74; 95% CI, 0.89–1.01). The study by Salas-huetos et al. (20) (prospective cohort, n = 229 women) was excluded from the quantitative synthesis for 2 reasons. First, the effect estimate was presented as predicted marginal proportions and it was not possible to infer the corresponding OR from the available data. Second, miscarriage probability was reported as part of composite outcome measures: "total pregnancy loss" and "clinical pregnancy loss." Total pregnancy loss was defined as any beta-human chorionic gonadotropin–confirmed pregnancies that did not result in live births. Clinical pregnancy loss was defined as any ultrasound-visualized pregnancies that did not result in a live birth. Neither of these definitions had an upper gestational cut-off and therefore would include stillbirths. The study quality was judged to be high and multiple confounders were adjusted for during the analysis. In this study, the investigators evaluated the association between couples' intake of omega-3 fatty acids, omega-3-rich food sources, and treatment outcomes after assisted reproductive therapy. The investigators concluded that women's intake of seafood that included dark fish, white fish, and shellfish was unrelated to the probabilities of pregnancy loss. For total pregnancy loss, the multivariable-adjusted probability in the lowest and the highest quartiles of seafood intake were 0.27 (95% CI, 0.09–0.58) and 0.17 (95% CI, 0.05–0.46) with a *P* value of .68. Clinical pregnancy loss also demonstrated similar results. The final study by Axmon et al. (14) was excluded from the meta-analysis because the miscarriage odds were reported as part of a composite measure for all pregnancy loss including stillbirth. The main aim of the study was to evaluate the effects of a high intake of fish from the Baltic Sea as a proxy measure of increased exposure to persistent organochlorine compounds. In the cohort that was suspected to have higher exposure to persistent organochlorine compounds, miscarriage odds were calculated between women with no or high fatty fish consumption. High intake was defined as fatty fish consumption of at least 2 meals per week. The investigators concluded that higher fish intake was not associated with an increased risk for miscarriages and stillbirths (OR, 0.51; 95% CI, 0.19–1.43). Despite the degree of uncertainty with wide CIs, it is noted that the direction of the point estimate suggests reduced miscarriage odds with higher fatty fish consumption. Overall, the evidence suggests that higher seafood intake may be associated with reduced miscarriage odds, but the effect may vary depending on the population and the type of seafood consumed.

Dairy products. Eight studies reported on the association between dairy product intake and miscarriage risk (17, 21, 23–28), of which 5 presented data suitable for meta-analysis (17, 21, 25, 27, 28). Two were prospective cohorts (17, 21) and 3 were case-control (30, 32, 33) in design. Three studies were considered to be high quality (21, 25, 27) and 2 studies of moderate quality (22, 33). High intake of dairy products may be associated with a 37% reduction in miscarriage odds (OR, 0.63; 95% CI, 0.54–0.73, I^2 = 45.0%, 5 studies, 9,664 women; Fig. 1). Subgroup analyses did not change our conclusions despite a notable increase in within-group heterogeneity in the middle-income group (Supplemental Fig. 2).

Three studies (28, 29, 31) were excluded from the meta-analysis for reasons previously discussed. The findings from Amini et al. (26) support the meta-analysis result, concluding that there was a notable difference in the intake of dairy products between the groups who did and did not miscarry (4.27 vs. 3.12 daily portions, P=.031). Wesselink et al. (23) concluded the association between dairy intake and miscarriage risk was relatively linear. The HRs of increasing dairy intake at the expense of another protein source were not presented. However, the investigators concluded that for the PRESTO cohort, there was uncertainty in the association between dairy intake and miscarriage risk. For the SF cohort, increasing dairy intake was associated with slightly lower hazards of miscarriage. Lastly, Zhang et al. (24) concluded that there was a difference in the consumption of a diet rich in calcium and protein-rich sources from milk products between good and poor pregnancy outcome groups (78% vs. 19%; P<.0001), hence suggesting that a diet rich in calcium and milk-derived protein-rich source may be associated with good pregnancy outcomes.

Eggs. Five studies (17, 23, 26–28) evaluated egg intake and its association with miscarriage risk, of which 3 presented data suitable for meta-analysis (17, 27, 28). One was a prospective cohort (17) and 2 were case-control (27, 28) in design. One study was judged to be high quality (27), and the rest of moderate quality (17, 28). Higher egg intake was associated with a reduction in miscarriage odds by 19% (OR, 0.81; 95% CI, 0.72–0.90, I^2 = 79.7%, 3 studies, 9,636 women; Fig. 1). Subgroup analysis did not change our conclusions for the high-income group despite an increase in within-group heterogeneity (OR, 0.80; 95% CI, 0.72–0.90, I^2 = 89.7%, 2 studies, 9,001 women; Supplemental Fig. 2). For the middle-income group, the direction of the effect estimate remained the same but the evidence became uncertain (OR, 0.92; 95% CI, 0.51–1.64, I^2 = 0%, 1 study, 635 women; Supplemental Fig. 2).

Two studies (23, 26) were excluded from the primary analysis for reasons stated previously. Amini et al. (26) corroborated the meta-analysis findings and concluded there was a substantial difference in the daily consumption of eggs between women who had live birth and those who miscarried (mean ± standard deviation 0.45 ± 0.33 vs. 0.45 ± 0.42 daily portions, P<.001). The evidence from Wesselink et al. (23) was conflicting. The association between egg intake and miscarriage appeared to be linear for the PRESTO cohort but not in the SF cohort. Neither cohort demonstrated a clear effect on miscarriage risk when egg intake was increased at the expense of plant-based proteins or dairy products. The investigators concluded that in the PRESTO cohort, increasing egg intake was associated with slightly higher hazards of miscarriage, whereas the opposite was observed in the SF cohort.

Cereal (grains). Three studies investigated the effect of cereal intake on miscarriage (17, 25, 26), 2 of which were suitable for meta-analysis (17, 25). One was a prospective cohort (17) deemed to be of moderate quality and the other was a case-control study (25) considered to be of high quality. Higher cereal intake may be associated with a 33% reduction in miscarriage odds compared with lower intake (OR, 0.67; 95% CI, 0.52–0.87, I^2 = 64.3%, 2 studies, 1,287 women; Fig. 1). Subgroup analysis was not performed for this category as all the studies originated from middle-income countries.

