Prepregnancy dietary patterns and risk of pregnancy loss[1–3]

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ABSTRACT

Background: Two previous case-control studies observed associations between specific food groups and risk of miscarriage; however, to our knowledge, no previous studies have investigated dietary patterns and risk of pregnancy loss.

Objective: We aimed to assess prepregnancy adherence to the alternate Healthy Eating Index 2010 (aHEI-2010), alternate Mediterranean diet (aMED), and Fertility Diet (FD) and risk of pregnancy loss.

Design: Our prospective cohort study included 15,950 pregnancies reported by 11,072 women in the Nurses' Health Study II between 1992 and 2009. Diet was assessed every 4 y starting in 1991 by using a validated food-frequency questionnaire. Prepregnancy dietary pattern scores were computed as the sum of a woman's score on each pattern's predefined components. Multivariable log-binomial regression models with generalized estimating equations were used to estimate RRs and 95% CIs.

Results: Incident spontaneous abortions and stillbirths were reported in 2756 (17.3%) and 120 (0.8%) pregnancies, respectively. None of the 3 dietary patterns were associated with risk of pregnancy loss. In the multivariable model, RR of pregnancy loss for a 1-SD increase in score was 1.02 (95% CI: 0.98, 1.05) for the aMED pattern, 1.01 (95% CI: 0.98, 1.05) for the aHEI-2010 pattern, and 0.98 (95% CI: 0.95, 1.01) for the FD pattern. Results were consistent when pregnancy loss was classified as either a spontaneous abortion (loss at $<$20 wk) or a stillbirth (loss at $\geq$20 wk).

Conclusion: Prepregnancy adherence to several dietary patterns was not associated with risk of pregnancy loss. *Am J Clin Nutr* 2014;100:1166–72.

INTRODUCTION

Fetal loss occurs after implantation in up to 30% of pregnancies, which makes it the most-frequent adverse pregnancy outcome (1, 2). In recognized pregnancies, the cumulative risk of miscarriage through week 20 of gestation ranges from 11% to 22% (3). Despite the commonness of this outcome, well-established risk factors for pregnancy loss are limited. Maternal age (4, 5), history of pregnancy loss (6), and infertility (7, 8) are the best characterized predictors of pregnancy loss, and all are nonmodifiable. Emerging evidence suggests that diet, which is a potentially modifiable factor, could have an impact on pregnancy loss (9, 10). However, although data are suggestive, there is a clear need for more research on the link between overall diet and pregnancy loss.

There are important challenges in addressing this relation. First, pregnancy loss is difficult to assess in epidemiologic studies as miscarriages are often not systematically recorded because women tend to underreport spontaneous abortions in face-to-face interviews (11), and this outcome is seldom recorded in disease registries (12). Case-control studies have been the main source of evidence thus far (9, 10). However, case-control studies are susceptible to a selection bias (because of the exclusion of early losses) and recall bias (due to the retrospective assessment of diet) (13). Furthermore, although previous studies have investigated single nutrients or specific food groups in relation to pregnancy loss, to our knowledge, no study has assessed dietary patterns with a comprehensive and complementary approach. Dietary patterns also tend to be more applicable to clinical and public health interventions because they more closely parallel the real world in which nutrients and foods are consumed in combination (14).

Therefore, the aim of this analysis was to determine the extent to which prepregnancy adherence to well-known dietary patterns is associated with risk of pregnancy loss in a large, prospective cohort of women.

SUBJECTS AND METHODS

Study population

We used data from the Nurses' Health Study II, which is an ongoing prospective cohort of 116,480 female nurses aged 24–44 y at the study's inception in 1989. Questionnaires are distributed every 2 y to update lifestyle and medical characteristics

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and capture incident health outcomes. Diet was first assessed in 1991 and has been updated every 4 y thereafter. Response rates for each questionnaire cycle have been >90%. Women were eligible for this analysis if they had no history of pregnancy loss in 1991 and reported at least one pregnancy during 1992–2009. Eligible participants contributed pregnancies until their first pregnancy loss or the end of follow-up. Of 19,451 eligible pregnancies, we excluded from the analysis pregnancies with missing data on diet (n = 2,475), implausible or missing gestational age (n = 111), or missing year of pregnancy (n = 619) and those in women with a diagnosis of type 2 diabetes (n = 69), cardiovascular disease (n = 86), or cancer (n = 141) before the pregnancy. The final sample consisted of 15,950 pregnancies from 11,072 women. This study was approved by the Institutional Review Board of the Partners Health Care System (Boston, MA) with the participants' consent implied by the return of questionnaires.

