Dietary patterns and fecundability in 2 prospective preconception cohorts

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ABSTRACT

Background: Diet is increasingly recognized as an important determinant of human fertility, with most research focused on specific nutrients or food groups. However, there has been limited assessment of the effect of dietary patterns on fertility.

Objectives: We evaluated the association between 4 dietary patterns [the alternative Mediterranean Diet (aMed), the Healthy Eating Index-2010 (HEI-2010), the Danish Dietary Guidelines (DDGI), and the Dietary Inflammatory Index (DII)] and fecundability in 2 preconception cohorts of couples trying to conceive: SF (SnartForaeldre.dk) in Denmark and PRESTO (Pregnancy Study Online) in North America.

Methods: Participants completed a baseline questionnaire on sociodemographic, anthropometric, and lifestyle factors and, 10 d later, a validated cohort-specific FFQ. We used data from these respective FFQs to calculate adherence to each dietary pattern. Participants completed bimonthly follow-up questionnaires for ≤12 mo or until pregnancy, whichever came first. We restricted analyses to 3429 SF and 5803 PRESTO participants attempting pregnancy for ≤6 cycles at enrollment. We used proportional probabilities regression models to estimate fecundability ratios (FRs) and 95% CIs, adjusting for potential confounders.

Results: Greater DII, indicative of a less anti-inflammatory diet (i.e., poorer diet quality), was associated with reduced fecundability in both SF and PRESTO (DII ≥ -1.5 compared with < -3.3: FR: 0.83; 95% CI: 0.71, 0.97 and FR: 0.82; 95% CI: 0.73, 0.93, respectively). In PRESTO, greater adherence to the aMed or to the HEI-2010 was associated with greater fecundability. In SF, there was no appreciable association between the aMed and fecundability, whereas greater adherence to the DDGI was associated with greater fecundability.

Conclusions: In prospective preconception cohort studies from Denmark and North America, higher-quality diets, including diets lower in inflammatory effects, were associated with greater fecundability.

Keywords: diet, dietary patterns, fecundability, pregnancy, Healthy Eating Index, Dietary Inflammatory Index, Mediterranean diet

Introduction

Approximately 10%–15% of couples in Western nations experience infertility, defined as the inability to conceive within 12 mo of unprotected intercourse (1). Infertility can exact a substantial psychological (2) and economic (3) toll on affected couples. Identifying risk factors for infertility and understanding

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Abbreviations used: aMed, alternative Mediterranean Diet; DDGI, Danish Dietary Guidelines Index; DHQII, Diet History Questionnaire II; DII, Dietary Inflammatory Index; FR, fecundability ratio; HEI-2010, Healthy Eating Index-2010; LMP, last menstrual period; MET, metabolic equivalent; NHS II, Nurses' Health Study II; PRESTO, Pregnancy Study Online; SF, SnartForaeldre.dk; SF-FFQ, SnartForaeldre.dk food-frequency questionnaire; TTP, time to pregnancy.

the mechanisms through which risk factors operate are important public health goals.

Diet is a complex and multifaceted lifestyle factor dictated by economic, geographic, political, cultural, social, and psychological drivers. Several studies have evaluated associations between individual nutrients or specific foods and fecundability (4), but it is difficult to translate these findings into dietary guidelines or behavioral advice for couples trying to conceive. Moreover, it is difficult to differentiate the independent effects of individual nutrients when evaluating hypotheses of dietary associations with health outcomes. This is because nutrients within foods are highly correlated and people eat foods (as part of larger dietary patterns), not individual nutrients. Thus, approaches that evaluate dietary patterns using dietary scoring systems are needed, because they provide useful measures of dietary behaviors by accounting for the quantity, variety, and combination of foods and beverages in a diet and how frequently they are consumed (5).

Prior studies have reported associations of dietary scoring systems, including the "fertility diet" (6) and Mediterranean-style dietary patterns (7), with infertility and clinical pregnancy rates among couples receiving infertility treatment. Three of 4 studies found that greater adherence to the Mediterranean diet was associated with an increased probability of clinical pregnancy (8–11). However, preconception dietary patterns have not been previously examined in a cohort of pregnancy planners without known fertility impairment, as far as we know.

To build on this research, we evaluated the extent to which 4 well-characterized dietary patterns—the alternative Mediterranean Diet (aMed) (12), cohort-specific dietary scoring systems based on government recommendations [Danish Dietary Guidelines Index (DDGI) (13) and the Healthy Eating Index-2010 (HEI-2010) (14)], and a dietary scoring system designed to measure the effect of dietary components on inflammation in the body [the Dietary Inflammatory Index (DII) (15)]—were associated with fecundability in 2 Internet-based preconception cohort studies in Denmark and North America. We hypothesized that pregnancy planners with dietary patterns characterized by high intake of fruit, vegetables, whole grains, and unsaturated fats, and low in added sugars, *trans* fatty acids, and inflammation-inducing foods and nutrients, would have higher fecundability than those with dietary patterns characterized by the inverse pattern of consumption of these food groups.

Methods

Study population

SF (SnartForaeldre.dk) is an ongoing Web-based prospective preconception cohort study in pregnancy planners in Denmark (enrolled from 2011 to present) (16). Female participants are aged 18–45 y and not using fertility treatment. Upon enrollment, participants complete a baseline questionnaire on sociodemographic, lifestyle, and reproductive histories. Beginning in February 2013, 10 d after enrollment, participants were invited to complete a 230-item FFQ (SF-FFQ) designed for and validated in this population (17). Women complete follow-up questionnaires every 8 wk to update pregnancy status until conception, or for 12 mo, whichever occurs first. Of 7680 eligible women who completed the baseline questionnaire, we excluded 172 whose last menstrual period (LMP) was >6 mo before study entry and 113 women with missing or implausible LMP information. We excluded 1887 women attempting to achieve pregnancy for >6 mo at study entry, and 995 women who filled out the baseline questionnaire before SF-FFQ implementation. We further excluded 1036 women who did not complete the SF-FFQ (response rate: 78%) and 48 women with implausible total energy intake (<600 or >3800 kcal/d), leaving a final analytic sample of 3429 women.