Amini et al. (26) was excluded from the quantitative synthesis for the previously discussed reason. In this study, the association was uncertain and there was insufficient evidence of a difference in the consumption of cereal between women who experienced live birth and women who miscarried (4.56 vs. 3.44 daily portions, P=.089).

Fat and oil. Three studies evaluated the association between fat and oil intake and miscarriage odds (25–27), all of which were high-quality case-control studies. Two studies were suitable for meta-analysis (25, 27). We are uncertain whether higher fat and oil intake is associated with increased miscarriage odds (OR, 1.00; 95% CI, 0.79–1.27, I^2 = 90.3%, 2 studies, 1,166 women; Fig. 1). Subgroup meta-analyses restricted to one study for each income group suggested that higher fat and oil intake may be associated with a 60% increase in miscarriage odds (OR, 1.60; 95% CI, 1.11–2.31, $I^2 = 0\%$, 1 study, 504 women; Supplemental Fig. 2). In contrast, higher fat and oil intake may be associated with 27% reduction in miscarriage risk in the middle-income setting (OR, 0.73; 95% CI, 0.54–0.99, $I^2 = 0\%$, 1 study, 662 women; Supplemental Fig. 2).

Amini et al. (26) was excluded for the same reasons stated in the previous analyses. The investigators performed a chi-squared test and concluded that there was sufficient evidence to suggest a difference in the consumption of fat between women who did and did not miscarry (P=.005).

Sugar substitutes. Two studies investigated the relationship between the intake of sugar substitutes and miscarriage odds (21, 28), all of which presented data suitable for meta-analysis. One was a prospective cohort study of high quality (21) and the other was a case-control study of moderate quality (28). We are uncertain whether higher sugar substitute intake is associated with increased odds of miscarriage (OR, 1.14; 95% CI, 0.90–1.44, $I^2 = 78.1\%$, P=.032, 2 studies, 7,296 women; Fig. 1). Subgroup analysis restricted to one study for each income setting did not change our conclusions for the high-income group. For the middle-income setting sensitivity analysis, results showed that higher consumption of sugar substitutes may be associated with higher miscarriage odds (OR, 7.50; 95% CI, 1.31–42.86, $I^2 = 0\%$, 1 study, 752 women; Supplemental Fig. 2).

Miscellaneous. There were 10 food items that were included in the quantitative synthesis: refined sugar, sweets, chocolate, soft drinks, nuts, soya products, processed meat, plant-based proteins, fast food, and fried food.

Two studies evaluated the intake of refined sugar (21, 26). Amini et al. (26) concluded that there was evidence of a difference in the consumption of simple sugar between the group who had live birth and those who miscarried (P=.021), although the direction of effect is unclear from the reported data. The findings from Setti et al. (21) were uncertain, with imprecise point estimate (OR, 1.1; 95% CI, 0.4–3.0, P=.789). Kalla et al. (17) reported on the association between intake of sweets and miscarriage odds and concluded that the evidence was uncertain (OR, 1.42; 95% CI, 0.89–2.26). Finally, Maconochie et al. (28) evaluated that the consumption of chocolate and concluded higher intake may be associated with reduced miscarriage odds (OR, 0.81; 95% CI, 0.68–0.97).

Two studies reported on the intake of soft drinks and miscarriage risk (17, 26), of which only one study (22) reported the data with a point estimate. Kalla et al. (17) concluded that the association between soft drink intake and miscarriage odds was uncertain (OR, 0.78; 95% CI, 0.49–1.24). In contrast, Amini et al. (26) concluded that there was a notable difference in soft drink consumption between those who did or did not miscarry (P<.001), although the direction of effect was not reported.

Salas-huetos et al. (20) presented the findings on total nut intake and miscarriage odds and concluded that higher intake of total nuts, including peanuts, walnuts, and other nuts, was unrelated to probabilities of pregnancy loss. For total pregnancy loss, the multivariable-adjusted probabilities in the lowest and the highest quartiles of total nut intake were 0.14 (95% CI, 0.03–0.45) and 0.21 (95% CI, 0.06–0.51), respectively, with a P value of .66. For clinical pregnancy loss, the findings were similar. Probabilities for the lowest and the highest quartiles were as follows: 0.11 (95% CI, 0.02–0.46) and 0.16 (95% CI, 0.04–0.46), P value = .85.

For higher intake of soya products, one study (28) concluded the association with miscarriage was uncertain (OR, 1.06; 95% CI, 0.66–1.70). Consumption of processed meat and plant-based proteins was evaluated by Wesselink et al. (23). Plant-based proteins included nuts, seeds, legumes, and soy. The investigators concluded that the relationship appeared relatively linear. Neither of these food groups showed sufficient evidence of association with miscarriage hazards when the intake was increased at the expense of other protein sources.