TABLE 1
Components of the dietary pattern adherence scores[1]

	aMED	aHEI-2010	FD
Fruit (servings/d)	↑	↑	—
Vegetables (servings/d)	↑	↑	—
Nuts, legumes, and soy (servings/d)	↑	↑	—
Red and processed meats (servings/d)	↓	↓	—
Fish and seafood (servings/d)	↑	—	—
Animal protein (% of energy/d)	—	—	↓
Vegetable protein (% of energy/d)	—	—	↑
Whole grains (servings/d)	↑	↑	—
Glycemic load	—	—	↓
High-fat dairy (servings/d)	—	—	↑
Low-fat dairy (servings/d)	—	—	↓
Sweetened beverages (servings/d)	—	↓	—
Moderate alcohol (g/d)	↑	↑	—
MUFA:SFA	↑	—	—
PUFA (no EPA or DHA)	—	↑	—
MUFA:*trans* fat	—	—	↑
trans Fat (% of energy/d)	—	↓	—
Omega-3 fats (EPA and DHA)	—	↑	—
Sodium (mg/d)	—	↓	—
Iron (mg/d)	—	—	↑
Multivitamin use (tablets/d)	—	—	↑

[1] Pearson's correlation coefficients for the aMED compared with aHEI-2010: 0.55; the aMED compared with FD: 0.24; and the aHEI-2010 compared with FD: 0.28. aHEI-2010, alternate Healthy Eating Index 2010; aMED, alternate Mediterranean diet; FD, Fertility Diet; ↑, encourages greater intake; ↓, encourages no or less intake.

Diet assessment

Diet was evaluated by using a validated 131-item food-frequency questionnaire (FFQ)[4] (15, 16). Women were asked to report how often, on average, they consumed specified amounts of each food and beverage included in the questionnaire during the previous year. We calculated nutrient intake by multiplying the frequency of intake of each food by its nutrient content and summing nutrient contributions across all food items. The nutrient content and portion size of each item were obtained from a nutrient database derived from the USDA and additional information from manufacturers (17). A validation study compared nutrients and foods assessed by the FFQ and multiple diet records. Overall, the mean correlation coefficient was 0.52 between food items and 0.59 between nutrients. The range for specific foods and nutrients included in our dietary pattern scores was 0.08 (spinach) to 0.87 (beer) for foods and 0.37 (polyunsaturated fats) to 0.75 (saturated fats) for nutrients (16, 18). To maintain a strictly prospective analysis of prepregnancy diet in relation to pregnancy loss, diet information from 1991 was related to pregnancies in 1992–1995, the 1995 diet information was used for pregnancies in 1996–1999; and so forth. If a woman was missing the most recent diet questionnaire before her pregnancy (<5% of women), most recent previous dietary data were carried forward.

Prepregnancy adherence scores to the alternate Healthy Eating Index 2010 (aHEI-2010), alternate Mediterranean diet (aMED), and Fertility Diet (FD) were computed for each FFQ cycle. These patterns were chosen because they have been associated with decreased oxidative stress (aMED) (19), improved endothelial function (aMED and aHEI-2010) (20), enhanced insulin sensitivity (aHEI-2010) (21), and decreased risk of infertility (FD) (22), all of which could influence risk of pregnancy loss (7, 23–25). Components included in each score are outlined in **Table 1**. Brief descriptions are as follows:

1) The aMED score (20) is based on dietary intakes of the following 8 items: vegetables (excluding potatoes), legumes and nuts, fruit, whole grains, red and processed meat, fish, alcohol, and the ratio of MUFAs to SFAs. Participants are assigned one point for being above the median of servings per day for each component, with the exception of red and processed meats, which was scored one point for being below the median intake. One point was assigned for moderate alcohol consumption (5–15 g/d). aMED scores range from 0 to 8.

2) The aHEI-2010 score is based on intakes of foods and nutrients consistently associated with lower risk of chronic disease in clinical and epidemiologic investigations (26). Points are given for intake of each component on a scale from 0 (worst) to 10 (best). Higher intake of vegetables (excluding potatoes), fruit, whole grains, nuts and legumes, long-chain (n−3) fats, polyunsaturated fat (PUFAs), and alcohol receive higher scores. The scoring is reversed for higher intakes of sugar-sweetened beverages and fruit juice, red and processed meat, *trans* fat, and sodium. aHEI-2010 scores range from 0 to 110.

3) The FD score is based on dietary factors associated with lowest risk of ovulatory infertility (22). Points are assigned for increasing the ratio of MUFA to *trans* fat and percentages of energy from vegetable protein, high-fat dairy, iron, and multivitamins from 1 to 5 points from the lowest to highest categories. For percentages of energy from animal protein, glycemic load, and low-fat dairy, the point assignment is reversed. FD scores range from 8 to 40.