PRESTO (Pregnancy Study Online) is an ongoing Web-based prospective preconception cohort study in pregnancy planners in North America (2013 to present), nearly identical in design to SF (18). Women aged 21–45 y and not using fertility treatment are eligible for participation. At baseline, participants complete questionnaires on sociodemographic, anthropometric, lifestyle, and reproductive histories. Ten days after enrollment, women are invited to complete the National Cancer Institute's 134-item Diet History Questionnaire II (DHQII). The DHQII has been previously validated (19, 20). Female participants complete follow-up questionnaires every 8 wk to update pregnancy status until conception or 12 mo, whichever occurs first. A total of 11,970 eligible women completed the baseline questionnaire and, after exclusion criteria were applied, we included a final analytic sample of 5803 women (**Supplemental Figure 1**).

SF is registered at Aarhus University (2016-051-000001, number 431) and complies with Danish and European Union legislation on data protection. SF and PRESTO were approved by the Institutional Review Board at Boston University Medical Campus. Participants in both cohorts provided online informed consent.

Exposure assessment

We derived dietary patterns from the respective FFQs utilized in each population at baseline. We estimated food group and macro- and micronutrient intakes in each cohort's diet questionnaire. In SF, we used the Danish Nutrient Database (21) and, in PRESTO, we used the National Cancer Institute's DIET∗CALC software (version 1.5.0). Nutrient estimates, including carbohydrate, protein, and fat, were previously validated for each population, using 4-d food diaries (SF-FFQ) and four 24-h recalls (DHQ) (deattenuated correlation coefficient: 0.67, 0.56, and 0.63, respectively, in SF and 0.69, 0.60, and 0.66, respectively, in the DHQ validation study population) (17–21).

In both SF and PRESTO, we classified adherence to the aMed (12) by calculating servings per day of 9 food components: vegetables, legumes, fruit, nuts, fish, whole-grain foods, red and processed meat, monounsaturated:saturated fats ratio, and alcohol. Individuals were assigned points based on their consumption relative to the median intake in the cohort. Greater consumption of vegetables, legumes, fruit, nuts, fish, whole-grain foods, higher monounsaturated:saturated fats ratio, and moderate alcohol intake yielded a higher score. Greater consumption of red and processed meat and low or high alcohol intake yielded a lower score. The scores of the components were summed to yield a maximum value of 9, with 0–3 points indicating low adherence, 4–5 indicating medium adherence, and ≥6 indicating high adherence. We assigned aMed categories based on the literature (22).

In SF, we classified adherence to the 6 dietary components of the DDGI: fruit and vegetables, fish, red and processed meat, saturated fat, added sugar, and whole grains (13). Food item scores range from 0 to 1, where 0 is no adherence and 1 is full adherence. Participants receive a score between 0 and 1 based on their intake of each dietary component compared with the recommendation. Greater consumption of fruit and vegetables, fish, and whole-grain foods yields a greater dietary adherence score; whereas, greater consumption of red and processed meat, saturated fat, and added sugar yields a lower dietary adherence score. The scores of the components were summed to yield a maximum value of 6, using the categories <3, 3, 4, and ≥5 to indicate low to high adherence. Discrete categories were selected a priori based on the distribution within the cohort.

In PRESTO, we classified adherence to the HEI-2010 by calculating the consumption of 12 food components: total fruit, whole fruit, total vegetables, greens and beans (including legumes), whole-grain foods, dairy, total protein foods, seafood and plant proteins, fatty acids, refined-grain foods, sodium, and empty calories (23). Each component is worth between 5 and 20 points and the 12 components are summed to yield a maximum score of 100, with a higher score reflecting higher diet quality. Greater consumption of total fruit, whole fruit, total vegetables, greens and beans, whole-grain foods, dairy, total protein foods, seafood and plant proteins, and fatty acids (greater intake of MUFAs and PUFAs and lower intake of SFAs) yields a greater dietary adherence score; whereas, greater consumption of refined grains, sodium, and empty calories yields a lower dietary adherence score. We categorized HEI-2010 as <60, 60–69, 70–79, and ≥80 based on the distribution within the cohort.

In SF and PRESTO, we classified adherence to the DII by calculating the intake of 29 dietary parameters (out of a possible 45 parameters) based on food intake alone and standardizing them to the DII database, details of which have been described elsewhere (15). The dietary parameters used for DII calculation in the present cohorts were alcohol, vitamin B-12, vitamin B-6, β-carotene, caffeine, carbohydrate, cholesterol, energy, total fat, fiber, folate/folic acid, iron, magnesium, MUFAs, niacin, omega (ω)-3 fatty acids, ω-6 fatty acids, protein, PUFAs, riboflavin, saturated fat, selenium, thiamin, *trans* fat, vitamin A, vitamin C, vitamin D, vitamin E, and zinc. Whereas the possible range of the DII is −8.87 to 7.98 across cohorts, we observed a range of −5.41 to −0.17. Higher (more positive) DII scores indicate a more inflammatory diet. We categorized the DII based on the approximate 25th, 50th, and 75th percentiles across cohorts, using the categories < −3.3, −3.3 to −2.2, −2.3 to −1.5, and ≥ −1.5. To use the same categories in both cohorts, categories for the DII were based on the distribution of the DII between both cohorts. We used Pearson's correlation coefficient (r) to evaluate correlation across the dietary patterns. Aside from the DDGI, all dietary pattern components were standardized to 2000 kcal, using the nutrient residual method.

Fecundability assessment

We estimated time to pregnancy (TTP) using data from baseline and follow-up questionnaires. At cohort entry, women reported their LMP date, menstrual cycle regularity, and the number of cycles for which they had attempted pregnancy. Women with regular cycles, defined as being able to "predict about when the next period would start" during times when they were not using hormonal contraception, were also asked about their usual menstrual cycle length. On each subsequent follow-up questionnaire, participants reported their LMP date, whether they had conceived, if they had initiated fertility treatment, and if they were still trying to conceive since the last questionnaire. For women with irregular cycles, we estimated cycle length based on LMP dates reported at baseline and during follow-up. In PRESTO, we attempted to identify outcome information on women lost to follow-up by contacting them via email or phone and searching online on social media or online infant registries. Fecundability, the per-cycle probability of pregnancy, was estimated based on total discrete menstrual cycles at risk, calculated as follows: cycles of attempt at study entry + [(LMP date from most recent follow-up questionnaire − date of baseline questionnaire completion)/usual cycle length] + 1. Females contributed observed cycles from baseline until reported conception, initiation of fertility treatment, cessation of pregnancy attempt, withdrawal, loss to follow-up, or 12 cycles, whichever came first.