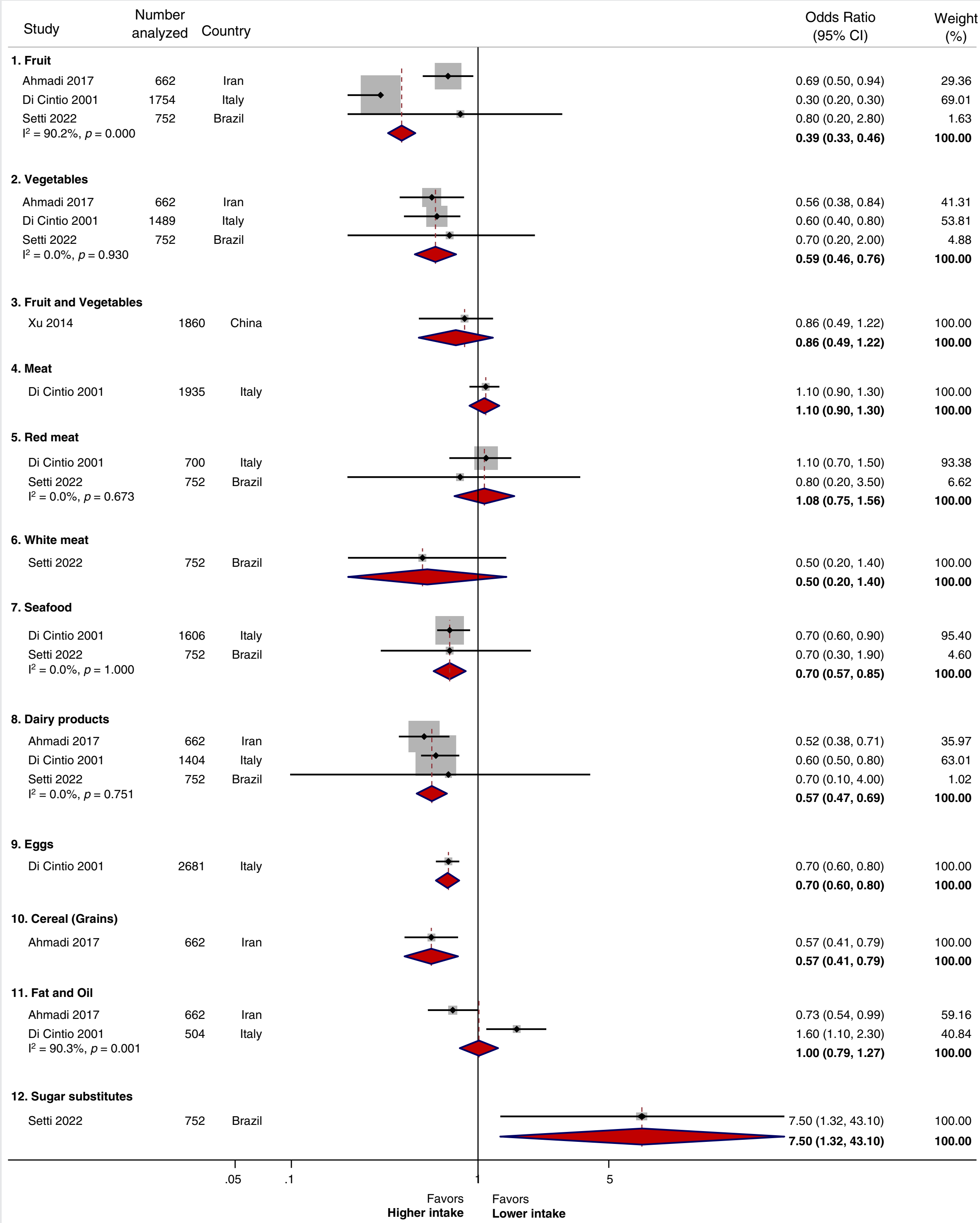
Fast food consumption was assessed by Amini et al. (26). The investigators concluded that there was a substantial difference in the consumption of fast food between women who had live birth compared with women who miscarried (P<.001), although the direction of effect was not reported. Finally, a case-control study by Zhang et al. (33) examined the association between preference for fried food and miscarriage risk in 544 women. It is unclear whether confounder adjustment was performed during the analysis and the study was considered to be at moderate risk of bias. An effect estimate was not provided but the study concluded with statistical confidence that women who experienced miscarriages were more likely to prefer fried food (39% vs. 28.1%; P=.013).

Sensitivity analysis. We conducted sensitivity analyses by limiting the meta-analysis to studies with results controlled for confounders and a low risk of bias (Fig. 2). The sensitivity analysis corroborated most of the conclusions drawn from the primary analyses with the direction of point estimate remaining the same for all food categories. In women with a higher intake of sugar substitutes, the odds of miscarriage were 7.5 times greater (OR, 7.50; 95% CI, 1.31–43.10, $I^2 = 0\%$, 1 study, 752 women; Fig. 2). For the fruit and vegetables category, the fall in power led to an imprecise point estimate and the conclusion became uncertain.

Whole diet. Seven studies (n = 38,050) (15, 16, 18, 19, 29, 30, 32) evaluated the relationship between whole diet and miscarriage risk. There were an insufficient number of studies with similar dietary patterns to pool for quantitative synthesis. Six studies (15, 16, 18, 19, 29, 20) used the a priori method for dietary pattern analysis and the remaining study (32) used the a posteriori method. All studies provided effect estimates after adjustment for confounders.

A priori. Three studies (15, 16, 18) (n = 14,247 women) assessed adherence to predefined dietary patterns. All the studies were prospective cohorts, judged to be of high quality and conducted in high-income countries. In total, 6 patterns were evaluated: alternate Mediterranean diet, which is theorized to improve endothelial function and reduction in oxidative stress; Fertility Diet, which has been associated with a reduction in ovulatory infertility; alternate Healthy Eating