Outcome assessment

Women were asked to report their pregnancies at baseline and in each biennial follow-up questionnaire. In the 2009

[4] Abbreviations used: aHEI-2010, alternate Healthy Eating Index 2010; aMED, alternate Mediterranean diet; FD, Fertility Diet; FFQ, food-frequency questionnaire.

questionnaire, women also reported information on the year, length, complications, and outcomes of all previous pregnancies. Options for pregnancy outcomes were a singleton live birth, multiple births, miscarriage or stillbirth, tubal or ectopic pregnancy, or induced abortion. Gestational lengths were reported in categories as <8, 8–11, 12–19, 20–27, 28–31, 32–36, 37–39, 40–42, and ≥43 wk of gestation. Self-reported pregnancy outcomes and gestation lengths have been previously shown to be validly reported (27). The main outcome in this study was pregnancy loss, which was defined as a fetal loss that occurred at any point during gestation. We also considered spontaneous abortions (a fetal loss at <20 wk) and stillbirths (a fetal loss at ≥20 completed weeks) as separate outcomes. The validity of a maternal recall of pregnancy loss has not been assessed in this population; however, the sensitivity of reporting a loss when one actually occurred has been estimated to be ~75% (28, 29). In the validation study by Wilcox et al (25), it was shown that the accuracy of a report depends greatly on the gestational age at the time of abortion. For instance, spontaneous abortions at <6 wk were recalled in 54% of cases, whereas abortions that occurred after 13 wk were recalled in 93% of cases (25). The comparison group was all pregnancies that did not end in fetal loss [live births (n = 12,298), induced abortions (n = 634), or tubal or ectopic pregnancies (n = 142)].

Covariate assessment

Information on potential confounding variables was assessed at baseline and during follow-up. For variables that were updated over follow-up, the most recent value before pregnancy was used. Maternal age was computed as the difference between year of birth and year of pregnancy. Physical activity was ascertained in 1991, 1997, 2001, and 2005 by using a previously validated questionnaire (30) from which metabolic equivalent task hours per week were derived. Weight, smoking status, multivitamin use, oral contraceptive use, and history of infertility were self-reported at baseline and updated every 2 y thereafter. History of ovulation inducing medication use was self-reported starting in 1993 and updated every 2 y thereafter. Marital status was reported in 1989, 1993, and 1997. Race and height were reported in 1989. Prepregnancy BMI (in kg/m^2) was calculated as weight divided by self-reported height squared. In a previous validation study, self-reported weight was highly correlated with weight measured by a technician in a similar group of nurses (r = 0.97) (31).

Statistical analysis

Baseline characteristics were derived from the 1991 questionnaire for all women who contributed eligible pregnancies. We divided women into groups according to quartiles of 3 dietary pattern adherence scores. Differences in baseline characteristics by prepregnancy dietary pattern adherence were compared by using a chi-square test for categorical variables and Kruskal-Wallis nonparametric tests for continuous variables.

Pairwise correlations between baseline continuous pattern scores were computed to assess the similarity of exposures. RR of pregnancy loss in relation to prepregnancy dietary pattern adherence was estimated by using log-binomial regression. Generalized estimating equations with an exchangeable working correlation structure were used to account for the within-person correlation between pregnancies. Dietary pattern adherence scores were analyzed both continuously for a 1-SD increase and categorically as quartiles. In categorical models, RR was computed as risk of fetal loss in a specific quartile compared with risk in the lowest quartile. Tests for linear trend across categories were conducted by using median values in each category as a continuous variable. In addition to age-, calorie-, and year-adjusted models, multivariable models were further adjusted for a priori–selected prepregnancy covariables. These covariables included BMI, smoking status, physical activity, history of infertility, marital status, and race. Fully adjusted models were run both with and without adjustment for nulliparity because adjustment for reproductive history might lead to overadjustment if ongoing dietary habits are related to the inability to carry a pregnancy to term, which, in this case, could manifest as nulliparity (32, 33). Categorical covariables included an indicator for missing data if necessary.

To assess the robustness of our findings, we investigated whether the relation of dietary patterns with pregnancy loss differed by gestational age at loss (<20 wk compared with ≥20 wk). We also performed analyses restricted to pregnancies from women ≤40 y old, pregnancies with no history of infertility, and first eligible pregnancies to address the potential of residual confounding by factors strongly related to risk of pregnancy loss. To minimize uncontrolled confounding by behaviors related to pregnancy planning and pregnancy recognition, we performed analyses restricted to married women who were not using oral contraception. Last, to address the potential of misclassification of exposure because of the interval between diet assessments, we restricted analyses to pregnancies in years closest to a diet assessment (1992, 1996, 2000, and 2004) (n = 5384 pregnancies).