Covariate assessment

At baseline, participants reported their age, weight, height, race, ethnicity, education, income, smoking status, alcohol intake, physical activity, parity, gravidity, last form of contraception, intercourse frequency, use of any methods to time intercourse (e.g., ovulation testing, menstrual charting), and multivitamin use. BMI was calculated as weight (kg) divided by height (m) squared (in kg/m^2). In SF, total metabolic equivalents (METs) were calculated using the International Physical Activity Questionnaire short-form by summing MET-hours from walking, moderate physical activity, and vigorous physical activity (24). In PRESTO, MET-hours were calculated by multiplying the average hours per week spent in various activities by METs estimated by the Compendium of Physical Activity (25). All other potential confounders were ascertained identically across cohorts, with the exception of race/ethnicity (PRESTO only; not ascertained in SF), education, and income; we harmonized data on the latter variables across both cohorts, using comparable categories for income and years of schooling.

Data analysis

We examined baseline characteristics, age-standardized to the analytic cohort at baseline, by adherence to each dietary pattern. We used proportional probabilities regression models to estimate fecundability ratios (FRs) and 95% CIs for the association between each dietary pattern and fecundability. The FR is the ratio of the average per-cycle probability of conception comparing the exposed category with the unexposed (reference) category. An FR < 1 indicates a longer TTP among exposed relative to unexposed women. The discrete-time proportional probabilities model includes indicator variables for cycles at risk to account for the decline in fecundability over time in the population at risk (26). We used the Andersen–Gill data structure, which outputs a single menstrual cycle per observation, to account for delayed entry into the risk set. We also examined the associations between each dietary index, coded as a continuous variable, and fecundability by fitting restricted cubic splines (27). Because splines were intended to be a descriptive analysis assessing the overall shape that would best describe the relation if it were not constrained to be linear, no formal tests were conducted to determine the nonlinear relation.

Potential confounders were determined by an a priori–specified directed acyclic graph and a change in estimate approach (28). Variables included age (<25, 25–29, 30–34, 35–39, ≥40 y), BMI (<18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥35), current smoker (yes compared with no), physical activity per week (<10, 10–19, 20–39, ≥40 MET-h/wk), hormonal last form of contraception (yes compared with no), intercourse frequency (<1, 1, 2–3, ≥4 times/wk), use of any method to improve pregnancy chances (e.g., ovulation testing), daily use of prenatal supplements or multivitamins, race/ethnicity (white/non-Hispanic, black/non-Hispanic, Asian/non-Hispanic, Hispanic, other or mixed race/non-Hispanic; PRESTO only), education (high school or less, some college, college graduate, graduate school), income (<25,000, 25,000–39,999, 40,000–79,999, ≥80,000 Danish krone/mo; <50,000, 50,000–99,999, 100,000–149,999, ≥150,000 US dollars/y), and parous (yes compared with no). Geographic location (Northeast, South, Midwest, West, and Canada) was assessed as a potential confounder in PRESTO but was omitted from the final models because it had no appreciable effect on the exposure–outcome association.

We stratified by pregnancy attempt time at study entry (<3 compared with 3–6 cycles) to assess the potential for reverse causation (i.e., women changing their diets out of concern about subfertility). We assessed the extent to which the association between each dietary pattern and fecundability varied by BMI (<25 compared with ≥25), because adiposity can affect the bioavailability of some nutrients (29). Lastly, we stratified the data by age (<35 compared with ≥35 y), a strong determinant of fecundability (30).

Missing data.

We used multiple imputation by fully conditional specification to impute missing data on covariates and pregnancy outcomes (31). We generated 20 imputed data sets with >200 covariates to predict missing values including demographics, lifestyle characteristics, and reproductive and medical history. We analyzed each imputed data set separately and we combined effect estimates and SEs across imputed data sets to account for between- and within-imputation variation using Rubin's rule (32). To reduce selection bias from dropouts, we assigned 1 cycle of follow-up to participants with no follow-up data who only completed the baseline questionnaire (SF, n = 235, 6.9%; PRESTO, n = 151, 2.6%) and imputed their pregnancy status (pregnant or not pregnant) using data from the baseline questionnaire (32). Missingness for covariates ranged from <1.0% (gravidity) to 10% (income) in SF and from <0.1% (gravidity) to 4% (income) in PRESTO.

Results

From 2013 to 2020, 3429 SF participants contributed a total of 2220 pregnancies and 12,392 cycles; 5803 PRESTO participants contributed a total of 3715 pregnancies and 24,272 cycles. Based on life-table methods, 74.1% (SF) and 52.4% (PRESTO) of participants conceived within 6 cycles of attempt. The median aMed score in both SF and PRESTO was 4 (IQR: 3–6). In SF, the median DDGI score was 4.2 (IQR: 3.6–4.7), and in PRESTO, the median HEI-2010 score was 66.9 (IQR: 58.6–74.1). The median DII score was −2.6 (IQR: −3.4 to −1.8) in SF and −2.2 (IQR: −3.2 to −1.3) in PRESTO (**Supplemental Figure 2**). In both cohorts, all DII scores were <0, indicating all scores were net anti-inflammatory.

Within the SF cohort, the aMed and DDGI dietary patterns were most strongly correlated with one another (r = 0.71), followed by the aMed and DII (r = −0.68) and the DII and DDGI (r = −0.63). Within PRESTO, the aMed and HEI-2010 showed the strongest correlation with one another (r = 0.77), followed by the HEI-2010 and DII (r = −0.55) and the aMED and DII (r = −0.46).

