

Mediterranean diet and female reproductive health over lifespan: a systematic review and meta-analysis



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OBJECTIVE: We conducted a systematic review and meta-analysis of the effects of Mediterranean diet on female reproductive health outcomes over the life-course.

DATA SOURCES: We searched PubMed, Embase, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and [ClinicalTrials.gov](https://www.clinicaltrials.gov) to identify eligible studies published till February 2022. Eligible references from identified studies and review articles were also considered.

STUDY ELIGIBILITY CRITERIA: Randomized controlled trials, prospective cohort studies, or nested case-control studies examining Mediterranean diet and major female reproductive outcomes over the lifespan, including clinical outcomes from childhood to adulthood (menarche, polycystic ovary syndrome, endometriosis, and outcomes related to fertility, pregnancy, and menopause), were included for review.

METHODS: Two independent reviewers screened and performed data extraction and risk-of-bias assessment. We performed random-effects meta-analysis to obtain summary relative risks and 95% confidence intervals for major female reproductive outcomes. Sub-group analyses were performed for several pregnancy outcomes according to timing of the interventions for randomized controlled trials and timing of the dietary assessment for observational studies.

RESULTS: Thirty-two studies (9 randomized controlled trials, 22 prospective cohort studies, and 1 nested case-control study) involving 103,204 predominantly White women (>95%) were included. The pooled relative risk (95% confidence interval) comparing randomization to Mediterranean diet vs a control diet based on 7 randomized controlled trials was 0.74 (0.55–0.99) for gestational diabetes mellitus, 0.45 (0.26–0.76) for preterm birth, 0.71 (0.51–1.00) for gestational hypertension, and 0.82 (0.54–1.22) for preeclampsia; the effect sizes for preterm birth were greater in randomized controlled trials that initiated the interventions in first trimester vs after first trimester (P heterogeneity=.02). We observed inverse associations for all the above-mentioned pregnancy outcomes based on 9 cohort studies. There was suggestive evidence of favorable associations between Mediterranean diet adherence with fertility and gestational weight management. Limited studies suggested associations between higher Mediterranean diet adherence and later time to menarche and fewer vasomotor menopausal symptoms, null associations for polycystic ovary syndrome-like phenotype and pregnancy loss, and positive associations for luteal phase deficiency.

CONCLUSION: Adherence to Mediterranean diet may lower risks of adverse pregnancy outcomes among predominantly White populations. For fertility-related outcomes, available evidence supporting potential beneficial effects is suggestive yet limited. For other reproductive outcomes across the lifespan, data remains sparse.

Key words: female fertility, female reproductive health, gestational diabetes mellitus, hypertensive disorders of pregnancy, Mediterranean diet, menopause, preterm birth, puberty development, systematic review

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This study was prospectively registered with the International Prospective Register of Systematic Reviews (registration number CRD42022306855) on February 22, 2022.

All data used in the study has been presented in the manuscript and [Supplementary Material](#).

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AJOG at a Glance

Why was this study conducted?

This study aimed to evaluate the effects of Mediterranean diet on female reproductive health by considering major female reproductive outcomes throughout the reproductive lifespan.

Key findings

Mediterranean diet during pregnancy was protective of gestational diabetes mellitus and preterm birth. Limited evidence suggested beneficial roles of Mediterranean diet on female fertility.

What does this add to what is known?

Mediterranean diet may be protective of adverse pregnancy outcomes. Despite suggestive benefits on female fertility, evidence concerning a potential causal relationship among women undergoing infertility treatment or the general population is lacking. Mediterranean diet during other reproductive periods with female reproductive outcomes remain largely unexplored. Data on Mediterranean diet with female reproductive health among non-White populations are sparse.

Introduction

Reproductive health is a key component of a woman's overall health, and it is a life-course concept. Concerns about female reproductive health are growing worldwide, potentially because of increased burdens of obesity, suboptimal lifestyle, and environmental chemical factors implicated in the etiology of female reproductive health.¹ Recent reviews report escalating rates of female reproductive disorders worldwide, which are as high as 30% for irregular menstruation,² 20% for polycystic ovarian syndrome (PCOS),³ 25% for infertility,⁴ 10% for hypertensive disorder in pregnancy (HDP),⁵ and 15% for gestational diabetes mellitus (GDM).⁶

The Mediterranean diet (MD) is a traditional dietary style in the Mediterranean regions, characterized by high intakes of fruits and vegetables, nuts, legumes, whole grains, healthy fats with olive oil (especially virgin and extra virgin olive oil [EVOO]) as the major source of fat; moderate intakes of dairy products, fish, and poultry; limited intakes of red and processed meats; and moderate wine consumption.⁷ As an overall dietary pattern, MD is low in saturated fatty acids, rich in unsaturated fatty acids, and high in complex carbohydrates and fibers.⁸ Intakes of fruits, vegetables, EVOO, and nuts also provide polyphenols and essential micronutrients such as key vitamins and minerals.^{8,9}

Given the shared mechanisms (eg, inflammation, oxidative stress, hormonal balance) underlying the physiology of common female reproductive outcomes and the roles of MD underpinning these mechanisms,^{9,10} epidemiologic evidence from randomized controlled trials (RCTs) and observational studies on MD and female reproductive health is emerging, particularly for outcomes related to fertility¹¹ and pregnancy.¹² However, such evidence has not been systematically summarized and synthesized. Furthermore, whether and to what extent MD is associated with other female reproductive outcomes awaits evaluation and summary. The degree of the available evidence across different regions or populations remains unknown.

Objectives

We undertook a comprehensive systematic review and meta-analysis of published RCTs and prospective observational studies to examine the roles of MD on major female reproductive outcomes over the reproductive lifespan.

Methods**Eligibility criteria, information sources, and search strategy**

A comprehensive search was performed across electronic databases in English. Given our capacity to search studies in Asian populations, we also searched

major Chinese and Korean databases. We searched PubMed, Embase, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov for English databases; National Knowledge Infrastructure (CNKI) and Wanfang Data for Chinese databases; and Korean Studies Information Service System and Research Information Sharing Service for Korean databases for studies published from inception through February 28, 2022. Keywords and medical subject headings were developed and applied in the search. "Mediterranean diet" as the exposure combined with a list of keywords related to female reproductive events or outcomes (puberty, menstrual cycle, PCOS endometriosis, fertility, pregnancy-related maternal outcomes, and menopause) were applied to define the search ([Supplementary Material](#)). We also scanned and hand-searched reference lists of identified studies and reviewed articles to identify additional studies. Two independent reviewers (J.Y. and Y.S.) developed the search terms and performed the search using the agreed search terms.

Studies that met all the following inclusion criteria were included in the review: (1) females; (2) RCTs (n>50), prospective cohort studies (n>100), or case-control studies nested within longitudinal cohort studies (n>100); and (3) studies assessing major female reproductive outcomes over the reproductive lifespan.

Study selection

Two independent reviewers (J.Y. and Y.S.) screened the title and abstract of identified studies from which irrelevant studies were excluded. Full-texts of relevant studies were assessed. Studies with insufficient sample size (n<50 for RCTs, n<100 for cohort or nested case-control studies) or irrelevant exposure, outcome, or study design were excluded. Any discrepancy was discussed with a third reviewer (C.Z.) and resolved as a group.