The effect modification by prepregnancy BMI (<25 and ≥25), prepregnancy smoking status (current and never or former smokers), and maternal age (<35 y compared with ≥35 y) was tested by using cross-product terms in the final multivariate model. Specific components of a dietary pattern were only investigated if the overall pattern was significantly associated with pregnancy loss. All tests of statistical significance were 2-sided, and a significance level of 0.05 was used. All data were analyzed with SAS 9.1 software (SAS Institute Inc).

RESULTS

Overall, 11,072 women met our inclusion criteria and contributed 15,950 pregnancies to the analysis during 18 y of follow-up. On average, women who were in the highest quartiles of the 3 patterns were slightly older, reported more physical activity, were less likely to be current smokers or current users of oral contraceptives, and had lower prepregnancy BMI (**Table 2**). Means (±SDs) of the dietary patterns were 4.1 ± 1.9, 48.1 ± 11.1, and 24.1 ± 4.2 for the aMED, aHEI-2010, and FD, respectively. Dietary pattern adherence scores were approximately normally distributed and moderately correlated with one another, with Pearson's correlation coefficients between the aMED and aHEI-2010 of 0.55, aMED and FD of 0.24, and aHEI-2010 and FD of 0.28. There were 2756 spontaneous abortions (17.3%) and 120 stillbirths (0.8%) reported during follow-up. Cumulative risk of pregnancy loss in our cohort was 6.4% by week 7, 13.6% by week 11, 17.3% by week 20, and 18.4% by week ≥43.

TABLE 2
Baseline demographic characteristics by quartile of baseline prepregnancy dietary pattern adherence scores in 1991 (n = 11,072 women)[1]