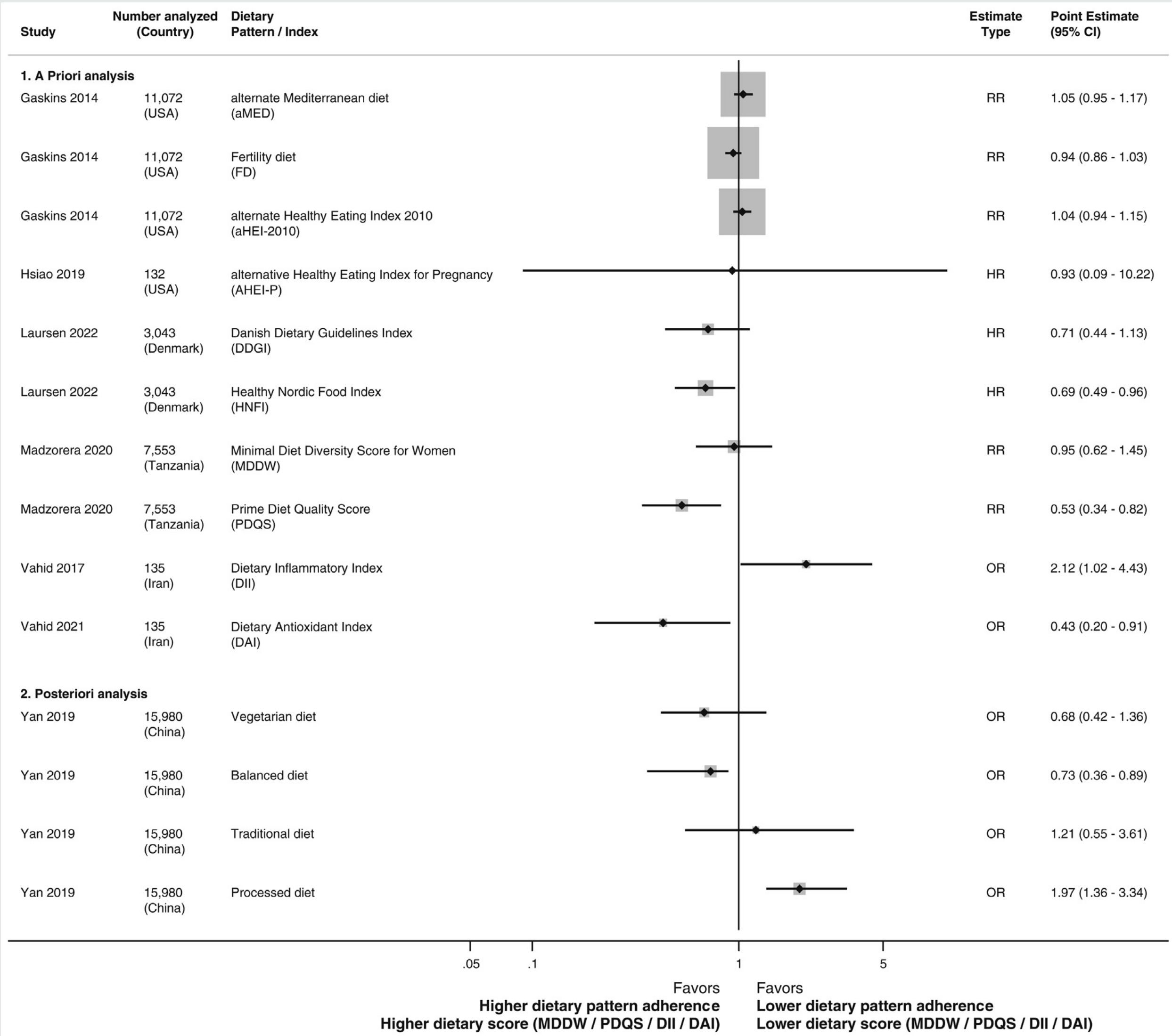
FIGURE 2



The association between food group and miscarriage risk in healthy women of reproductive age: sensitivity analysis including studies with low risk of bias and confounder adjusted estimates.

Chung. Maternal diet and miscarriage risk. Fertil Steril 2023.

FIGURE 3



A summary graph describing the association between whole diet evaluation and miscarriage risk in healthy women of reproductive age.

Chung. Maternal diet and miscarriage risk. Fertil Steril 2023.

Index 2010 (aHEI-2010), which has been associated with lower risk of chronic diseases; alternate Healthy Eating Index for Pregnancy, which is similar to aHEI-2010 but adapted by replacing alcohol with components thought to be important for pregnancy; Danish Dietary Guidelines Index, which is based on the national Danish dietary guidelines and aims to reduce the risk of non-communicable diseases; Healthy Nordic Food Index (HNFI), which was developed to reflect dietary choices from a range of traditional and commonly eaten Nordic foods, considered to be healthy. The first 3 dietary patterns (alternate Mediterranean diet, Fertility Diet, and aHEI-2010) were evaluated by Gaskins et al. (15) using the data from the Nurses' Health Study II. Hsiao et al. (16) used the data from the Lifestyle and Fertility study (ISIS) to evaluate alternate Healthy Eating Index for Pregnancy. Finally, Laursen et al. (18) evaluated Danish Dietary Guidelines Index and HNFI using the data from SF study that were described previously for the food group analyses. The degree of adherence was calculated as a score: a higher score indicating greater adherence to the dietary pattern or index of interest. Using the score, women were grouped into quantiles and then miscarriage risk was compared between the lowest adherent group and the highest adherent group. Out of the investigated dietary patterns, HNFI was the only pattern that demonstrated clear evidence of a reduction in miscarriage hazards with higher adherence to the index (HR, 0.69; 95% CI, 0.49–0.96) (Fig. 3).

The remaining 3 studies (19, 29, 30) evaluated dietary patterns using selected scoring systems. Madzorera et al. (19) (n = 7,553 women) used 2 scoring systems: Women's Dietary Diversity Score, which was produced by the United Nations to measure dietary diversity and predict micronutrient adequacy in women of reproductive age from low- and middle-income countries; and Prime Diet Quality Score (PDQS), developed as a simple measure of diet quality by differentiating healthy foods from unhealthy ones based on association with chronic conditions such as cardiovascular disease. Examples of food groups that were considered healthy were green or cruciferous vegetables, whole fruits, poultry, fish, and egg. Foods such as red or processed meat, refined grains, sugar, or fried foods were considered unhealthy. Using the scoring system, women were grouped into quintiles and miscarriage risk was compared between the lowest and the highest quintiles. Diet diversity, when assessed using Women's Dietary Diversity Score, was not confidently associated with miscarriage risk (risk ratio, 0.95; 95% CI, 0.62–1.45; Fig. 3). In contrast, a higher PDQS score was associated with a 47% reduction in miscarriage risk (risk ratio, 0.53; 95% CI, 0.34–0.82; Fig. 3), therefore suggesting that high diet quality may contribute to reduced miscarriage risk. Vahid et al. group published 2 studies evaluating Dietary Inflammatory Index (DII) (30) and Dietary Antioxidant Index (DAI) (29) in the same population of women with a history of recurrent miscarriages (n = 135 women). DII was developed to quantitatively measure diet-associated inflammation in any population, with a high DII score indicating increased levels of proinflammatory components in the diet. DAI examines the total antioxidant properties of an individual diet with a higher score corresponding to a diet rich in antioxidant food groups. The studies found that women who consumed high levels of proinflammatory diet exhibited increased odds of miscarriage (OR, 2.12; 95% CI, 1.02–4.43; Fig. 3). However, in women who consumed a diet with high levels of antioxidant rich foods, the odds of miscarriage were reduced by 57% (OR, 0.43; 95% CI, 0.20–0.91). The investigators concluded that a diet rich in antiinflammatory factors may reduce miscarriage odds.