Data extraction

We used a predesigned form to extract relevant information from included

studies. For RCTs: (1) study characteristics, including first author, publication year, and study location; (2) population characteristics, including eligibility criteria, study size by intervention or control arm, baseline age, and race or ethnicity; (3) study design, including study setting, time of baseline and intervention duration, and descriptions of intervention(s) and control; and (4) outcome data. For cohort or case-control studies: (1) study characteristics, including first author, publication year, and study location; (2) population characteristics, including study size, baseline age, and race or ethnicity; (3) exposure assessment; (4) outcome assessment; (5) effect sizes of outcomes; and (6) adjusted covariates and matching factors if any (case-control studies only).

Assessment of risk of bias

For RCTs, the risk of bias was assessed by the revised Cochrane risk-of-bias tool for randomized trials.¹³ A study was rated as low, with some concerns, or high for overall risk of bias based on 5 domains of randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported results. Risk of bias for cohort or case-control studies was evaluated by the Newcastle-Ottawa Scale based on selection (4 points), comparability (2 points), and outcome (3 points) with greater score indicating higher quality.¹⁴ A study was rated as high risk for bias if it was scored “1” for selection or outcome, or “zero” for any of the 3 domains, medium risk for bias if it was scored “2” or “3” for selection, “1” for comparability, and “2” for outcome, and low risk for bias if it was scored full points across all the 3 domains (ie, 4 for selection, 2 for comparability, and 3 for outcome). Two reviewers (J.Y. and Y.S.) independently scored studies; any discrepancy was discussed and resolved by a third reviewer (C.Z.).

Data synthesis

We conducted a quantitative systematic review for included studies and a meta-analysis when appropriate, according to

types of study design (ie, RCT, cohort, and case-control). Because most of the non-RCT studies categorized MD scores into quantile groups, we reported measures of associations based on outcome data of the highest vs the lowest quantile of MD; significance of linearity across quantile groups was reported when available. For dichotomous outcome data, we reported the risk estimates (ie, relative risks [RRs], odds ratios [ORs], and hazard ratios [HRs] with 95% confidence interval [CI]) with adjustment of the greatest number of covariates. For continuous outcome data, we reported most-adjusted mean differences comparing the highest vs the lowest quantile of MD, or group-specific mean or median values from the highest and the lowest quantile when estimate of the difference was not available.

Meta-analysis was performed for a given outcome when there were at least 3 eligible studies quantitatively assessing MD on the same outcome. We pooled adjusted-risk estimates from individual studies and reported summary RRs with 95% CIs comparing the highest vs the lowest quantile of MD using the DerSimonian and Laird random-effects models, accounting for both within-study and between-study components of variance.¹⁵ When a study reported group-specific count data or proportions rather than adjusted-risk estimates, RR and standard error were derived using 2-by-2 table before pooling them together with those from other studies. For studies examining GDM using multiple clinical diagnostic criteria, the risk estimate following the most commonly adopted criteria in other studies (ie, International Association of Diabetes and Pregnancy Study Group [IADPSG] criteria) was selected and pooled. One cohort study reported risk of overall HDP instead of risk by subtypes; we used the overall estimate when calculating subtype-specific summary RRs of gestational hypertension and preeclampsia, given that the authors reported no differences in the associations for subtypes of HDP with MD.¹⁶ Overall heterogeneity across studies was quantified using the Cochran's Q test and the I^2 statistic (<25%, 25%–75%, and >75%

indicating low, moderate, and high levels of statistical heterogeneity, respectively).^{17,18} Publication bias was evaluated by the Egger test¹⁹ and the Begg test,²⁰ with a P value of <.05 considered as evidence for publication bias. For pregnancy-related outcomes, we performed a priori subgroup analyses to evaluate heterogeneity by timing of intervention initiation (first trimester [before 12 gestational weeks (GWs)] vs after first trimester [at or after 12 (GW)]) for RCTs, and timing of the MD adherence assessed (prepregnancy vs inpregnancy) for cohort studies, when there were at least 2 studies in each subgroup; subgroup heterogeneity was assessed by the Cochran's Q test. In addition, we performed sensitivity analyses to exclude studies which did not report adjusted-risk estimates (ie, reported crude outcome count data, crude risk estimates, or adjusted group-specific proportions) or studies rated high for risk of bias. All the analyses were performed with R language (version 4.1.1) and “metafor” package (version 3.4-0), with a 2-sided P value of .05 considered statistically significant.

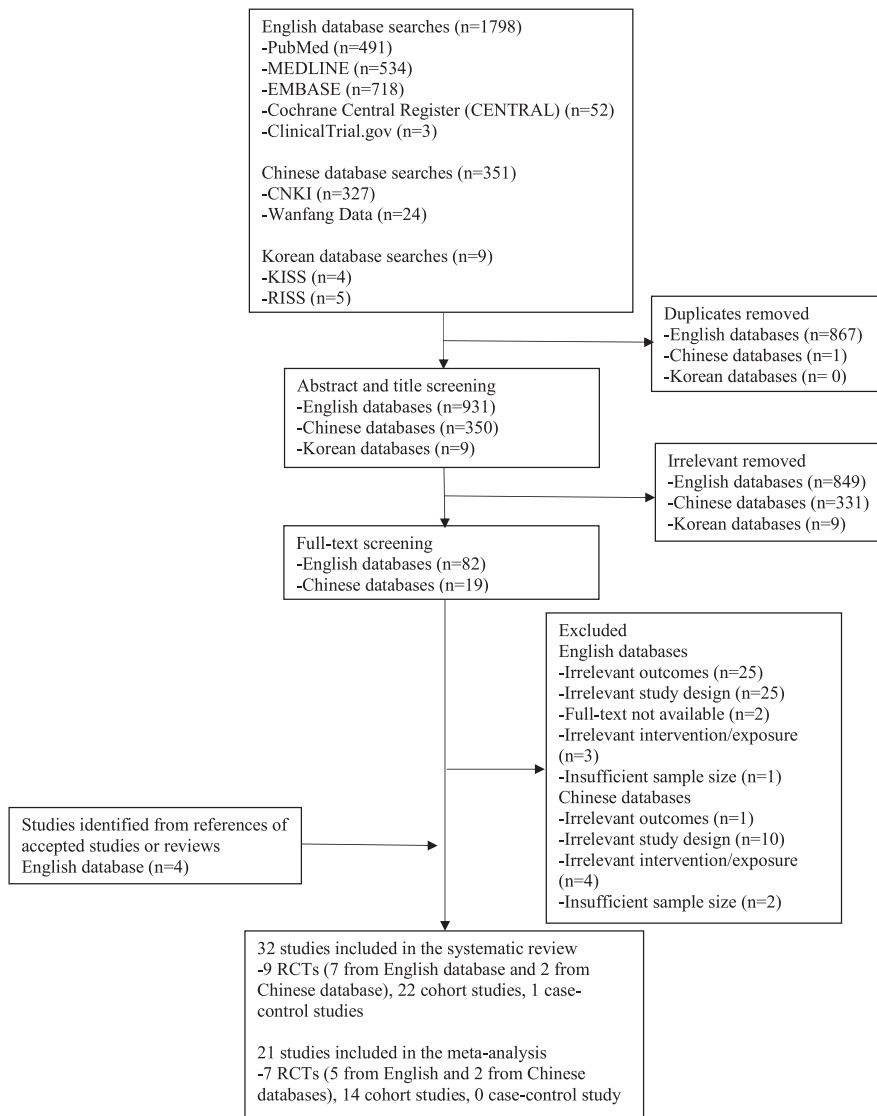
Assessment of quality of evidence

We assessed the quality of evidence for outcomes that were meta-analyzed according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system.²¹ The detailed methodology and the rating criteria were described in the [Supplementary Material](#). GRADE assessment was conducted by 2 reviewers (J.Y. and Y.S.). Inconsistencies were resolved by a group discussion (J.Y., Y.S., and C.Z.).