	aMED		aHEI-2010		FD	
	Q1 (n = 2356)	Q4 (n = 2677)	Q1 (n = 2908)	Q4 (n = 2743)	Q1 (n = 2398)	Q4 (n = 2951)
Diet score	1.0 (0.0, 2.0)[2]	6.0 (6.0, 7.0)*	37.0 (33.0, 39.0)	62.0 (59.0, 67.0)*	19.0 (17.0, 20.0)	29.0 (28.0, 30.0)*
Age (y)	30.0 (28.0,33.0)	32.0 (30.0, 35.0)*	30.0 (28.0, 33.0)	32.0 (30.0, 35.0)*	31.0 (29.0, 33.0)	32.0 (29.0, 34.0)*
BMI (kg/m^2)	22.5 (20.6, 25.3)	22.0 (20.4, 24.5)*	22.6 (20.6, 25.7)	22.0 (20.4, 24.3)*	22.6 (20.7, 25.5)	22.0 (20.3, 24.6)*
Physical activity (MET-h/wk)	10.9 (4.4, 23.3)	20.8 (9.8, 40.0)*	9.7 (4.0, 21.6)	23.7 (11.0, 43.7)*	12.9 (5.4, 27.3)	18.2 (7.6, 37.4)
Smoking status [n (%)]						
Never	1688 (71.7)	1891 (70.6)*	2206 (75.9)	1806 (65.8)*	1773 (74.0)	2038 (69.1)*
Former	399 (16.9)	587 (21.9)	415 (14.3)	707 (25.8)	398 (16.6)	679 (23.0)
Current	267 (11.3)	194 (7.3)	282 (9.7)	226 (8.2)	221 (9.2)	231 (7.8)
White [n (%)]	2190 (93.0)	2520 (94.0)	2725 (93.7)	2555 (93.2)	2236 (93.2)	2756 (93.4)
Married [n (%)]	1634 (69.4)	1916 (71.6)	2279 (78.4)	1696 (61.8)*	1708 (71.2)	2094 (71.0)
OC use [n (%)]						
Never	330 (14.0)	483 (18.0)*	468 (16.1)	450 (16.4)	380 (15.9)	493 (16.7)*
Past	1357 (57.6)	1676 (62.6)	1752 (60.3)	1680 (61.3)	1350 (56.3)	1931 (65.4)
Current	669 (28.4)	517 (19.3)	688 (23.7)	612 (22.3)	668 (27.9)	526 (17.8)
History of infertility [n (%)][3]	204 (8.7)	246 (9.2)	281 (9.7)	237 (8.6)*	208 (8.7)	287 (9.7)
History of infertility medication use [n (%)][4]	228 (9.7)	302 (11.3)	309 (10.6)	300 (10.9)	262 (10.9)	328 (11.1)
Nulliparity [n (%)]	1078 (45.8)	1181 (44.1)	1017 (35.0)	1550 (56.6)*	991 (41.3)	1362 (46.2)*
Multivitamin use [n (%)]	1040 (44.1)	1582 (59.1)*	1467 (50.5)	1448 (52.8)	376 (15.7)	2522 (85.5)*
Total energy (kcal/d)	1461 (1176, 1805)	2064 (1716, 2447)*	1927 (1573, 2317)	1648 (1329, 2039)*	1743 (1410, 2117)	1709 (1390, 2090)*
Carbohydrate (% of energy/d)	47.9 (43.3, 52.8)	53.1 (48.9, 57.4)*	49.8 (45.4, 54.3)	52.2 (47.1, 57.1)*	49.0 (44.3, 53.7)	52.1 (47.4, 56.7)*
Protein (% of energy/d)	19.1 (16.8, 21.4)	18.8 (16.9, 20.9)*	18.0 (16.1, 20.0)	19.9 (17.5, 22.2)*	20.3 (18.2, 22.2)	18.0 (16.2, 20.1)*
Total fat (% of energy/d)	33.0 (29.5, 36.8)	28.7 (25.4, 31.9)*	32.8 (29.5, 36.3)	28.2 (24.7, 31.9)*	31.0 (27.5, 34.6)	52.1 (47.4, 56.7)*
MUFA (% of energy/d)	12.4 (10.8, 14.1)	10.8 (9.4, 12.3)*	12.5 (11.1, 14.1)	10.4 (8.9, 11.9)*	11.7 (10.2, 13.4)	11.4 (9.8, 12.9)*
PUFA (% of energy/d)	5.1 (4.4, 5.9)	5.5 (4.8, 6.3)*	5.1 (4.4, 5.8)	5.6 (4.7, 6.5)*	5.2 (4.4, 6.0)	5.4 (4.7, 6.3)*
SFA (% of energy/d)	12.4 (11.0, 14.0)	9.7 (8.4, 11.0)*	12.1 (10.8, 13.6)	9.6 (8.2, 11.1)*	11.2 (9.8, 12.7)	10.8 (9.2, 12.4)*
trans (% of energy/d)	1.7 (1.4, 2.2)	1.3 (1.0, 1.6)*	1.9 (1.5, 2.2)	1.1 (0.9, 1.4)*	1.7 (1.3, 2.1)	1.3 (0.2, 1.7)*
Alcohol (g/d)	0.9 (0.0, 2.7)	2.6 (0.0, 6.6)*	0 (0.0, 2.0)	2.8 (0.9, 6.9)*	1.0 (0.0, 3.1)	1.8 (0.0, 4.8)*
Caffeine (mg/d)	127 (49, 303)	144 (45, 350)	117 (44, 225)	150 (50, 357)*	124 (46, 251)	142 (44, 347)

[1] Higher scores indicate greater pattern adherence. *$P < 0.05$ from a chi-square test for categorical variables or a Kruskal-Wallis test for continuous variables for comparison of baseline participant characteristics across 4 quartiles of intake. aHEI-2010, alternate Healthy Eating Index 2010; aMED, alternate Mediterranean diet; FD, Fertility Diet; MET-h, metabolic equivalent task-hours; OC, oral contraceptive; Q, quartile.

[2] Median; 25th, 75th percentiles in parentheses (all such values).

[3] Assessed in 1989 and 1991.

[4] Assessed in 1993 (first time question was asked).

None of the 3 dietary patterns were associated with risk of pregnancy loss (**Table 3**). For the comparison of participants in the fourth quartile (greatest dietary pattern adherence) with those in the first reference quartile (lowest dietary pattern adherence), RR of pregnancy loss was 1.05 (95% CI: 0.95, 1.17; P-trend = 0.25) for the aMED score, 1.04 (95% CI: 0.94, 1.15; P-trend = 0.66) for the aHEI-2010 score, and 0.94 (95% CI: 0.86, 1.03; P-trend = 0.24) for the FD score in the fully adjusted models (model 2). Similarly, none of the dietary patterns were associated with risk of pregnancy loss when modeled as a continuous variable for a 1-SD increase in adherence (aMED SD: 1.9, aHEI-2010 SD: 11.1; FD SD: 4.2). In the fully adjusted multivariable model (with adjustment for the same covariates in model 2), RR of a 1-SD increase in score was 1.02 (95% CI: 0.98, 1.05) for the aMED pattern, 1.01 (95% CI: 0.98, 1.05) for the aHEI-2010 pattern, and 0.98 (95% CI: 0.95, 1.01) for the FD pattern. Results were similar after additional adjustment for parity (model 3). There were no significant associations between adherence to different dietary patterns and spontaneous abortion or stillbirth when these were considered separate outcomes (**Table 4**).