A posteriori. One study by Yan et al. (32) (case-control, moderate quality, n = 15,980) used the factor analysis statistical method to derive dietary patterns from the dataset. Four patterns were identified and were named to reflect the main components of the diet: vegetarian, a diet characterized by high fruit and vegetable intake; balanced diet, a diet with high diversity including animal proteins, seafood, fruit, vegetables, and nuts; traditional, a diet rich in food such as rice porridge, noodles, eggs, and dairy products; and processed, a diet rich in processed food sources. The evidence of association was uncertain for the vegetarian (OR, 0.68; 95% CI, 0.42–1.36; Fig. 3) and traditional (OR, 1.21; 95% CI, 0.55–3.61; Fig. 3) diets. Greater adherence to a balanced diet was associated with reduced miscarriage odds (OR, 0.73; 95% CI, 0.36–0.89; Fig. 3) and miscarriage odds nearly doubled in those with greater adherence to a processed diet (OR, 1.97; 95% CI, 1.36–3.34; Fig. 3). The investigators concluded that a balanced diet with a low intake of processed food sources may be associated with reduced miscarriage risk.

DISCUSSION

Summary of Evidence

In this systematic review and meta-analysis of 20 observational studies evaluating a total of 63,838 women, we aimed to investigate the association between periconceptual dietary intake and miscarriage risk in healthy women of reproductive age. We found that miscarriage rates were lower in women who exhibited a higher intake of fruit, vegetables, fruit and vegetables, seafood, dairy products, eggs, and cereal. The primary analysis findings were unclear for meat, red meat, white meat, fat and oil, and sugar substitutes. We identified 10 other food categories that could not be grouped for meta-analysis. For these food groups, the evidence was conflicting for refined sugar and soft drinks, and uncertain for sweets, nuts, soya products, processed meat, and plant-based proteins. There was some evidence of a difference in the consumption of fast food between those who did or did not miscarry. Finally, a preference for fried food or a lower intake of chocolate may be associated with higher miscarriage odds. When evaluating the whole diet, we found evidence of 14 dietary patterns, from which 6 demonstrated evidence of an association with miscarriage risk. Four were a priori and 2 were posteriori patterns. Adherence to healthy Nordic food groups (HNFI), a better quality diet with healthy foods (PDQS), antioxidant rich food sources (DAI), and balanced diets were associated with a reduction in miscarriage odds. In contrast, higher consumption of a proinflammatory diet or processed food was found to increase the miscarriage odds. Overall, the evidence suggests that diets rich in foods conventionally perceived as healthy, including fruit and vegetables, and absent in perceived unhealthy choices, such as processed foods, may be associated with a reduction in miscarriage risk. However, the paucity of evidence limits the certainty of these findings and further high-quality studies are required to elucidate potential causative associations between diet and miscarriage risk.

Food categories. Most of the studies included in this review evaluated the association between lower vs. higher intake of food categories and miscarriage risk. For 5 food categories, the evidence was unclear of an effect on miscarriage risk because of imprecision (wide CIs) and inconsistency (substantial heterogeneity). The potential source of heterogeneity was investigated with subgroup analyses and we detected differences in the strength and certainty of pooled effect estimates based on the country's income. For the high-income group, the subgroup analyses did not change our conclusion, except for fat and oil where the association became clearer and suggested that higher intake may be associated with an increase in miscarriage odds. For the middle-income group, the findings became uncertain for 3 categories (fruit and vegetables, seafood, and eggs). The subgroup analysis findings are in keeping with epidemiological evidence demonstrating that socioeconomic status at the individual or country level influences dietary choice and quality (35–38). The cost and affordability of a healthy diet vary across countries, and the data from "The State of Food Security and Nutrition in the World 2022" suggest that the proportion of a population unable to afford a healthy diet increases with the fall in a country's national income status (41). This effect does not appear to be equal across all food categories, and studies have demonstrated that some food choices may be more susceptible to influence by fluctuation in diet costs and income (36). After the stratified analyses by country income status, the within-group heterogeneity fell for the majority of food groups. However, for some food groups, the level of within-group heterogeneity remained substantial. This suggested that country income status does not fully account for the variation between studies. The sensitivity analyses supported most of the conclusions drawn from the primary analyses, except for one food group (fruit and vegetables) where the reduction in power led to uncertainty around the findings.

Our results largely agree with existing evidence on diet and other reproductive outcomes. Our study found that food groups that are commonly considered to be healthy, with high levels of essential nutrients, were found to have protective effects on miscarriage risk. A systematic review and meta-analysis of observational studies by Zadeh et al. (42) found that "healthy", or so-called "prudent" diets with a higher intake of fruits or vegetables, are associated with a reduction in the risk of gestational diabetes. There is overwhelming evidence on the effects of a higher intake of fruit and vegetables in reducing the risk of cancer and cardiovascular diseases (CVD) (43, 44). However, data on the benefit of fruit and vegetable intake in late-onset diabetes have not been consistent. Fruits and vegetables are 2 food groups with many similarities in nutritional content, and as such, the classification of a food item may alternate between the 2 groups depending on whether botanical or culinary criteria are used. Therefore, many studies group fruits and vegetables together and interpret the findings concurrently. However, it should be noted that distinct differences also exist with fruits typically richer in sugar and calorific content. This difference likely contributes to the inconsistency in the beneficial effects demonstrated by studies on fruit and vegetable consumption. A meta-analysis by Carter et al. (45) found consumption of green leafy vegetables to be associated with a significant reduction in type 2 diabetes risk. However, no association was seen with the consumption of fruits, vegetables, or fruits and vegetables. An observational study (46) assessing the effects of maternal fruit and vegetable consumption on newborn anthropometric measurements found high collinearity between consumption of the 2 food groups intake. However, only vegetable intake was associated with SGA risk and no relationship was seen with the consumption of fruits. In our review, all 3 groups (fruit, vegetables, and fruit and vegetables) demonstrated a clear reduction in miscarriage odds with higher consumption. The investigators note with interest that the beneficial effect appeared most profound with fruit intake, albeit with significant heterogeneity across studies. The reasons for this are unclear and will need further evaluation in future studies. In contrast, vegetable intake demonstrated consistent effect estimates across studies with imperceptible heterogeneity. All of these suggest that the consumption effects of fruit and vegetables may be type and dose dependent. The shared beneficial effects of fruits and vegetables are likely to be multifactorial and include the following: high availability of a variety of nutrients such as phytochemicals, vitamins including folate, minerals, and fiber; synergy or interactions of bioactive compounds; and antioxidation and antiinflammatory effects of these nutrients. Antioxidant effects of fruits and vegetables are hypothesized to be one of the key mechanisms in delaying the progression of the atherosclerotic disease through low density lipoprotein oxidation (47) and consequently CVD. Evidence suggests that oxidative stress plays a key role in both the initiation and progression of multiple disease processes (48). Reproductive health is not an exception, and both direct and indirect evidence have demonstrated that oxidative stress has a negative impact on female and male fertility (49, 50). Studies in women undergoing in vitro fertilization show that oxidative stress measured by the reactive oxygen species levels in oocyte follicular fluid exerts deleterious effects on oocyte quality, fertilization, and embryo quality (51–53). Maternal and paternal oxidative stress has also been linked with increased miscarriage risk (52, 54). On the background of this, treatment with antioxidant supplements has been intensely investigated but a meaningful improvement in clinical outcome is yet to be demonstrated (55, 56). In our review, among many dietary patterns that were evaluated, a standardized assessment based on antioxidant nutrient content and capacity was one of the few patterns associated with a reduction in miscarriage risk (29). Fruits, vegetables, and fish are example food items that are rich in dietary antioxidants and have shown a strong linear correlation with the composite antioxidant index (57).