Results

Study selection

Out of 2162 studies (2158 from all the databases and 4 from handsearching), after removing duplicates, 1294 were eligible for title and abstract screening. Out of the 1294 screened studies, 105 were relevant and subsequently eligible for full-text screening. After removing studies with insufficient sample size ($n=3$), irrelevant outcomes ($n=26$), study design ($n=35$), or exposure ($n=7$), or nonavailable full-text ($n=2$),

FIGURE 1**Identification process for eligible studies**

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32 studies were retained. There were 9 RCTs, 22 cohort studies, and 1 nested case-control study (Figure 1).²²

Study characteristics

Included randomized controlled trials

Of the 9 RCTs (total n=5066), 6 (74.7%) were conducted in North America or Europe among predominantly White populations,^{23–28} and the remaining 3 (25.3%) were conducted in China^{29–31} (Table). Eight studies had 2 arms comparing a MD intervention to a non-MD control diet; 1 study in Spain²⁸ had 2

different intervention arms (MD and mindful-based stress-reduction, respectively) and a control arm. The MD intervention in the majority of the RCTs emphasized major components of MD, such as fruits and vegetables, whole grains, healthy plant-based oils (ie, EVOO, rapeseed oil, or sunflower oil), and nuts. Six studies^{23,25–29} supplemented olive oil and/or nuts (ie, walnuts, pistachios, or mixed nuts), and one²⁷ out of the 6 studies additionally provided fruits and vegetables to the participants assigned to the MD intervention. The

other 3 studies only provided MD-based dietary advice.^{24,30,31} Participants in the control group of 8 RCTs did not receive supplemented foods, and they were advised to follow a usual diet, standard recommended diet, or diets emphasizing limited fat intake; 1 RCT²³ provided sunflower products and a placebo drink to the control group. With respect to the intervention timing, 1 study (n=111) evaluated effects of a 6-week MD on fertility among females before their invitro fertilization (IVF) treatment.²³ Seven studies (n=4826) evaluated effects of MD during pregnancy on maternal outcomes^{24–26,28–31}; gestational timing of the intervention varied by studies, with the start of the intervention(s) ranging between 8 to 12 and 19 to 23 GW. One study (n=129) examined effects of a 4-month MD at 18 weeks postpartum on postpartum weight status.²⁷

Included prospective cohort studies

We included 22 prospective cohort studies (n=95,984) conducted in European countries^{32–39} (8 studies; 72.9%), the United States^{40–48} (United States; 9 studies from 7 distinct cohorts; 19.9%), Australia^{49–51} (3 studies, all from the Australian Longitudinal Study on Women's Health; 6.3%), China⁵² (1 study; 0.6%), and United Arab Emirates⁵³ (1 study; 0.3%) (Supplementary Table 1, 2, and 3). Overall, adherence to MD was assessed and quantified by various MD metrics, including original or the modified MD score by Panagiotakos (0–55)^{33,40} or Trichopolou (0–9 with alcohol or 0–8 without alcohol),^{34,38,42–44,46–48,52,53} self-defined MD index (0–5),^{35,36} and data-driven scoring algorithms using principal component analysis (PCA)^{32,37,39} or factor analysis^{49,50} (Supplementary Table 4). Despite varied MD metrics, most of the studies assessed common components of MD, including fruits and vegetables, whole grains, nuts/soy/legumes, fish, and healthy fats (ie, unsaturated fats, low-fat dairy products); moderate alcohol was included in some^{33,34,37,40–44,46,47,49–51} but not all the studies. All the metrics except metrics defined by PCA or factor analysis accounted for “unhealthy” food intakes.

TABLE

Characteristics of study participants and study design of included randomized-controlled trials (9 studies)

Author, y(country)	Study size (intervention vs control)	Eligibility criteria ^a	Baseline mean age (y) and BMI (kg/m ²)	Race or ethnicity	Study setting and design	Baseline time, intervention duration	Intervention: description	Control: description	Outcomes
Before pregnancy									
Kermack et al, ²³ 2020 (United Kingdom)	111 (55 vs 56)	18–41 y of age, BMI 18–32 kg/m ² , <2 cycles of unsuccessful IVF, AMH level > 2 p/mol, and overall healthy	33.4; 24.7	White European (90%)	Academic IVF unit, double-blinded	Before IVF cycle, 6 wk intervention preceding IVF treatment cycle	Received olive oil, olive oil-based spread, and daily supplement drink enriched with omega-3 fatty acids and vitamin D; PA not mentioned	Received sunflower oil, sunflower-based bread spread, and daily control drink; PA not mentioned	Time taken for completion of cell cycles, embryo quality, pregnancy rate, live birth rate
During pregnancy									
Khoury et al, ²⁴ 2005 (Norway)	290 (141 vs 149)	21–38 y of age, BMI 19–32 kg/m ² , singleton pregnancy, overall healthy	29.7; 24.6	White	Hospital-based, randomized controlled	From 17–20 GW until delivery	MD-like cholesterol-lowering advice with recommended fatty fish, fruits and vegetables, olive or rapeseed oil, nuts, low-fat dairy, and legumes; PA not mentioned	Usual diet without additional introduction of oils, low-fat meat, and dairy products; PA not mentioned	Gestational hypertension, preterm birth, maternal weight gain, lipids profile
Assaf-Balut et al, ²⁵ 2017 (Spain)	874 (440 vs 434)	>18 y of age, singleton pregnancy, normoglycemic (<92 mg/dL) pregnant women and overall healthy	33.0; 23.9	White (68%), Hispanic (29%), others (3%)	Unicentric, clinic-based, randomized controlled	From 8–12 GW until delivery	MD advice supplemented with EVOO (1 L/wk) and pistachios (150 g/wk), dietitian-led sessions; recommended 30 min/d of walk	Standard dietary advice with limited fat intake; recommended 30 min/d of walk	Glucose control, GDM, blood pressure, preterm birth, gestational hypertension, preeclampsia, maternal weight gain
Kang et al, ³⁰ 2019 (China)	660 (332 vs 328)	18–45 y of age, singleton pregnancy, normoglycemic (6 mmol/L)	32.1; NA for BMI	Chinese	Unicentric, clinic-based, randomized controlled	From 8–12 GW until delivery	MD advice with recommended walnuts (25–30 g/d) and sunflower seed oil (25–40 mL/d); PA not mentioned	Standard dietary advice with limited fat and sugar intake; PA not mentioned	GDM, gestational hypertension, preeclampsia, preterm birth, maternal weight gain