To assess the robustness of our findings and reduce residual confounding, we did a variety of sensitivity and subanalyses (*see* Supplemental Table 1 under "Supplemental data" in the online issue). There was no relation between the 3 dietary patterns and pregnancy loss when analyses excluded high-risk pregnancies (women >40 y and women with a history of infertility) or when analyses were restricted to the first eligible pregnancy for each woman or the most likely pregnancy planners in our cohort (ie, married women who were not using oral contraception). However, higher adherence to the FD score was related to lower risk of pregnancy loss when analyses were restricted to pregnancies from years immediately after diet assessment. In this analysis, women in the fourth quartile (highest adherence) of the FD score had 18% reduced risk of pregnancy loss [RR: 0.82 (95% CI: 0.69, 0.96) compared with women in the first quartile (lowest adherence) (P-trend = 0.04)]. When modeled as a continuous variable, RR of a 1-SD increase in the FD score was 0.94 (95% CI: 0.89, 1.00). The other patterns remained unassociated with pregnancy loss in these analyses [RR for a 1-SD increase in the aMED: 1.02 (95% CI: 0.96, 1.09); RR for a 1-SD increase in the aHEI-2010: 1.03 (95% CI: 0.97, 1.09)].

TABLE 3
Quartiles of prepregnancy dietary adherence scores and RRs (95% CIs) of pregnancy loss[1]

	Q1	Q2	Q3	Q4	*P*-trend
aMED					
No. of pregnancy losses/total pregnancies (%)	568/3355 (16.9)	1030/5786 (17.8)	546/2923 (18.7)	732/3886 (18.8)	—
Model 1	1.0 (reference)	1.04 (0.95, 1.14)	1.07 (0.97, 1.19)	1.05 (0.94, 1.16)	0.31
Model 2	1.0 (reference)	1.05 (0.96, 1.15)	1.09 (0.98, 1.22)	1.07 (0.96, 1.19)	0.16
Model 3	1.0 (reference)	1.05 (0.95, 1.15)	1.09 (0.98, 1.21)	1.05 (0.95, 1.17)	0.26
aHEI-2010					
No. of pregnancy losses/total pregnancies (%)	652/4063 (16.2)	703/3876 (18.1)	710/3950 (18.0)	811/4088 (19.8)	—
Model 1	1.0 (reference)	1.07 (0.98, 1.18)	1.03 (0.94, 1.14)	1.06 (0.97, 1.17)	0.33
Model 2	1.0 (reference)	1.08 (0.98, 1.19)	1.04 (0.94, 1.15)	1.08 (0.98, 1.19)	0.23
Model 3	1.0 (reference)	1.07 (0.97, 1.18)	1.02 (0.93, 1.13)	1.04 (0.94, 1.15)	0.67
FD					
No. of pregnancy losses/total pregnancies (%)	664/3548 (18.7)	718/4074 (17.6)	722/4092 (17.6)	772/4236 (18.2)	—
Model 1	1.0 (reference)	0.94 (0.85, 1.03)	0.92 (0.84, 1.01)	0.93 (0.85, 1.02)	0.15
Model 2	1.0 (reference)	0.94 (0.86, 1.04)	0.93 (0.85, 1.02)	0.95 (0.87, 1.04)	0.34
Model 3	1.0 (reference)	0.94 (0.86, 1.03)	0.92 (0.84, 1.02)	0.94 (0.86, 1.03)	0.22

[1] Model 1 was adjusted for age (continuous) and total energy intake (continuous). Model 2 was adjusted as for model 1 and for BMI (in kg/m^2; <18.5, 18.5–24.9, 25–29.9, ≥30, and missing), smoking status (never, former, current, and missing), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, 27–41.9, and ≥42 metabolic equivalent task-hours per week, and missing), history of infertility (no, yes, and missing), year (continuous), marital status (married and not married), and race (white and nonwhite). Model 3 was adjusted as for model 2 and for nulliparity (yes and no). Analyses were run by using a log-binomial generalized linear model with an exchangeable working correlation structure to compute RR estimates. aHEI-2010, alternate Healthy Eating Index 2010; aMED, alternate Mediterranean diet; FD, Fertility Diet; Q, quartile.