We examined participant characteristics ascertained on the baseline questionnaire, age-adjusted to the cohort at baseline, by dietary pattern scores (**Tables 1** and **2**). In both SF and PRESTO, individuals with greater adherence to the aMed, cohort-specific recommended dietary pattern (DDGI or HEI-2010), or a more anti-inflammatory DII, had lower BMI and were less likely to currently smoke or have had a previous birth. They also drank fewer sugar-sweetened beverages, had higher education and income, were more likely to take a multivitamin or prenatal supplement, and were less likely to have used hormonal contraception as their last method of contraception. In PRESTO, greater adherence to each of the dietary patterns was associated with greater physical activity. In addition, dietary patterns differed by geographic region in PRESTO. Participants in the Northeast were more likely to adhere to the HEI-2010 diet and aMed, whereas participants in the South and Midwest were more likely to have high DII scores (i.e., more inflammatory diet).

aMed

In SF, after adjustment for covariates, we observed no appreciable association between adherence to the aMed and fecundability (**Figure 1**A, **Table 3**). Associations between the aMed and fecundability were similar across strata of pregnancy attempt time at enrollment (**Supplemental Table 1**). Although the CIs were wide, among women with BMI < 25 or age ≥ 35 y, greater adherence to the aMed was associated with higher fecundability (aMed score ≥ 6 compared with <3, FR: 1.11; 95% CI: 0.97, 1.26; and FR: 1.25; 95% CI: 0.79, 1.99, respectively).

In PRESTO, greater adherence to the aMed was associated with greater fecundability (Figure 1B, Table 3). Compared with low adherence, those with medium and high adherence had FRs of 1.11 (95% CI: 1.03, 1.20) and 1.15 (95% CI: 1.06, 1.24), respectively. When examined using restricted cubic splines, we observed a threshold association between aMed adherence and fecundability, because we observed an increase in fecundability up until an aMed score of ∼6 and no additional increase beyond 6 (Figure 1B). Results were consistent when stratified by age and attempt time at study entry (**Supplemental Table 2**). When stratified by BMI, results were stronger among leaner women (BMI < 25).

DDGI and HEI-2010

In SF, we observed that those with the greatest DDGI adherence had greater fecundability (**Figure 2**, Table 3). Compared with meeting cohort-specific recommendations for <3 components, the FR for meeting ≥5 recommended components was 1.11 (95% CI: 0.92, 1.30). When modeled continuously, we observed greater fecundability for each 1-unit increase in

TABLE 1 Baseline characteristics of SF participants by selected dietary patterns[1]

	Alternative Mediterranean Index		Danish Dietary Guidelines Index		Dietary Inflammatory Index		
					More anti-inflammatory	Less anti-inflammatory	
	Low (0–3)	High (≥6)	Low (<3)	High (≥5)	(< −3.3)	(≥1.5)	Overall cohort
Women, *n*	1212	1091	278	365	858	857	3429
Age, y, mean	28.7	29.6	28.2	29.8	29.4	28.6	29.1
BMI, kg/m^2, mean	25.4	23.1	26.8	22.6	23.7	24.8	24.3
Current smoker, %	12.6	7.8	20.3	5.2	8.1	15.5	11.4
Parous, %	39.4	30.2	41.0	31.3	31.6	32.6	34.7
Alcohol intake, drinks/wk, mean	2.0	2.7	2.1	2.5	2.6	2.3	2.4
Physical activity, MET/wk, mean	61.9	60.6	67.2	66.4	69.7	57.2	63.0
Last birth control method hormonal, %	61.0	51.2	65.4	49.4	52.3	62.0	57.1
Intercourse, freq/wk, %							
≤1	45.6	36.8	52.4	34.5	36.9	45.5	40.9
2–3	43.9	48.6	39.7	49.6	46.6	42.6	45.9
≥4	10.6	14.7	7.9	15.9	16.5	11.9	13.2
Method to improve pregnancy, %	74.3	74.5	71.5	75.3	74.6	75.8	74.1
Daily use of multivitamin or prenatal supplement, %	67.2	77.0	60.1	83.0	77.0	66.5	71.6
Sugar-sweetened beverage, drinks/wk, mean	1.2	0.5	2.4	0.4	0.5	1.3	0.9
Energy intake, kcal/d, mean	1721.0	2165.0	1795.0	2222.0	2373.3	1407.3	1936.0
Education, %							
≤High school	7.2	2.7	12.8	3.1	3.0	7.2	5.2
Some college	20.5	6.8	29.2	9.6	9.9	20.8	15.0
College	39.2	36.8	36.3	33.5	40.7	36.0	37.9
Graduate school	33.2	53.7	21.7	53.8	46.3	36.0	41.9
Income, USD, %							
<50,000	10.2	11.1	14.2	12.6	11.7	11.0	11.6
50,000–99,999	20.4	18.0	26.6	17.2	17.7	19.8	19.7
100,000–149,999	42.0	37.1	40.6	39.0	41.0	39.7	39.1
≥150,000	27.4	33.8	18.6	31.2	29.6	29.4	29.6

[1]$n = 3429$. Values were standardized to the age distribution of the cohort at baseline. Race/ethnicity and geographic region were not assessed in the SF cohort. MET, metabolic equivalent; SF, SnartForaeldre.dk; USD, United States dollars.

recommendations adhered to (FR: 1.07; 95% CI: 1.01, 1.13). When modeled using restricted cubic splines, we observed a threshold effect between adherence to the DDGI and greater fecundability in women with adherence score > 4 (Figure 2). Results were consistent when stratified by current age. Associations were stronger among women with pregnancy attempt time < 3 cycles at study entry (Supplemental Table 1). We observed no appreciable association between DDGI adherence and fecundability in women with an attempt time at enrollment of ≥3 cycles. In addition, we observed a stronger association between DDGI adherence and fecundability among women with BMI ≥ 25.

In PRESTO, greater adherence to the HEI-2010 was associated with greater fecundability (Table 3, **Figure 3**). Compared with HEI-2010 scores < 60, FRs for HEI-2010 scores of 60–69, 70–79, and ≥80 were 1.11 (95% CI: 1.02, 1.20), 1.15 (95% CI: 1.06, 1.25), and 1.17 (95% CI: 1.04, 1.32), respectively. Associations were consistent across strata of attempt time at study entry, BMI, and age (Supplemental Table 2).

DII

In SF, we observed greater fecundability among women consuming a more anti-inflammatory diet (Table 3, **Figure 4**A). Compared with the most anti-inflammatory diet (< −3.3), a less anti-inflammatory diet (≥ −1.5) was associated with lower fecundability (FR: 0.83; 95% CI: 0.71, 0.97). Associations were consistent when stratified by attempt time at study entry and BMI (Supplemental Table 1) but were slightly stronger among women aged ≥ 35 y.