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(continued)

TABLE

Characteristics of study participants and study design of included randomized-controlled trials (9 studies) (continued)

Author, y(country)	Study size (intervention vs control)	Eligibility criteria ^a	Baseline mean age (y) and BMI (kg/m ²)	Race or ethnicity	Study setting and design	Baseline time, intervention duration	Intervention: description	Control: description	Outcomes
Al Wattar et al, ²⁶ 2019 (United Kingdom)	1138 (553 vs 585)	>16 y of age, singleton pregnancy, with metabolic risk factors (eg, BMI>30 kg/m ²)	31.2; 69.4% with BMI>30.0	White (38.1%), Asian (46.3%), Black (17.8%), Other (3.7%)	Multicenter, clinic-based, randomized controlled	From 18 GW until delivery	MD advice supplemented with mixed nuts (30 g/d of walnuts, hazelnuts, and almonds) and EVOO (0.5 L/wk); PA not mentioned	Standard dietary advice as per UK national recommendations for antenatal care; PA not mentioned	GDM, preeclampsia, preterm birth, maternal weight gain, lipids profile
Song and Lili, ³¹ 2020 (China)	120 (62 vs 58)	Pregnant women with PCOS	28.2; 24.0	Chinese	Hospital-based, randomized controlled	Baseline intervention time unclear, 6 months	MD advice with recommended olive or rapeseed oil to replace animal-based oil; recommended 30 min/d of walk	Standard dietary advice as per national guidelines; recommended 30 min/d of walk	Preterm birth, GDM, gestational hypertension, body fat composition, lipids profile, reproductive hormones (FSH, LH)
Zhao et al, ²⁹ 2022 (China)	560 (280 vs 280)	>18 y of age, singleton pregnancy, normoglycemic, overall healthy	28.7; 24.1	Chinese	Hospital-based, randomized controlled	8–12 GW until delivery	MD advice with supplemented olive oil (40 mL/d) and pistachios (25–30 g/d); recommended 30 min/d of walk	Standard dietary guideline with limited fat intake; received lifestyle guideline including PA	glucose control, GDM, gestational hypertension, preeclampsia, preterm birth, maternal weight gain, blood pressure
Crovetto et al, ²⁸ 2021 (Spain)	1184 (392 vs 391 vs 401)	>18 y of age, singleton pregnancy, high-risk for SGA (eg, BMI <20 or >25 kg/m ²), otherwise overall healthy	37.3; 24.0	White (78.6%), Black (1.9%), Asian (1.9%), Hispanic (15.4%)	Hospital-based, 3 parallel-group randomized controlled	19–23 GW until 34–36 GW	MD advice supplemented with EVOO (2 L/mo) and walnuts (15 g/d); PA not mentioned	Mindful-based stress reduction arm, control arm receiving usual pregnancy care per institutional protocols; PA not mentioned	Preterm birth, preeclampsia, GDM, maternal weight gain

After pregnancy

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(continued)

TABLE
Characteristics of study participants and study design of included randomized-controlled trials (9 studies) (continued)

Author, y(country)	Study size (intervention vs control)	Eligibility criteria ^a	Baseline mean age (y) and BMI (kg/m ²)	Race or ethnicity	Study setting and design	Baseline time, intervention duration	Intervention: description	Control: description	Outcomes
Stendell-Hollis et al. ²⁷ 2013 (United States)	129 (65 vs 64)	18–40 y of age, overall healthy	29.7; 27.1	75.2% non-Hispanic White (75.2%), Hispanic (24.8%)	Unicentric, community-based randomized controlled following a 4-wk wash-out period	Baseline at 18 wk postpartum, 4 mo	MD advice: supplemented walnuts (28 g/d), EVOO (1–2 teaspoons/d), fruits/vegetables (7+ serving/d); PA not mentioned	USDA MyPyramid diet emphasizing healthy eating; nuts, EVOO and increase in fruits/vegetables were deemphasized; PA not mentioned	Postpartum change in body weight, inflammatory markers from baseline

BMI, body mass index; CG, control group; EVOO, extra-virgin olive oil; GDM, gestational diabetes mellitus; GW, gestational week; IG, intervention group; MD, Mediterranean diet; PA, physical activity; SGA, small for gestational age.

^a BMI was specified if it was among the study eligibility criteria.

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Six studies examined adherence to MD with fertility-related outcomes among females presenting at fertility clinic^{32–34,40,41,52} (Supplementary Table 1). Eleven studies examined prepregnancy^{39,42,44,49,50} or in-pregnancy^{35–38,45,53} adherence to MD with maternal outcomes, and 1 study examined postpartum adherence to MD with postpartum weight retention (PPWR)⁴³ (Supplementary Table 2). Studies on other reproductive outcomes were limited. We identified 4 studies with 1 for each of the following outcomes: time to menarche,⁴⁸ luteal phase deficiency (LPD, luteal phase <10 days)⁴⁶ and subclinical PCOS among eumenorrheic females,⁴⁷ and menopause-related vasomotor symptoms⁵¹ (Supplementary Table 3). Owing to the limited number of studies, individual study findings were reported for these 4 outcomes.

Included prospective case-control studies

One case-control study (485 cases and 1669 controls, Spain) nested within a longitudinal cohort examined adherence to MD with self-reported difficulty conceiving⁵⁴ (Supplementary Table 5).