We also evaluated whether there was an interaction between adherence to the dietary patterns and other covariates in relation to risk of pregnancy loss. Higher adherence to the aMED pattern was associated with higher risk of pregnancy loss in the 31.6% of women who were overweight or obese before pregnancy (RR for a 1-SD increase: 1.16; 95% CI: 1.09, 1.23) but not in women who were lean before pregnancy (RR for a 1-SD increase: 1.02; 95% CI: 0.98, 1.07) (*P*-interaction = 0.005). No specific component of the aMED appeared to be driving this association because all components (except legumes) had a slightly positive,

TABLE 4
Quartiles of prepregnancy dietary adherence scores and RRs (95% CIs) of spontaneous abortion and stillbirth[1]

	SAB		Stillbirth	
Q (median)	No. of SABs/total pregnancies (%)	Multivariate RR (95% CI)[2]	No. of stillbirths/total pregnancies (%)	Multivariate RR (95% CI)[2]
aMED				
Q1 (2)	551/3355 (16.4)	1.0 (reference)	17/2664 (0.6)	1.0 (reference)
Q2 (4)	981/5786 (17.0)	1.03 (0.94, 1.14)	49/4543 (1.1)	1.71 (0.98, 2.99)
Q3 (5)	529/2923 (19.2)	1.10 (0.98, 1.22)	17/2263 (0.8)	1.15 (0.58, 2.29)
Q4 (6)	695/3886 (17.9)	1.05 (0.94, 1.17)	37/2973 (1.2)	1.82 (0.98, 3.37)
P-trend	—	0.27	—	0.13
aHEI-2010				
Q1 (36)	625/4036 (15.5)	1.0 (reference)	27/3270 (0.8)	1.0 (reference)
Q2 (44)	676/24.5 (17.4)	1.09 (0.98, 1.20)	27/3034 (0.9)	1.04 (0.61, 1.78)
Q3 (51)	682/3950 (17.3)	1.04 (0.94, 1.15)	28/3105 (0.9)	0.97 (0.56, 1.66)
Q4 (61)	773/4088 (18.9)	1.07 (0.97, 1.19)	38/3034 (1.3)	1.28 (0.76, 2.15)
P-trend	—	0.29	—	0.36
FD				
Q1 (19)	632/3548 (17.8)	1.0 (reference)	32/2730 (1.2)	1.0 (reference)
Q2 (22)	692/4074 (17.0)	0.96 (0.87, 1.05)	26/3215 (0.8)	0.71 (0.42, 1.19)
Q3 (25)	697/4092 (17.0)	0.94 (0.86, 1.04)	25/3196 (0.8)	0.65 (0.39, 1.10)
Q4 (29)	735/4236 (17.4)	0.95 (0.86, 1.05)	37/3302 (1.1)	0.95 (0.59, 1.53)
P-trend	—	0.32	—	0.97

[1] Analyses were run by using a log-binomial generalized linear model with an exchangeable working correlation structure to compute RR estimates. The reference group for spontaneous abortions was all pregnancies, and the reference group for stillbirths was all pregnancies that lasted >20 wk. aHEI-2010, alternate Healthy Eating Index 2010; aMED, alternate Mediterranean diet; FD, Fertility Diet; SAB, spontaneous abortion; Q, quartile.

[2] Multivariate models were adjusted for age (continuous), total energy intake (continuous), BMI (in kg/m^2; <18.5, 18.5–24.9, 25–29.9, ≥30, and missing), smoking status (never, former, current, and missing), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, 27–41.9, and ≥42 metabolic equivalent task-hours per week, and missing), history of infertility (no, yes, and missing), year (continuous), marital status (married and not married), and race (white and nonwhite).

nonsignificant association with pregnancy loss in overweight or obese women. No significant differences in effect estimates were seen when we assessed adherence to dietary patterns and risk of pregnancy loss in current compared with never or former smokers and in young compared with older women (<35 y compared with ≥35 y, respectively).

DISCUSSION

In this large, prospective cohort study, adherence to aHEI-2010, aMED, or FD patterns before pregnancy was not associated with risk of pregnancy loss. Although the associations of the aMED and aHEI-2010 with pregnancy loss were consistently null in various subanalyses, stronger adherence to the FD score was inversely associated with fetal loss in analyses restricted to pregnancies closer in time to a diet assessment. Thus, despite evidence that has linked these eating habits to lower risk of chronic disease (34, 35) and, in the case of the FD, lower risk of ovulatory infertility (22), these dietary patterns do not appear to be related to pregnancy loss.