In PRESTO, we also observed greater fecundability with a more anti-inflammatory diet (Table 3, Figure 4B). Compared with diets that were more anti-inflammatory (< −3.3), diets that were less anti-inflammatory (≥ −1.5) were associated with lower fecundability (FR: 0.82; 95% CI: 0.73, 0.93). To assist with the interpretation of FRs, 69.7% of participants with a less anti-inflammatory diet (≥1.5) conceived within 12 cycles of pregnancy attempt time, compared with 77.1% of participants with a more anti-inflammatory diet (< −3.3). Results were

TABLE 2 Baseline characteristics of Pregnancy Study Online participants by selected dietary patterns[1]

	Alternative Mediterranean Index		Healthy Eating Index-2010		Dietary Inflammatory Index		
	Low (0–3)	High (≥6)	Low (<58)	High (≥79)	More anti-inflammatory (< −3.3)	Less anti-inflammatory (≥1.5)	Overall cohort
Women, *n*	2166	1789	1368	620	1325	1727	5803
Age, y, mean	29.2	30.8	29.3	31.0	30.7	29.4	30.1
BMI, kg/m^2, mean	29.7	24.9	30.1	24.0	25.8	28.4	27.2
Current smoker, %	8.1	1.2	10.6	0.4	2.7	5.2	4.3
Parous, %	37.7	23.2	39.0	20.3	26.4	33.2	30.8
Alcohol intake, drinks/wk, mean	3.0	3.5	3.2	3.0	3.6	2.6	3.2
Physical activity, MET/wk, mean	27.6	43.6	25.2	48.4	44.6	27.3	35.1
Last birth control method hormonal, %	41.8	33.8	43.0	34.7	34.5	42.5	38.2
Intercourse, freq/wk, %							
≤1	43.0	38.4	42.8	35.8	38.2	44.0	40.5
2–3	42.0	47.7	42.0	47.7	45.4	44.2	44.9
≥4	15.1	13.9	15.2	16.5	16.4	11.8	14.5
Method to improve pregnancy, %	76.4	75.2	76.1	76.0	76.0	77.3	76.7
Daily use of multivitamin or prenatal supplement, %	78.8	88.9	75.8	89.6	86.8	78.7	84.2
Sugar-sweetened beverage, drinks/wk, mean	3.9	1.1	4.5	1.0	1.9	2.9	2.4
Energy intake, kcal/d, mean	1591	1586	1555	1611	2074	1147	1574
Race/ethnicity, %							
White, non-Hispanic	87.0	88.1	85.0	88.3	87.4	85.8	86.9
Black, non-Hispanic	2.1	1.2	2.9	1.0	1.7	2.7	1.9
Asian, non-Hispanic	1.1	2.3	1.2	2.5	2.5	1.6	1.9
Other, non-Hispanic	4.7	3.5	5.0	3.2	3.0	4.6	4.0
Hispanic	5.2	4.9	6.0	5.0	5.4	5.4	5.3
Education, %							
≤High school	5.6	1.0	6.9	0.3	1.8	4.6	3.2
Some college	28.3	9.5	30.6	8.6	14.1	22.8	18.2
College	33.7	34.5	33.0	31.6	33.7	36.0	35.2
Graduate school	32.5	55.0	29.5	59.5	50.8	35.8	43.4
Income, USD, %							
<50,000	22.8	10.1	26.9	7.7	13.4	20.1	16.2
50,000–99,999	43.8	33.0	42.6	31.8	35.4	40.9	38.4
100,000–149,999	21.3	31.7	19.3	32.9	29.0	24.5	27.4
≥150,000	12.1	25.3	11.2	27.5	22.2	14.5	18.1
Geographic region							
Northeast	19.5	27.5	18.3	29.9	26.4	21.8	23.9
South	24.4	19.3	28.6	17.5	19.4	25.4	22.4
Midwest	26.6	17.0	27.0	12.6	16.9	24.5	20.8
West	15.3	19.3	15.7	17.3	17.9	14.9	16.7
Canada	14.2	16.8	10.3	22.8	19.3	13.4	16.1

[1] $n = 5803$. Values were standardized to the age distribution of the cohort at baseline. MET, metabolic equivalent; USD, United States dollars.

consistent when we stratified by attempt time at study entry or by BMI (Supplemental Table 2). Results were slightly stronger among women aged ≥ 35 y.

Discussion

Adherence to greater diet quality, as assessed using the aMed, DDGI, HEI-2010, and DII, was associated with increased fecundability among 2 prospective cohorts of pregnancy planners. Participants with a less anti-inflammatory diet had reduced fecundability, suggesting that diets with anti-inflammatory properties may be important for improving fecundability. Results were similar when restricted to those with <3 cycles of attempt time at study entry. Within both cohorts, the association between a diet lower in anti-inflammatory properties and lower fecundability was stronger among women with BMI ≥ 25 and in women aged ≥ 35 y. This study builds on prior work examining the association between individual nutrients and fertility, by comprehensively evaluating the impact of dietary patterns on