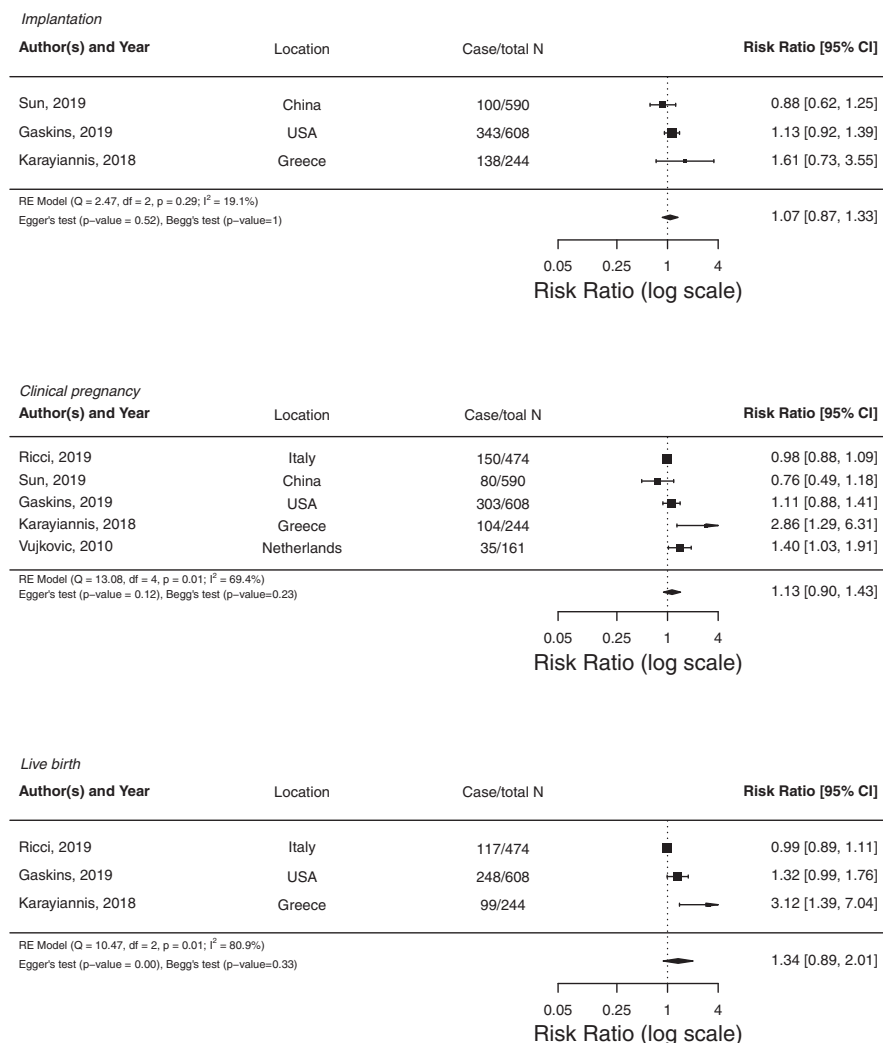
Risk of bias of included studies

Seven RCTs were rated as low, and 2 RCTs from China were rated as having some concerns for risk of bias owing to evidence of unbalanced randomization process²⁹ or lack of description on outcome assessment³¹ (Supplementary Table 6). For cohort studies, 1 study showed a low risk for bias; 20 studies showed a medium risk for bias; and 1 study showed a high risk for bias owing to high risk in domains of selection and outcome³⁹ (Supplementary Table 7). The case-control study showed a medium risk for bias (Supplementary Table 7).

Synthesis of results

Associations between Mediterranean diet and fertility-related outcomes in randomized controlled trials

One RCT (n=111) examined effects of 6-week supplemented EVOO and EVOO-based spread and supplemented drinks enriched with omega-3 fatty acids/vitamin D (MD group) vs supplemented

FIGURE 2**Summary relative risks of fertility-related outcomes with adherence to Mediterranean diet in prospective cohort studies**

Risk estimates with the greatest number of covariate adjustment from individual studies were pooled to calculate summary relative risk and 95% confidence interval of each outcome, comparing the group with the highest vs the lowest quartile of adherence to Mediterranean diet. Heterogeneity across studies was evaluated by the Cochran Q test and the I^2 statistics. Publication bias was evaluated by the Egger test and the Begg test.

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sunflower oil and sunflower oil-based spreads and placebo drink.²³ The study reported better embryo development assessed by a series of markers of embryo development in the MD group vs the control group (Table). Rates of clinical outcomes of successful clinical pregnancy (MD vs control: 52.6% vs 57.1%; $P=.96$) and live birth (MD vs control: 41.5% vs 32.7%; $P=.60$) were similar between the 2 groups.

Associations between Mediterranean diet and fertility-related outcomes in prospective cohort studies

Of the 6 fertility-related cohort studies among women undergoing infertility treatment, clinical outcomes examined included success of implantation (3 studies, $n=1191$),^{33,40,52} clinical pregnancy (5 studies, $n=1504$),^{32–34,40,52} and live birth (3 studies, $n=1075$)^{33,34,40} (Supplementary Table 1). Intermediate

outcomes, including antral follicle count (1 study, $n=363$),⁴¹ oocyte yield and quality (3 studies, $n=1308$),^{33,34,52} rate of fertilized oocytes out of total oocytes (3 studies, $n=995$), and embryo count and/or quality (4 studies, $n=1469$)^{32–34,52} were also evaluated. Summary RR (95% CI) was 1.07 (0.87–1.33) for implantation ($I^2=19.1\%$), 1.13 (0.90–1.43) for clinical pregnancy ($I^2=69.4\%$), and 1.34 (0.89–2.01) for live birth ($I^2=80.9\%$) (Figure 2). Evidence of potential publication bias was noted for live birth (Egger test, $P<.01$). For intermediate clinical outcomes, no clear patterns were observed. Although a study in China observed positive correlations between the rate of fertilized oocytes and the number of embryos available with MD, the magnitudes of the correlation coefficients were weak (0.10 and 0.09)⁵² (Supplementary Table 1).

In the sensitivity analysis, after excluding 2 studies which did not report adjusted association measures, summary RR of successful clinical pregnancy with MD became stronger but remained statistically nonsignificant (RR, 1.36; 95% CI, 0.88–2.11) (Supplementary Figure 1). *Associations between Mediterranean diet and fertility-related outcomes in case-control studies*

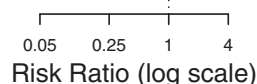
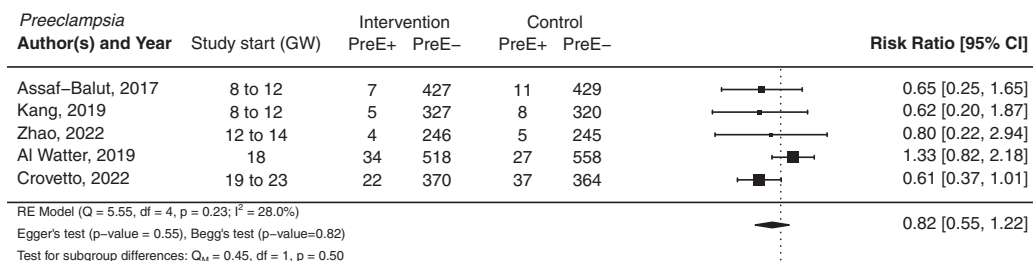
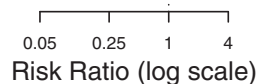
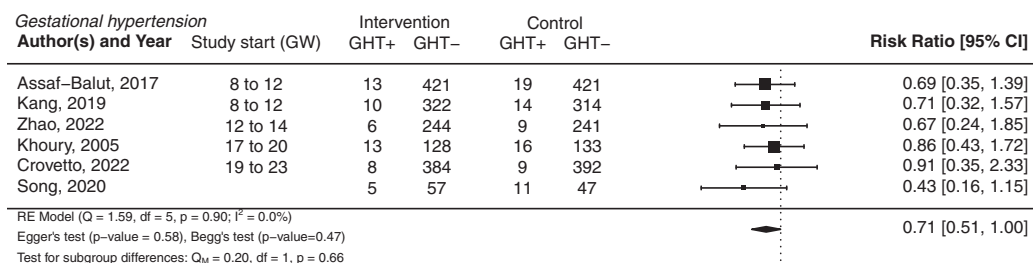
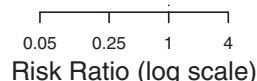
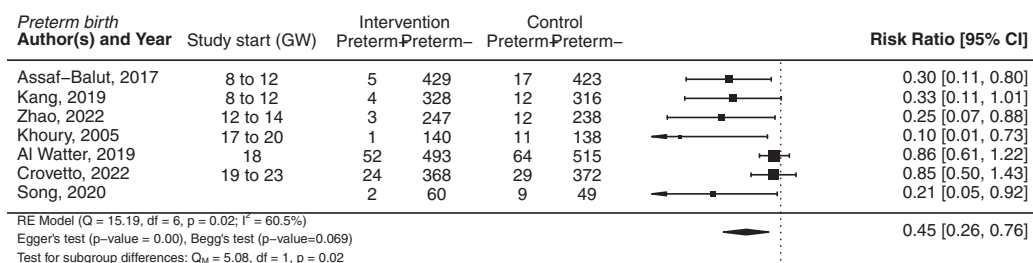
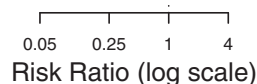
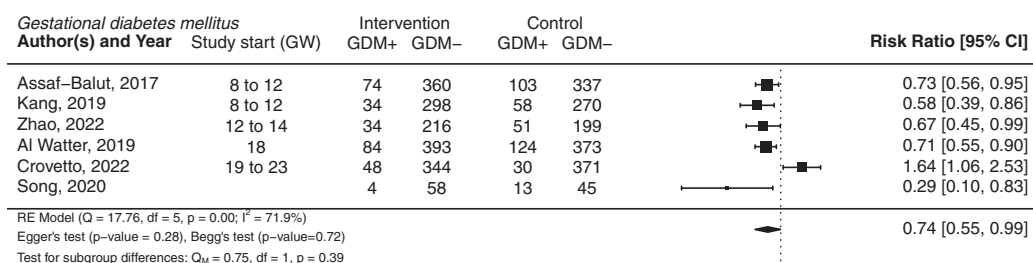
A lower risk of difficulty conceiving with greater adherence to MD was reported among healthy women (1 study; OR, 0.56; 95% CI, 0.35–0.90 comparing the highest vs the lowest quartile of MD adherence)⁵⁴ (Supplementary Table 5).