There was less certainty around meat intake. Meat is an important source of protein, also rich in vitamin B, phosphorus, and iron (58). Different types of meat exhibit varying amounts of saturated fat, salt, and nitrates, which may be added through food processing techniques. These latter components have been associated with impaired glucose intolerance and insulin resistance (59, 60). Furthermore, higher intake of red or processed meat has been associated with an increased risk of gestational diabetes (42, 61–63) and hypertensive disorders of pregnancy (64). Overall, the association between meat and miscarriage risk remains uncertain.

The evidence on seafood was conflicting. The overall findings from the quantitative synthesis suggested that a higher intake of seafood may reduce the miscarriage risk. However, this was not fully corroborated by the evidence included in the narrative synthesis. Seafood is a noteworthy food group, containing high-quality protein and essential nutrients such as niacin, vitamin B, vitamin D, selenium, and omega-3 fatty acids (65). Although these nutrients clearly provide a favorable effect on people's reproductive health, seafood is also a recognized source of environmental toxins and contaminants. It may be high in mercury, persistent organic pollutants, and polychlorinated biphenyls (66, 67). This may explain the conflicting evidence identified, possibly suggesting a nonlinear relationship between seafood intake and miscarriage risk. Evidence linking seafood consumption and other pregnancy outcomes also demonstrates conflicting results. High shellfish consumption is associated with increased small for gestational age (SGA) risk (63). However, fish, another food item in the seafood category, does not appear to have a relationship with SGA risk (63). Therefore, the investigators conclude that the protective effects of seafood may also be dose and type dependent.

Dairy products are also good sources of protein with high nutrient density and bioavailability. They are rich in calcium, phosphorus, potassium, and vitamin B12, among others (68). Increasing maternal dairy intake has consistently been associated with promoting fetal and neonatal growth (69). Eggs are an affordable and nutrient-dense food source for protein, omega-3 fatty acids, vitamin A, B, D, and selenium (65). The egg yolk is cholesterol rich and therefore its association with CVD has long been subject to much debate and ongoing interest on the background of conflicting findings (70). However, recent evidence demonstrates that moderate egg consumption is not associated with overall CVD and for some populations, egg consumption appears to have a protective effect against CVD (71, 72). Supporting this further, epidemiological studies have consistently demonstrated the lack of correlation between dietary and serum cholesterol levels (73). As demonstrated by Wesselink et al. (23), the relationship between egg intake and miscarriage risk is unlikely to be linear and the strength and direction of effect may be dose dependent.

Cereal, also called grain, is an excellent source of carbohydrates and is cholesterol free, low in saturated fat, and often high in fiber. Pregnancy is a state of physiological stress with increased demand for calorie intake, especially in the third trimester (74, 75). Cereal is an important nutrient source that readily helps to meet this demand. It is important to note that the effect of grain consumption may be influenced by multiple factors including grain type or processing techniques. For example, when grains are refined, the bran and germ layers are stripped, leaving only the endosperm that is mostly starch in content but devoid of beneficial nutrients such as fiber, vitamins, minerals, antioxidants, and phytochemicals. Then refined grains are often consumed with added sugar, fat, and salt. There was a lack of information on the type, processing technique, or fortification status of the grain that was consumed by the study participants. Therefore, it was not possible to conduct further analysis to infer potential mechanisms behind the observed association in our review. A high intake of whole grains is associated with a reduced risk of coronary heart disease, CVD, diabetes, total cancer, and mortality from all causes as well as other chronic diseases (76). However, data on grain types and pregnancy outcomes are limited and unclear. A meta-analysis of 13 cohort studies suggested that high consumption of refined (77, 78) grains as part of the "western diet" is associated with an increased risk of gestational diabetes (42). However, a subsequently published randomized trial of 248 healthy women demonstrated conflicting results and no significant difference in the risk of gestational diabetes or neonatal outcomes was seen between the groups that were randomly allocated to a diet rich in whole vs. refined grain during pregnancy (79).