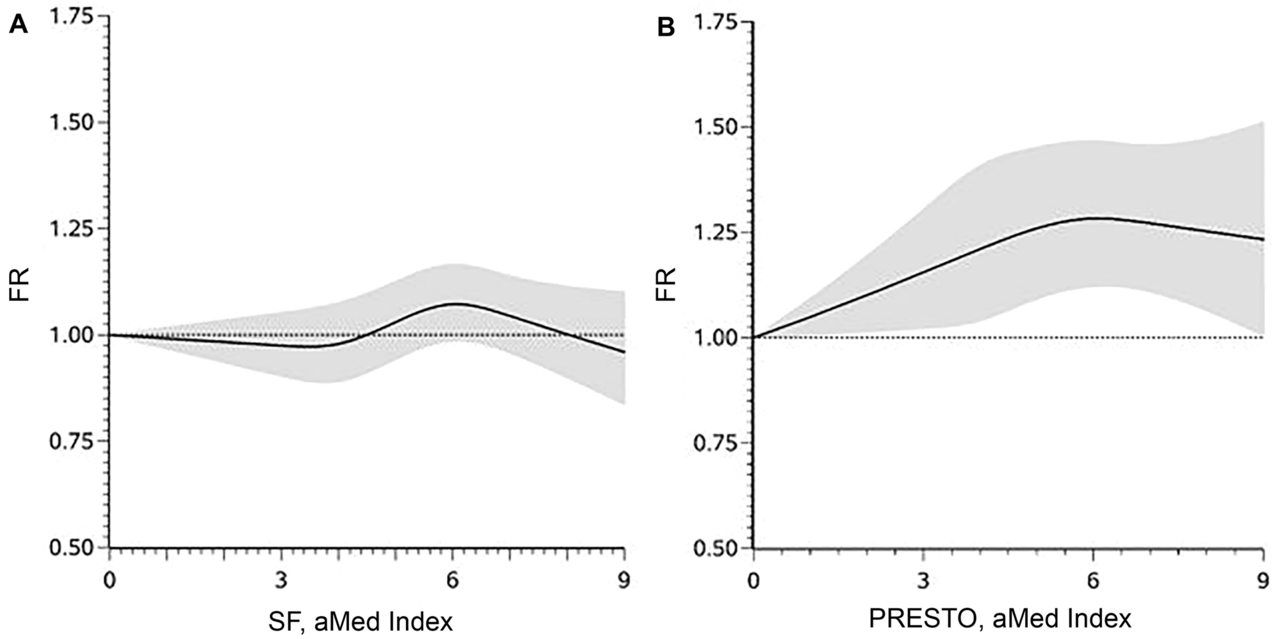

FIGURE 1 Association between aMed Index and fecundability among 3429 female SF participants and 5803 female PRESTO participants fitted by restricted cubic splines. The reference level for the FR is the lowest value in the data (0). Splines have 4 knot points, at the 25th (3), 50th (4), 75th (6), and 90th (7) percentiles. Splines are adjusted for age, BMI, current smoker, physical activity, last form of birth control hormonal, married, intercourse frequency, using method to improve pregnancy chances, daily use of prenatal supplement or multivitamin, race/ethnicity, education, income, parity, and energy intake (kcal/d). aMed, alternative Mediterranean Diet; FR, fecundability ratio; PRESTO, Pregnancy Study Online; SF, SnartForaeldre.dk.

fecundability in 2 prospective cohorts. Effect sizes within this study were small and may not be clinically meaningful.

The present study evaluating the association between healthy dietary patterns and fecundability extends the existing literature with the inclusion of pregnancy planners, and with the DII, a novel dietary pattern with respect to fertility research. In Spain, female university graduates who followed a Mediterranean-style diet had lower risk of difficulty conceiving, defined as individuals who reported that they "consulted a physician because of difficulty getting pregnant" (7). Other literature on dietary patterns has primarily been in populations receiving treatment at in vitro fertilization (IVF) clinics. Three of 4 studies conducted in couples undergoing infertility treatment found that greater adherence to the Mediterranean diet was associated with greater probability of clinical pregnancy (8–11). Investigators from the Nurses' Health Study II (NHS II), a large prospective cohort in the United States, derived the "fertility diet," a dietary pattern used to predict the risk of ovulatory infertility (6). In the NHS II, women with the greatest adherence to the fertility diet had lower risk of ovulatory infertility.

Findings based on the DII, which has not been previously examined in relation to fecundability or fertility, help illuminate potential biological mechanisms underlying the association between diet and reproductive outcomes. Inflammation has been shown to play a major role in the development of insulin resistance, an important determinant of ovulatory function (33).

Whereas we observed that consuming a more anti-inflammatory diet was associated with greater fecundability across both cohorts, results for the other dietary patterns were not entirely consistent. Although many established healthy dietary patterns share components, there are important differences between them. The aMed differs from the DDGI and the HEI-2010 in that it has no recommendations based on saturated fat or added sugar. The omission of added sugar in the aMed could explain the weaker associations observed for this pattern relative to the other dietary patterns (36). In addition, because the aMed is calculated using median intake within each cohort, it is not entirely comparable across populations. The HEI-2010 and the DDGI were created within current dietary habits and taste preferences of their respective target populations. Differences in diet quality and population preferences across regions may explain why we observed greater fecundability in PRESTO when using country-specific guidelines and only in the highest category for SF. Although the aMed, the DDGI, and the HEI-2010 all have anti-inflammatory components, the DII is unique in its focus on how strongly each dietary component may affect 6 inflammatory biomarkers (15). In addition, the DII is the only scoring system to include micronutrients. Although these micronutrients were included owing to their anti-inflammatory effects, they could have other important relations with fecundability beyond their effects on inflammation.

Although FFQs are validated instruments well-suited to estimating long-term dietary exposures (38), given that diet was assessed only once during the preconception period, some misclassification of dietary intake is expected. However, because diet was evaluated prospectively relative to the outcome (pregnancy), misclassification is likely nondifferential, attenuating associations for extreme exposure categories toward the null. Although both FFQs ask about usual diet within the past 12 mo, some participants who enrolled later in their pregnancy attempt may have changed their diet in response to subfertility and may have reported a more proximal diet. However, findings were

TABLE 3 Association between the dietary patterns and fecundability, by cohort[1]

	SnartForaeldre.dk (n = 3429)				PRESTO (n = 5803)			
	Pregnancies, n	Cycles, n	Unadjusted, FR (95% CI)	Adjusted,[2] FR (95% CI)	Pregnancies, n	Cycles, n	Unadjusted, FR (95% CI)	Adjusted,[2] FR (95% CI)
Alternative Mediterranean Index								
<3	758	4408	1.00 (Ref.)	1.00 (Ref.)	1256	9616	1.00 (Ref.)	1.00 (Ref.)
4–5	745	4145	1.04 (0.95, 1.14)	1.04 (0.94, 1.14)	1223	7597	1.19 (1.10, 1.28)	1.11 (1.03, 1.20)
≥6	717	3839	1.08 (0.99, 1.19)	1.06 (0.96, 1.18)	1236	7059	1.26 (1.17, 1.35)	1.15 (1.06, 1.24)
Per 1-unit increase			1.01 (1.00, 1.03)	1.01 (0.99, 1.03)			1.05 (1.04, 1.06)	1.03 (1.01, 1.05)
Danish Dietary Guidelines Index								
<3	161	994	1.00 (Ref.)	1.00 (Ref.)				
3	697	4137	1.06 (0.91, 1.24)	0.96 (0.82, 1.13)				
4	1107	5992	1.15 (0.99, 1.34)	1.01 (0.86, 1.19)				
≥5	255	1268	1.26 (1.05, 1.50)	1.11 (0.92, 1.30)				
Per 1-unit increase			1.10 (1.05, 1.16)	1.07 (1.01, 1.13)				
Healthy Eating Index-2010								
<60					943	7447	1.00 (Ref.)	1.00 (Ref.)
60–69					1225	7736	1.21 (1.12, 1.31)	1.11 (1.02, 1.20)
70–79					1211	7195	1.26 (1.17, 1.36)	1.15 (1.06, 1.25)
≥80					336	1894	1.32 (1.18, 1.48)	1.17 (1.04, 1.32)
Per 5-unit increase							1.05 (1.03, 1.06)	1.03 (1.01, 1.05)
Dietary Inflammatory Index								
< −3.3	625	3386	1.00 (Ref.)	1.00 (Ref.)	898	5311	1.00 (Ref.)	1.00 (Ref.)
−3.3 to −2.2	730	4046	0.97 (0.88, 1.07)	0.93 (0.84, 1.03)	960	6013	0.96 (0.89, 1.04)	0.94 (0.86, 1.02)
−2.3 to −1.5	501	2701	0.99 (0.90, 1.10)	0.93 (0.82, 1.06)	831	5388	0.93 (0.86, 1.02)	0.90 (0.82, 1.00)
≥ −1.5	364	2258	0.87 (0.77, 0.98)	0.83 (0.71, 0.97)	1026	7560	0.84 (0.77, 0.91)	0.82 (0.73, 0.93)
Per 1-unit increase			0.96 (0.92, 1.00)	0.93 (0.88, 0.99)			0.95 (0.93, 0.97)	0.94 (0.91, 0.98)