Associations between Mediterranean diet and pregnancy-related outcomes in randomized controlled trials

Outcomes of GDM (6 studies, $n=3921$),^{25,26,28–31} preterm birth (7 studies, $n=3964$),^{24–26,28–31} gestational hypertension (6 studies, $n=3237$),^{24,25,28–31} and preeclampsia (5 studies, $n=3964$),^{25,28–31} maternal weight gain (6 studies, $n=3585$),^{24,25,28–31} and postpartum weight change (1 study, $n=129$)²⁷ were examined in the included RCTs either as primary or secondary outcomes (Table). Summary RR (95% CI) was 0.74 (0.55–0.99) for GDM ($I^2=71.9\%$), 0.45 (0.26–0.76) for preterm birth ($I^2=60.5\%$), 0.71 (0.51–1.00) for gestational hypertension ($I^2=0.0\%$), and

FIGURE 3

Summary relative risks of pregnancy-related outcomes with Mediterranean diet in randomized controlled trials



0.82 (0.55–1.22) for preeclampsia ($I^2=28.0\%$) (Figure 3). Potential publication bias was detected for preterm birth (Egger test, $P<.01$). Subgroup heterogeneity by the timing of intervention initiation was significant for outcome of preterm birth ($P=.02$): the effect sizes were greater in the RCTs that initiated their interventions in the first trimester than those after the first trimester. Results of maternal weight gain were mixed: compared with the control group, both less^{24,26,29,30} or similar weight gain^{24,25,28,29} was reported in the intervention group. One RCT observed significant postpartum weight loss comparing before and after a 4-month postpartum MD intervention, yet there was no between-group difference in postpartum weight loss between the intervention and the control groups²⁷ (Table).

Associations between Mediterranean diet and pregnancy-related outcomes in prospective cohort studies

The following pregnancy outcomes were available in the cohort studies: pregnancy loss (spontaneous abortion [if <20 GW] and stillbirth [if ≥ 20 GW] combined; 1 study, $n=11,072$),⁴⁴ GDM (5 studies, $n=25,283$),^{38,39,42,45,49} preterm birth (3 studies, $n=63,383$),^{35,36,45} gestational hypertension (2 studies, $n=4939$),^{37,45} preeclampsia (2 studies, $n=4939$),^{37,45} hypertensive disorders in pregnancy (HDP; gestational hypertension and preeclampsia combined) (1 study, $n=3582$),⁵⁰ maternal weight gain (1 study, $n=243$),⁵³ and postpartum weight change from prepregnancy (2 studies, $n=1379$)^{43,53} (Supplementary Table 2). Summary RR (95% CI) was 0.70 (0.58–0.85) for GDM ($I^2=36.6\%$), 0.60 (0.41–0.87) for preterm birth ($I^2=0.0\%$), 0.65 (0.51–0.82) for gestational hypertension ($I^2=0.0\%$), and 0.61 (0.46–0.80) for preeclampsia ($I^2=0.0\%$); no evidence of publication bias

was noted (Figure 4). No significant subgroup heterogeneity by timing of the dietary assessment was detected for GDM ($P=.55$). Based on risk estimates reported from individual studies, protective associations were only observed for prepregnancy MD with HDP but not for first or second trimester MD adherence. For other outcomes with insufficient number of studies to conduct meta-analysis, no associations were observed between prepregnancy adherence to MD and pregnancy loss (Supplementary Table 2).⁴⁴ One study reported that adherence to MD in late pregnancy was associated with lower risks of both insufficient and excessive gestational weight gain (GWG).⁵³ Lastly, for the outcome of postpartum weight change, the same study reported late-pregnancy MD was associated with less PPWR.⁵³ The other study did not find associations of postpartum adherence to MD with PPWR (Supplementary Table 2).⁴³

After excluding 1 cohort study with high risk of bias, summary RR of GDM by pooling the remaining 4 studies remained significant (RR, 0.67; 95% CI, 0.58–0.78) (Supplementary Figure 2). *Associations between Mediterranean diet and other reproductive outcomes in prospective cohort studies*

Four cohort studies prospectively examined adherence to MD with reproductive outcomes other than fertility-related or pregnancy-related outcomes (Supplementary Table 3). A study of US teenage girls (baseline age, 10.0 years) reported that greater adherence to MD was associated with lower risk of early menarche (HR, 0.45; 95% CI, 0.28–0.71).⁴⁸ Two studies from a US cohort of healthy eumenorrheic females (baseline mean age, 27.3 years) examined LPD and PCOS-like phenotypes: MD was positively associated with risk of

LPD in a continuous fashion⁴⁶; no clear relationship was observed between MD and PCOS-like phenotypes.⁴⁷ Finally, adherence to MD was inversely associated with risk of vasomotor menopausal symptoms (OR, 95% CI, 0.80, 0.69–0.92) (baseline age, 50–55 years).⁵¹

Quality of evidence (GRADE)

Based on findings from cohort studies, the conclusion of the quality of evidence was rated as very low for implantation, clinical pregnancy, and live birth. Based on findings from RCTs, the quality of evidence was rated as high for preterm birth and moderate for GDM, gestational hypertension, and preeclampsia (Supplementary Table 8).