Our findings were uncertain about an association between the consumption of fat and oil, and miscarriage risk. The investigators recognize that "fat and oil" is an oversimplified categorization of this food group. Dietary fatty acids vary greatly in their structure, function, and biochemical properties depending on the number and position of double bonds (saturated, mono- and polyunsaturated, and trans). For nonobstetric outcomes, particularly for cardiovascular events, a high intake of saturated or trans fatty acids has long been considered a risk factor for disease (80, 81). However, there is now increasing consensus that the metabolic and physiological effects of fatty acid consumption are complex and simple delineation based on the total or type of fat intake may be erroneous. Lipid and fatty acid concentration rise in maternal plasma during pregnancy and sufficient maternal fat intake is critical for optimal growth and neurological development in the fetus (82). Some studies have suggested that higher consumption of polyunsaturated fat may be associated with a reduced risk of preeclampsia (83) and glucose intolerance during pregnancy (84). However, the effects of pregnancy supplementation with omega-3 fatty remain unclear with no clear difference seen in preeclampsia, gestational diabetes, preterm birth, and fetal growth restriction risk (85, 86). The effects of trans fat intake during pregnancy have also demonstrated mixed results with an inverse relationship seen with preeclampsia risk in some (87, 88) but not all studies (83, 89). Considering the above, the absence of an association seen between the total fat and oil intake and miscarriage risk in this review is unlikely to translate to the absence of an association but is simply a reflection of insufficient evidence and the need for further high-quality research. To add, considering the effect of total fat intake alone may not be the most valid analytic approach to determine optimal maternal dietary fat intake. To infer any meaningful conclusions, further analysis based on the origin, type, and consumption amount is important.

Finally, sugar substitutes are often considered a healthier alternative to refined sugar. However, there is emerging evidence to indicate that sugar substitutes may exert a harmful effect on health. It has been linked to weight gain (90), insulin resistance (91), type 2 diabetes (92), and cardiovascular complications (93–95). Higher sugar substitute intake has also been associated with an increased risk of preterm delivery, reduction in gestational age at birth, and increased birth weight (96). Sugar substitutes are a broad food group that may include polypeptides and artificial sweeteners to naturally occurring sugar alternatives. The short- and long-term health effects are likely to be complex and multifactorial. Some argue that consumption of sugar substitutes exerts metabolic and endocrine impairment (97–101). Although the evidence remains conflicted and a recently published network meta-analysis by Zhang et al. (102) suggests beverages with noncaloric sweeteners did not affect 2-hour postprandial levels of glucose or hormones related to metabolic control and appetite. Furthermore, erythritol, a naturally occurring sugar alcohol substitute, has been associated with an increased risk of major cardiovascular events (103) despite having no effect on serum glucose or insulin levels. In vitro experiments demonstrate that erythritol exposure triggers platelet aggregation, therefore an increased thrombosis potential, a key mechanism for atherosclerotic plaque formation. The health effects of sugar substitutes on miscarriage risk likely depend on the type and dose of intake and further studies are warranted to elucidate the potential size and mechanism of effect in the pregnant population.

Whole diet. Our review findings confidently demonstrate the lack of a predefined dietary pattern that is categorically superior to others, highlighting that strict adherence to a single predefined dietary pattern may not reliably optimize one's reproductive health. Instead, the data suggest that clinicians should be recommending holistic food choices that are rich in healthy food groups with high antioxidant components and ideally devoid of unhealthy food groups that are highly refined, processed, and proinflammatory. It is also important to note that dietary patterns, even if dominantly composed of healthy food sources, if too restrictive, may inadvertently increase the risk of poor reproductive outcomes through nutritional deficiency. For example, a vegetarian diet has been linked with a reduction in birth weight (104). Therefore, dietary choices should be both healthy and balanced to meet the nutritional demands of an individual. Adherence to dietary choices reflecting healthy Nordic food groups (HNFI), better diet quality with healthy foods (PDQS), and antioxidant rich food sources (DAI) was associated with a reduction in miscarriage odds. Higher consumption of proinflammatory diet was also found to double the miscarriage odds. Dietary patterns identified using a posteriori method supported the above findings and suggested that a balanced diet may reduce miscarriage odds but diets with unhealthy components such as processed food increase the odds of pregnancy loss.

Strengths and Limitations

The findings of this systematic review and meta-analysis are strengthened by its comprehensive search and selection process. The search strategy was not limited to English or publication status, therefore minimizing the inclusion bias and increasing the generalizability of the findings. This review summarizes dietary evidence from a wide range of countries, incorporating study data from 5 continents. Another strength of this study is the large number of women who were included in the review ($n = 63,838$), increasing the precision of pooled estimates. Furthermore, we included dietary evidence from published data spanning a period of 22 years.

The investigators recognize important methodological limitations in this systematic review. First, it is not possible to rule out selection bias as most of the included studies were limited to women who conceived naturally with no history of sub- or infertility. Second, despite the extensive literature search, the quantity and quality of evidence on diet and miscarriage risk were relatively low. No studies of the experimental design that addressed the question were identified. Although the majority of studies included in this review were deemed to be of high quality, observational studies are inherently at a high risk of bias. Observational studies on diet, whether prospective or retrospective, are typically based on self-reported dietary information. Eleven studies used validated questionnaires or tested for reproducibility, strengthening the validity of the dietary data included in this review. It should be noted that even for experimental studies, dietary data tend to be self-reported and based on participant recollection. This may result in recall and social desirability bias, which are relatively unavoidable in nutrition research (105, 106). In an ideal study design, the accuracy of nutritional exposure would need to be supported by an objective assessment or biological data (e.g., micronutrient level). Therefore, the investigators emphasize that it is not possible to draw any causative conclusions between dietary intake and miscarriage risk based on the currently existing evidence, and thus, pooled effect estimates from this review should be interpreted and applied to clinical practice with caution.

It is noted that heterogeneity remained significant for some of the pooled estimates in the secondary analyses. Some of this heterogeneity may be attributable to the lack of uniformity in defining food consumption amount or upper gestational threshold for miscarriage across the included studies. As previously discussed, we hypothesize that the magnitude of the effect after nutritional exposure is likely to depend on multiple factors such as dose and duration of the exposure. The mechanism of effect, hence the implications of exposure, is also likely to differ depending on the stage of reproduction and the timing of exposure. Overall, the pathways through which nutrition may affect reproductive health appear complex and are yet to be fully elucidated. Modulation of DNA methylation and oxidative stress have been proposed as potential mechanisms (107, 108). The theory is supported by the findings from this review, demonstrating an increase in miscarriage risk with the consumption of proinflammatory diet. Furthermore, the investigators encountered an analytical challenge when grouping food items into categories. It is noted that some food categories were too broad, but insufficient data were available to create subcategories for better estimation of pooled effects. An example food group is meat, which was subcategorized when possible to reflect the differences in the nutritional content. Ideally, we would have preferred to subcategorize this further depending on the level of saturated fat (lean vs. fat) and the type and presence of processing technique, but there was insufficient evidence to allow for such an approach. There is increasing research suggesting an association between ultraprocessed foods and adverse health outcomes. Ultraprocessing is defined as "formulations of food substances often modified by chemical processes and then assembled into ready-to-consume hyper-palatable food and drink products using flavors, colors, emulsifiers and other cosmetic additives" (109) and is estimated to account for 25%–60% of daily energy intake in many countries. The investigators found no evidence that examined the degree and method of food processing with miscarriage risk but note that this is an area that clearly warrants further evaluation.