[1]Proportional probabilities regression models were used to estimate FRs and 95% CIs for the association between each dietary pattern and fecundability. FR, fecundability ratio; PRESTO, Pregnancy Study Online.

[2]Adjusted for age, BMI, current smoker, physical activity, last form of birth control hormonal, intercourse frequency, using method to improve pregnancy chances, daily use of prenatal supplement or multivitamin, education, income, parity, energy intake (kcal/d), and (PRESTO only) race/ethnicity. The Danish dietary guidelines were not adjusted for caloric intake.

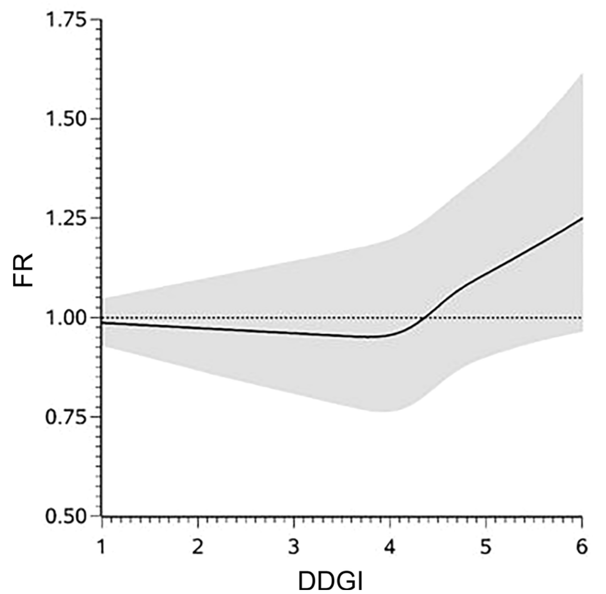

FIGURE 2 Association between DDGI and fecundability among 3429 female SnartForaeldre.dk participants fitted by restricted cubic splines. The reference level for the FR is the lowest value in the data (0). The spline curve has 4 knot points, at the 25th (3.6), 50th (4.19), 75th (4.65), and 90th (5.03) percentiles. The spline curve is adjusted for age, BMI, current smoker, physical activity, last form of birth control hormonal, married, intercourse frequency, using method to improve pregnancy chances, daily use of prenatal supplement or multivitamin, race/ethnicity, education, income, parity, and energy intake (kcal/d). DDGI, Danish Dietary Guidelines Index; FR, fecundability ratio.

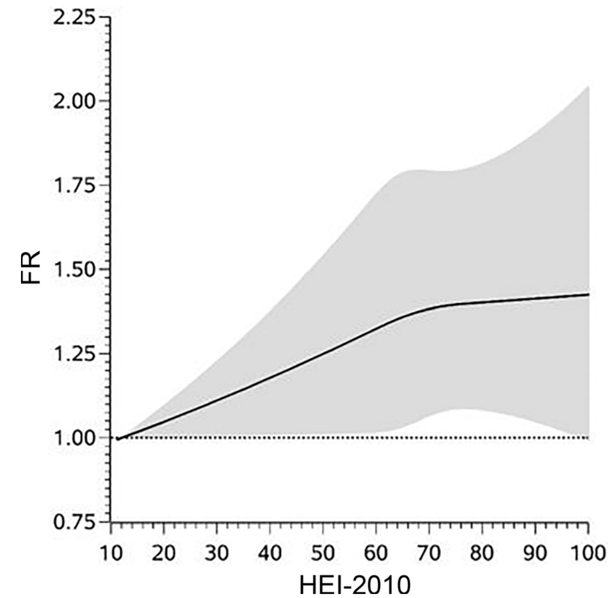

FIGURE 3 Association between HEI-2010 and fecundability among 5803 female Pregnancy Study Online participants fitted by restricted cubic splines. The reference level for the FR is the lowest value in the data (11). The spline curve has 4 knot points, at the 25th (57), 50th (65), 75th (73), and 90th (79) percentiles. The spline curve is adjusted for age, BMI, current smoker, physical activity, last form of birth control hormonal, married, intercourse frequency, using method to improve pregnancy chances, daily use of prenatal supplement or multivitamin, race/ethnicity, education, income, parity, and energy intake (kcal/d). FR, fecundability ratio; HEI-2010, Healthy Eating Index-2010.

consistent among women with <3 cycles of pregnancy attempt time at enrollment, indicating that selection bias and reverse causation are unlikely explanations of our findings. In addition, women who completed the FFQ were less likely to have a history of infertility and had shorter pregnancy attempt times at study entry than women who did not complete the FFQ, indicating low potential for selection bias. Therefore, it is unlikely that completion of the FFQ was related to dietary patterns (exposure) and subfertility (outcome). In the PRESTO cohort, compared with participants who did not complete the FFQ, participants who completed the FFQ had a similar mean age (30.3 compared with 29.3 y), a slightly lower BMI (27.9 compared with 30.3), were less likely to be current smokers (5.5% compared with 14.3%), and were slightly more likely to be white, non-Hispanic (83.6% compared with 75.1%). Characteristics of participants who did not complete the FFQ compared with those who did complete the FFQ were similar in the SF cohort. However, because women typically complete the FFQ within 30 d of enrollment, before pregnancy, differences in these characteristics are unlikely to result in selection bias. Our study (39) and others (40, 41) have found that, even when participation at cohort entry is associated with factors such as age and cigarette smoking, measures of association show little bias due to self-selection.