Comment

Principal findings

We conducted a comprehensive systematic review and meta-analysis on studies of adherence to MD and common female reproductive health outcomes over the reproductive lifespan. Findings from the RCTs suggest protective effects of MD during pregnancy on GDM and preterm birth. Beneficial associations of MD before pregnancy with GDM, gestational hypertension, and preeclampsia were suggested in the cohort studies. Evidence on MD and fertility-related outcomes was relatively limited, although possible beneficial effects of MD cannot be ruled out. High-quality studies of MD on other reproductive outcomes were sparse.

Comparison with existing literature

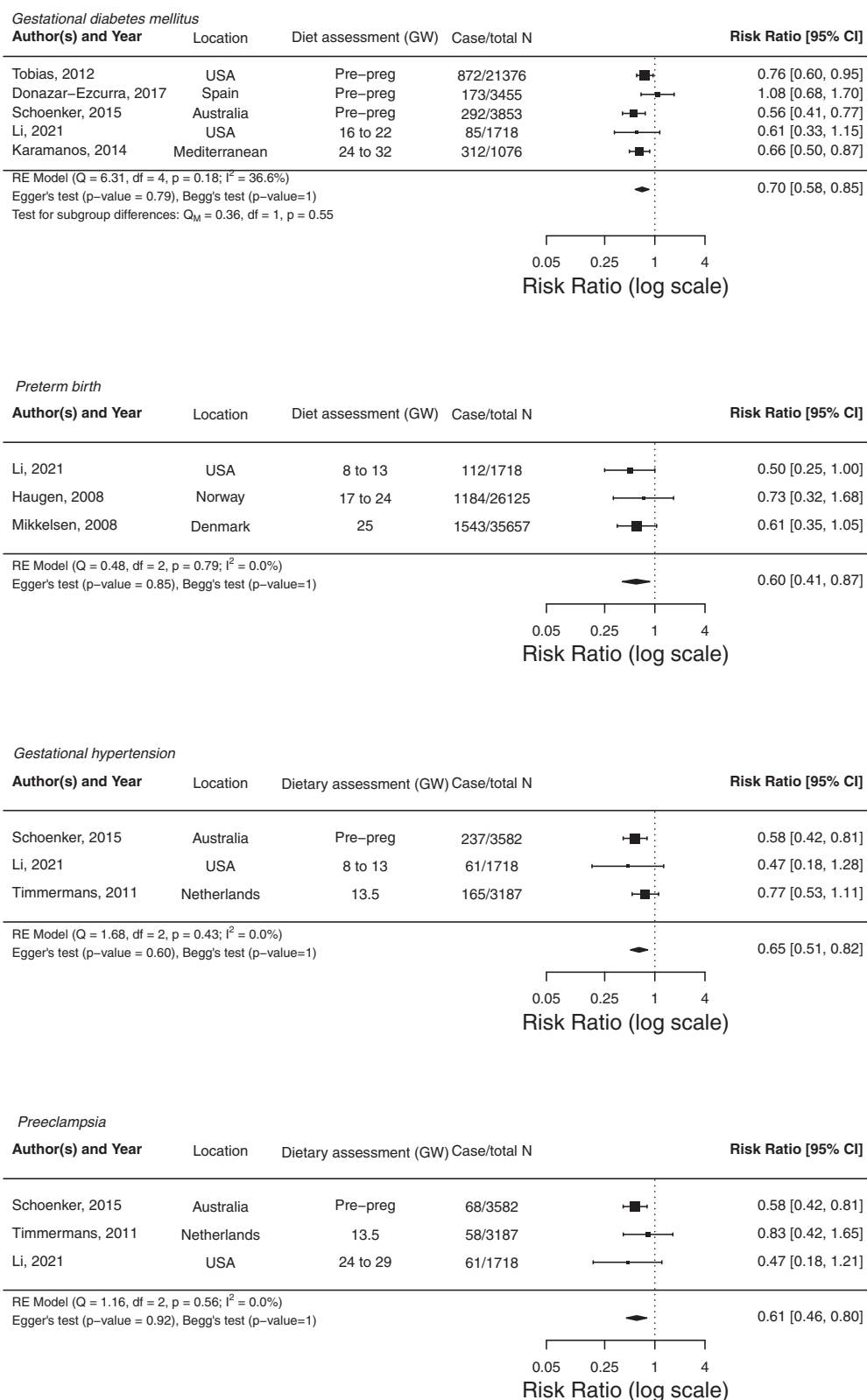
Mediterranean diet and fertility-related outcomes

This review identified 1 RCT and 6 prospective cohort studies among women utilizing IVF and 1 nested case-control study in the general population that evaluated MD with fertility. The

Intervention arm-specific count data from individual randomized controlled studies were extracted and pooled to calculate summary relative risk and 95% confidence interval of each outcome, comparing the group assigned to the Mediterranean diet vs the control group heterogeneity across studies was evaluated by the Cochran Q test and the I^2 statistics. Publication bias was evaluated by the Egger test and the Begg test. Test for subgroup differences by timing of the start of the intervention (before 12 GWs vs at or after 12 GWs) was performed when there were at least 2 eligible studies within each subgroup.

GW, gestational week.

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FIGURE 4**Summary relative risks of pregnancy-related outcomes with adherence to Mediterranean diet in prospective cohort studies**

6-week RCT randomized women to an intervention that supplemented several components and nutrients of MD (eg, EVOO products, omega-3 fatty acids, and vitamin D), which cannot sufficiently represent the overall MD pattern emphasizing intakes of whole grains, fruits, and vegetables or completely separate the individual effect(s) of EVOO, a major component of MD.²³ Therefore, the underlying effects of MD on female fertility cannot be inferred based on findings from this RCT. Overall, no evidence of a statistically significant, beneficial association was observed from cohort studies examining successful implantation, clinical pregnancy, or live birth following IVF; however, the effect estimates were suggestive of a benefit albeit with wide CIs. When examining the association between MD and fertility among women conceiving without medical assistance, we only identified 1 case-control study, which indicated that greater adherence to MD was associated with a lower risk of difficulty conceiving.

Biologically, MD may exert potential benefits on female fertility through mechanisms related to weight management, reduction of inflammation and oxidative stress, and improvement of mental health.⁵⁵ However, despite the biological plausibility, there was only limited evidence, yet of modest quality, linking adherence to MD to fertility endpoints. Moreover, the bulk of current studies focused on women undergoing infertility treatment. The relation between MD and fertility in women trying to conceive without medical assistance remains largely unknown.

Mediterranean diet and pregnancy-related outcomes

Evidence from RCTs on MD adherence during pregnancy and pregnancy outcomes is mounting, whereas no RCTs on preconception MD were found.

Summary findings from 6 and 7 RCTs support a beneficial effect of MD during pregnancy on lower risk of GDM and preterm birth, respectively. Results from 6 and 5 RCTs examining in-pregnancy MD suggested borderline protection for development of gestational hypertension and no effects on risk of preeclampsia. Of note, for preterm birth and suggestively for GDM, beneficial effects of MD were greater in RCTs that initiated their interventions in the first trimester vs RCTs that initiated the interventions after the first trimester. These findings suggest that the benefits of MD may differ by gestational timing, with greater benefits observed when MD interventions are initiated earlier gestation.