Traditionally, nutrition research has been limited to a reductionist approach, considering parts of diet rather than the whole (110). To date, this continues to be the dominant approach. However, there is increasing recognition of the need to move toward evaluating diet as a whole, recognizing that food is not consumed in isolation. The interaction between different foods may modify the overall nutritional effect on health outcomes. Furthermore, when making nutritional choices, if one food group is removed from the diet, then it is likely to be substituted by another. Finally, the traditional approach does not account for collinearity between nutrients (111). Data-driven nutrition research has consistently demonstrated that food choices are concurrent with each other and typically identifies 2 main dietary patterns (112): a prudent dietary pattern characterized by a higher intake of fruits, vegetables, legumes, and whole grains, and western dietary pattern characterized by a higher intake of processed meat, red meat, butter, high-fat dairy products, and refined grains.

Multiple confounders influence dietary choices and miscarriage risk, both known and unknown. Food choices are often made through a series of selection processes, influenced by environmental and individual factors. Environmental factors include food supply, pricing, advertising, and education. Individual factors include taste and perceived value of food groups. Miscarriage risk is known to be associated with multiple factors such as age, body mass index, previous history of miscarriages, and lifestyle choices such as smoking and alcohol intake. The investigators note that the majority of included studies have adjusted for a variety of potential confounders. Although it is not possible to rule out the presence of residual and unknown confounding, our conclusions did not change for the majority of pooled estimates in the sensitivity analyses, suggesting that any residual confounding is unlikely to have had a large effect on the interpretation of the results.

CONCLUSIONS

This systematic review and meta-analysis provides evidence of a protective association between fruit, vegetables, seafood, dairy products, eggs, and cereal against miscarriage. Furthermore, an overall dietary exposure that is high in quality with healthy nutrient sources and low in proinflammatory factors or unhealthy food groups such as highly refined, processed meat, or sugar substitutes may be associated with a reduction in miscarriage risk. This supports the positive effect of healthy dietary choices on fertility, maternal, and fetal outcomes. Therefore, women who wish to reduce their risk of pregnancy loss should be encouraged to make healthy food choices. Studies of experimental design are needed to further elucidate the relationship between diet and miscarriage risk. Specifically, evidence to examine whether this relationship is causal and accurately estimate the effectiveness of periconception dietary interventions on miscarriage risk is crucial to better guide clinicians on which dietary advice should be provided, during the critical stages of pregnancy establishment and development.

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La asociación entre los patrones alimentarios y el riesgo de aborto espontáneo: una revisión sistemática y metaanálisis

Importancia: La evidencia sobre la asociación entre la dieta y el riesgo de aborto espontáneo es escasa y contradictoria.

Objetivo: Resumir la evidencia sobre la asociación entre la dieta periconcepcional y el riesgo de aborto espontáneo en mujeres sanas en edad reproductiva.

Fuente de datos: Se realizaron búsquedas en bases de datos electrónicas desde el inicio hasta agosto de 2022, sin restricción de regiones, tipos de publicación o idiomas.

Selección y síntesis de estudios: Fueron incluidos estudios experimentales y observacionales. La población estaba formada por mujeres sanas en edad reproductiva. La exposición fue la dieta periconcepcional. La calidad de los estudios se evaluó mediante la escala Newcastle-Ottawa modificada. Se calcularon los tamaños del efecto (odds ratio [OR] con intervalo de confianza [IC] del 95%) para cada categoría de alimentos.

Principales medidas de resultados: Tasa de abortos (según la definición de los estudios principales).

Resultados: Se incluyeron 20 estudios (11 de cohortes y 9 de casos y controles), de los cuales 6 presentaban datos adecuados para el metanálisis (2 de cohortes y 4 de casos y controles, n=13.183 mujeres). Nuestros análisis principales sugieren una reducción de las probabilidades de aborto espontáneo con una ingesta elevada de los siguientes grupos de alimentos: fruta (OR, 0,39; IC 95%, 0,33-0,46), verdura (OR, 0,59; IC 95%, 0,46-0,76), fruta y verdura (OR, 0,63; IC 95%, 0,50-0,81), marisco (OR, 0,81; IC 95%, 0,71-0,92), productos lácteos (OR, 0,63; IC 95%, 0,54-0,73), huevos (OR, 0,81; IC 95%, 0,72-0,90), y cereales (granos) (OR, 0,67; IC del 95%, 0,52-0,87). La evidencia fue incierta para la carne, la carne roja, la carne blanca, la grasa y el aceite, y los sustitutos del azúcar. No se encontraron pruebas de una asociación entre la adherencia a patrones dietéticos predefinidos y el riesgo de aborto espontáneo. Sin embargo, una dieta completa que contuviera alimentos saludables según la percepción de los autores del ensayo, o con una puntuación elevada del Índice de Antioxidantes en la Dieta (OR,0,43; IC 95%, 0,20-0,91) podría asociarse a una reducción del riesgo de aborto espontáneo. Por el contrario, una dieta rica en alimentos procesados demostró su asociación con un mayor riesgo de aborto espontáneo (OR, 1,97; IC del 95%, 1,36-3,34).

Conclusiones y Relevancia: Una dieta abundante en fruta, verdura, marisco, lácteos, huevos y cereales puede estar asociada a una menor probabilidad de aborto espontáneo. Se necesitan más estudios de intervención para evaluar con precisión la eficacia de las modificaciones dietéticas periconcepcionales en el riesgo de aborto espontáneo.