It is plausible that our results may not be entirely generalizable, because both cohorts in the present analysis had comparatively higher diet quality than the general population (23). In addition, because no individual in either cohort had a DII > 0, results may be stronger in populations with a wider distribution of dietary quality. PRESTO and SF respondents differed from the general population in terms of socioeconomic status (e.g., higher education and income) and behaviors (e.g., lower smoking prevalence) (42), which may limit the generalizability of results to other populations, especially if socioeconomic status or behavioral factors modify the association between dietary factors and fecundability. Inclusion of alcohol in the dietary pattern score may have led to a distortion of measures of association; however, in a prior publication from our Danish cohort, consumption of <14 servings of alcohol per week (which reflects the intake of the vast majority of the cohort) had no discernible effect on fecundability (43).

Our results may be affected by unmeasured confounders, such as the food environment or male dietary factors. Although we controlled for many covariates, we cannot rule out residual confounding by factors not captured in measured variables (i.e., socioeconomic status). If confounding was the sole source of bias, then the minimum risk ratio that an unmeasured confounder would need to have for the outcome [the "e-value" (44)], conditional upon the included confounders, to explain fully the strongest association seen in the present study would be 1.74 (95% CI: 1.37, 2.08). Although all pregnancies included in the present analysis were self-reported, we expect misclassification to be inconsequential, because on follow-up questionnaires 96% of participants in SF and PRESTO reported using home pregnancy tests to confirm their pregnancy status.

Lastly, we did not collect data on the cause of subfertility, and because dietary factors may have a different influence on specific

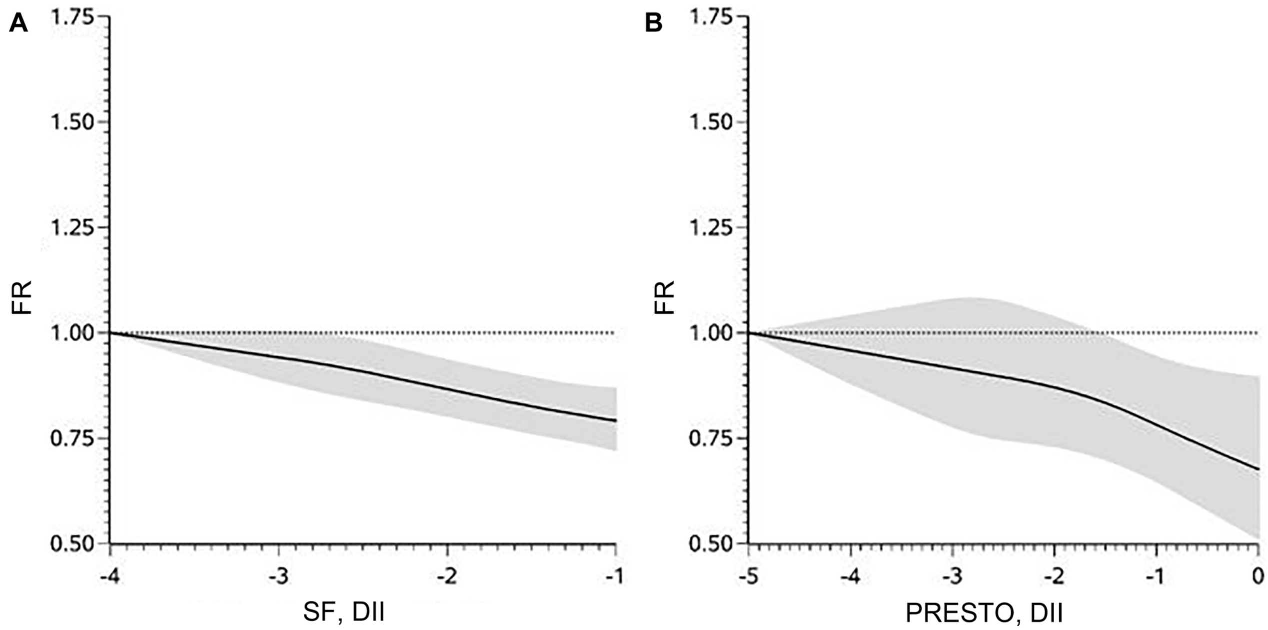

FIGURE 4 Association between DII and fecundability among 3429 female SF participants and 5803 female PRESTO participants, fitted by restricted cubic splines. The reference level for the FR is the lowest value in the data (−4.6 and −5.4, respectively). Splines have 4 knot points, at the 25th (−0.71 and −0.85, respectively), 50th (−1.32 and −1.44, respectively), 75th (−2.22 and −2.62, respectively), and 90th (−3.20 and −3.34, respectively) percentiles. Splines are adjusted for age, BMI, current smoker, physical activity per week, last form of birth control hormonal, married, intercourse frequency, using method to improve pregnancy chances, daily use of prenatal supplement or multivitamin, race/ethnicity, education, income, parity, and energy intake (kcal/d). DII, Dietary Inflammatory Index; FR, fecundability ratio; PRESTO, Pregnancy Study Online; SF, SnartForaeldre.dk.

etiologies of subfertility (e.g., anovulation, uterine factors, tubal factors), we are limited in being able to assess mechanisms or compare our results with prior literature (45).

In conclusion, in 2 prospective preconception cohort studies from Denmark and North America, we observed that higher-quality diet was associated with greater fecundability, and diets higher in anti-inflammatory properties were associated with greater fecundability, especially among women with overweight or obesity. These data provide additional evidence that inflammation may contribute to the association between diet quality and fecundability. Future work should consider dietary patterns unique to the preconception window that may be associated with fecundability. Examining and identifying relevant dietary patterns, as opposed to nutrients or food groups, provides useful information that can inform policy recommendations for reproductive-age women.

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Data availability

The code book and analytic code will be made available upon request pending application and approval.

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