Adherences to MD before and during pregnancy in relation to pregnancy complications were evaluated in several cohort studies. Greater adherence to MD during pregnancy was associated with lower risks of GDM and preterm birth, consistent with findings from RCTs. Two cohort studies additionally suggested beneficial roles of prepregnancy MD on GDM. While summary RRs based on cohort studies for gestational hypertension and preeclampsia were significant, study-specific risk estimates were only significant for 1 study that examined MD before pregnancy with overall HDP risk but not in studies that examined MD during pregnancy. The association between adherence to MD before pregnancy and risk of pregnancy loss was only evaluated in 1 US cohort of female nurses, and null findings were reported.⁴⁴

Protective roles of MD on improving pregnancy outcomes including GDM, preterm birth, and HDP are biologically plausible. MD as an overall dietary pattern has been linked with favorable profiles of glucose and lipid metabolism, insulin sensitivity, body weight, and lower blood pressure.⁴⁵ Major

components of MD (eg, EVOO and nuts) have antiinflammatory and antioxidative stress properties.⁵⁶ These proposed mechanisms have been suggested in RCTs of both pregnant²⁵ and non-pregnant¹⁰ female individuals, with improved cardiometabolic endpoints or intermediate markers in the MD group.⁵⁶

Findings from RCTs and cohort studies on maternal or postpartum weight change were largely mixed. Reassuringly, no trials reported greater maternal or postpartum weight gain with MD intervention compared with the control. In contrast, included RCTs demonstrated benefits of MD on lipid and glucose metabolism during pregnancy and the postpartum period,^{25–27,29,30} suggesting its beneficial roles in obesity-related health outcomes. However, it should be noted that for RCTs examining GWG or postpartum weight change, the intervention of MD involving changing food patterns and food quality may naturally have implication in modulating weight change.

Mediterranean diet and other reproductive outcomes

Pubertal development,⁴⁸ LPD⁴⁶ and PCOS-like phenotype among eumenorrheic individuals,⁴⁷ and vasomotor menopausal symptoms⁵¹ were examined with adherence to MD in 4 cohort studies. Although the relevant literature is still too preliminary to draw any conclusion, this review suggested potential beneficial roles of MD in optimal initiation of puberty and relief of vasomotor symptoms. MD may support female reproductive health during puberty development and around the time of menopause by influencing sex-hormone concentrations through pathways related to inflammation and obesity.⁵⁷

Positive associations of adherence to MD with menstrual cycle irregularity and null associations with subclinical

Risk estimates with the greatest number of covariate adjustment from individual studies were pooled to calculate summary relative risk and 95% confidence interval of each outcome, comparing the group with the highest vs the lowest quantile of adherence to Mediterranean diet. Heterogeneity across studies was evaluated by the Cochran Q test and the I^2 statistics. Publication bias was evaluated by the Egger test and the Begg test. Test for subgroup differences by timing of the dietary assessment (pregnancy vs in-pregnancy) was performed when there were at least 2 eligible studies within each subgroup.

Yang. Mediterranean diet and female reproductive health over the life-course. Am J Obstet Gynecol 2023.

PCOS were reported from a US female cohort with a sample size of <300 participants. These findings warrant future replication and evaluation in more detail in populations of greater sample size and diversity.

Public health implication and directions for future research

A suboptimal reproductive profile at early age may increase the vulnerability of subsequent adverse reproductive outcomes, particularly in the presence of other risk factors, such as aging and obesity. Accordingly, it may be more beneficial to adopt a healthy lifestyle including healthy diet at an earlier age.⁵⁸ Although components of MD may individually benefit reproductive health, studies have suggested that there are likely synergistic effects of the overall MD pattern on one's health.⁷ Nonetheless, even though alcohol in moderation is part of the MD, roles of alcohol on health remain controversial.⁵⁹ Of note, given the topic of female reproductive health, pregnant women or women planning for pregnancy should not be encouraged at any level to consume alcohol given its known harms to the fetus, irrespective of any potential health benefits of moderate alcohol consumption.⁶⁰

Preconception is a critical period for a successful pregnancy and subsequently optimal fetal development; however, it is underexamined with MD. This review suggests that greater adherence to MD before pregnancy may have benefits to improved fertility; it may have similar or even greater benefits to several pregnancy outcomes compared with in-pregnancy MD. These findings require further investigation in future RCTs. In this review, most of the studies evaluated MD around the time of pregnancy, and little is known regarding its roles on female reproductive health at other stages across the lifespan. We did not identify any studies related to PCOS or endometriosis, which have substantial long-term health consequences. A few cross-sectional or retrospective studies reported benefits of MD on PCOS-related symptoms;^{57,61} however, whether MD may prevent PCOS and/or

improve PCOS prognosis warrants further prospective investigation.

The current literature evidence is largely drawn from predominantly White populations, raising concerns in view of the escalating reproductive health burdens in non-White populations. For example, fertility rates have reached historically low numbers among Asian populations⁶²; meanwhile, several major pregnancy complications such as GDM is of highest risk among Asians compared with populations of other races or ethnicities.⁶³ Notably, evidence of the protective effects of MD on GDM consistently observed in the 3 RCTs conducted in China support their potential benefits. The roles of MD or MD-like dietary patterns warrant further investigation in such populations with high reproductive health burdens.

Strengths and limitations

This study is one of the first systemic reviews and meta-analysis that considered all the available evidence from RCTs and prospective observational studies to systematically review and summarize the roles of MD on a wide range of female reproductive outcomes throughout the life-course. Several potential limitations merit discussion. First, given limited evidence on the topics of interest, not all female reproductive outcomes were covered in this review. Some, but not all outcomes were meta-analyzed. Because of the limited number of eligible studies, tests of overall or subgroup heterogeneity and publication bias for those meta-analyzed outcomes should be interpreted with caution. The lack of published data also limited us from formally evaluating potential heterogeneity across diverse populations or in the presence of other effect modifiers. We were aware of the great heterogeneity across individual trials, because of different study population, design, and intervention(s). Concerns about the impact of study quality on the results were noted in a few of the included RCTs and cohort studies. No RCTs were rated as high risk of bias. We performed a sensitivity analysis by excluding 1 cohort study which was rated as high risk of bias.³⁹ Lastly, in terms of confounding in

observational studies, we conducted the review based on the effect sizes, with the greatest number of covariates adjusted in individual studies. All the original observational studies included in this review were adjusted for major confounding factors except for 1 fertility study in China.⁵² We excluded this study in a sensitivity analysis and did not observe any changes in major conclusions.

Conclusions and implications

Greater adherence to MD during pregnancy may reduce risks of GDM and preterm birth. Greater adherence to MD before pregnancy might be associated with lower risks of GDM and HDP as well, with evidence mainly from cohort studies. Available evidence suggests possible benefits of MD to female fertility, despite a limited number of studies. Future intervention studies or prospective cohort studies of high quality on the effects of MD on other female reproductive outcomes are warranted. Studies among non-White populations are and needed. ■

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