Studies on the association between dietary patterns and risk of pregnancy loss have been sparse. Results presented in the current study were not entirely consistent with 2 previous studies on dietary habits and risk of pregnancy loss. A case-control study from Italy showed higher risk of spontaneous early miscarriage with lower intakes of green vegetables, fruit, and dairy products coupled with higher intake of fat (9). Similarly, a population-based case-control study from the United Kingdom showed that lower intakes of fresh fruit and vegetables, dairy, and chocolate were associated with increased odds of a spontaneous abortion (10). Although a direct comparison with our results is difficult, we did not show evidence that a diet rich in fruit and vegetables (eg, the aMED or aHEI-2010) or dairy products (eg, the FD) was associated with pregnancy loss.

However, some important methodologic limitations of previous studies are worth noting. First, both previous studies assessed diet after the outcome was recorded by using a nonvalidated dietary questionnaire with ≤13 food groups. In that setting, recall bias and unmeasured confounding by other dietary variables are potential concerns. Cases or control subjects may be more likely to alter their reporting resulting in recall bias. Furthermore, if physical activity is protective against pregnancy loss (36), the failure to control for calorie intake (a marker of physical activity) could overestimate effect estimates. Second, the Italian study defined their control subjects as women who gave birth to a healthy infant at term. If diet quality is related to low birth weight (37) or preterm birth (38), then the choice of control subjects with full-term normal deliveries may be selectively choosing women with a better diet quality. Finally, both previous studies asked about diet in the first trimester of pregnancy, which tends to suffer from strong confounding by pregnancy symptoms. Pregnancy symptoms such as nausea (and aversions to tastes or smells) can influence dietary behavior (39), and these symptoms are more frequent or severe in pregnancies that are eventually carried to term than in those that miscarry (40). Although the direction of this bias may be debated, pregnancy symptoms are, nevertheless, a challenging variable to measure and account for in analyses.

Although our study expanded on previous research, it is important to consider the limitations in light of the null findings. First, misclassification of dietary intake was likely mainly because diet information was updated every 4 y. Although this type of misclassification was likely nondifferential, it would have tended to attenuate effects to the null and could be one explanation for our lack of significant findings. With this in mind, when we limited our analyses to pregnancies in the years closest to a diet assessment (1992, 1996, 2000, and 2004), the FD score was inversely associated with pregnancy loss, suggesting that some of the components of this pattern may be related to risk of pregnancy loss, particularly lower intake of animal protein and more-frequent consumption of multivitamins. Second, there has been some concern about differential misclassification of fetal loss by pregnancy intention. Specifically, pregnancy planners might be more likely to have a healthful diet and to recognize a loss. Although plausible, when we restricted our population to the most likely pregnancy planners, results remained null. Third, it was likely that many early losses were unrecognized and, thus, not reported. To cause a bias, however, this underreporting would have needed to be differential with respect to the diet assessment, which was unlikely because of the prospective nature of the study. Fourth, despite our adjustment and stratification for a variety of potential confounders, we could not rule out the possibility that there may have been residual confounding in our analyses. However, differences between unadjusted and multivariate-adjusted effect estimates were small, which suggested that any residual confounding was unlikely to have had a large effect on the interpretation of our results. Finally, our study did not distinguish chromosomally normal from abnormal miscarriages. Because chromosomally abnormal miscarriages are likely less susceptible to the effects of diet, this heterogeneity in outcome would have tended to attenuate our results toward the null. Despite these limitations, our study had many strengths including a large number of pregnancy losses (specifically stillbirths), prospective design, nearly complete follow-up over the 18 y, and inclusion of early pregnancy losses.

In conclusion, our results indicate that prepregnancy adherence to well-characterized dietary patterns was not associated with risk of pregnancy loss. However, secondary analyses suggested that the FD pattern was inversely related to pregnancy loss in pregnancies occurring shortly after diet assessment, suggesting that some of the null findings may be the result of exposure misclassification. Note that, despite our null findings on specific dietary patterns, other dietary patterns or specific foods and nutrients might be related to pregnancy loss. Our findings should not discourage women from eating a healthy diet before pregnancy because a healthier diet has been related to an increased probability of conceiving (41) as well as decreased risk of adverse pregnancy and infant outcomes (37, 38, 42, 43). Future prospective cohort studies that enroll couples preconceptionally and measure diet immediately before conception are needed to further elucidate the relation between dietary patterns and risk of pregnancy loss.

The authors' responsibilities were as follows—JWR-E, SAM, and JEC: acquired data; AJG, JWR-E, RH, PLW, MWG, and JEC: analyzed and interpreted data; AJG, JWR-E, RH, PLW, MWG, AP, SAM, and JEC: provided critical revision of the manuscript for important intellectual content; AJG, PLW, and JEC: performed the statistical analysis; AJG and JEC: had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. None of the authors declared a conflict of interest.

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