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Glycemic Load, Dietary Fiber, Added Sugar, and Spontaneous Abortion in Two Preconception Cohorts

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ABSTRACT

Background: Spontaneous abortion (SAB)—pregnancy loss before the 20th week of gestation—has adverse psychological and physical sequelae. Some medical conditions known to affect insulin sensitivity, including polycystic ovary syndrome and diabetes, can affect the risk of SAB. No prior studies have examined glycemic load and incidence of SAB in populations without conditions known to affect insulin sensitivity.

Objectives: We prospectively evaluated the association between preconception glycemic load and intake of carbohydrates, dietary fiber, and added sugar and risk of SAB.

Methods: During 2013–2020, we recruited pregnancy planners from Denmark (SnartForaeldre.dk; SF) and the United States and Canada (Pregnancy Study Online; PRESTO). Participants completed a baseline questionnaire and a cohort-specific FFQ evaluated for validity. We estimated preconception glycemic load and intake of carbohydrates, dietary fiber, and added sugar from individual foods and mixed recipes. We included 2238 SF and 4246 PRESTO participants who reported a pregnancy during the course of the study. SAB data were derived from questionnaires and population registries. We used Cox proportional hazards regression to estimate HRs and 95% CIs.

Results: In the study population, 15% of SF participants and 22% of PRESTO participants experienced SAB. Across both cohorts, there was no appreciable association between glycemic load, carbohydrate quality, dietary fiber, or added sugar intake and SAB. Compared with daily mean glycemic load <110, the HR for women with daily mean glycemic load ≥130 was 0.76 (95% CI: 0.52, 1.10) in SF and 1.01 (95% CI: 0.86, 1.19) in PRESTO.

Conclusions: Diets with high glycemic load, carbohydrates, and added sugars were not consistently associated with risk of SAB in parallel analyses of 2 preconception cohort studies of women in North America and Denmark. *J Nutr* 2022;152:2818–2826.

Keywords: glycemic load, carbohydrate, dietary fiber, added sugar, pregnancy loss, spontaneous abortion

Introduction

Spontaneous abortion (SAB), defined as the loss of pregnancy before the 20th week of gestation, occurs in 18–22% of recognized pregnancies (1, 2) and 30% of postimplantation pregnancies (3, 4). SAB has adverse psychological and physical sequelae and there are few known modifiable risk factors (1). Prior work conducted in populations with polycystic ovary syndrome (PCOS) and diabetes indicates that poor glycemic control during early pregnancy, defined by persistently elevated blood glucose concentrations, is associated with greater risk of SAB (5–11).

The GI is an estimate of the expected glycemic response when an individual consumes a quantity of food containing a fixed amount of carbohydrates (typically 50 g) (12). Because the glycemic response to a given food is largely dependent on the quantity of food eaten, glycemic load combines carbohydrate quality (through GI) and carbohydrate quantity (through portion size). Glycemic load values predict how an individual's diet might influence their glycemic response (13). Glycemic load has been associated with reduced fecundability (14) and ovulatory infertility (15) in 2 prospective cohorts of reproductive-aged women, suggesting a potential role in human reproduction.

Although no prior studies have examined glycemic load and incidence of SAB, poor preconception maternal nutrition can be associated with SAB in populations without conditions known to affect insulin sensitivity. Two case-control studies found that a healthier preconception dietary pattern, characterized by high consumption of vegetables, fruit, dairy, poultry, and fish, was

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associated with lower risk of SAB (16, 17). In a prospective cohort study of nurses, there was no meaningful association between preconception Healthy Eating Index-2010 (HEI-2010) score or the alternative Mediterranean diet score and risk of SAB (18). Conversely, in the same cohort, greater adherence to the Fertility Diet Score [a dietary pattern characterized by a greater monounsaturated/*trans*-fat ratio, greater intake of vegetable protein and iron, lower intake of animal protein, dairy (higher intake of high-fat dairy and lower intake of low-fat dairy), multivitamin use, and lower glycemic load] was associated with lower risk of SAB when restricting to those with a dietary assessment taken within a year before pregnancy (18). In a second small prospective cohort study, participants with greater dietary quality [measured using the alternative HEI for pregnancy (aHEI-P)] were more likely to achieve both clinical pregnancy and live birth (19). Although none of these studies specifically examined the association between glycemic load and risk of SAB, high glycemic load is typically associated with poorer diet quality (12). Therefore, we hypothesized that individuals with high glycemic load diets would have greater risk of SAB than those with low glycemic load diets. We evaluated the extent to which glycemic load, total carbohydrates, dietary fiber, and added sugars were associated with SAB in 2 internet-based preconception cohort studies of pregnancy planners residing in Denmark and North America.

Methods

Study population

Snart Foraeldre (SF) ("Soon Parents") is an ongoing prospective preconception cohort study of couples attempting to conceive in Denmark. Launched in 2011, SF is an expansion of Snart Gravid ("Soon Pregnant"), described in detail elsewhere (20). Eligible participants are women aged 18–45 y, attempting pregnancy, and not using fertility treatment. Beginning in February 2013, female participants who completed the baseline questionnaire were invited to complete an FFQ with ∼220 food and beverage items (SF-FFQ), designed for and evaluated for validity in this population (21). There were 6099 eligible women who completed the SF baseline questionnaire from January 2013 through June 2020 (**Figure 1**). We excluded 2076 women who did not complete the SF-FFQ (66% completion), 78 women whose energy intake was <600 or >3800 kcal/d, and 46 women who completed the FFQ ≥6 wk into their pregnancy or after experiencing an SAB. We further restricted our analytic population to 2238 women who conceived during 12 mo of follow-up.

Pregnancy Study Online (PRESTO) is an ongoing prospective preconception cohort study of couples attempting to conceive in the United States and Canada, initiated in 2013 and modeled after SF (22). Eligible participants are women aged 21–45 y, attempting pregnancy, and not using fertility treatments. Female participants complete a baseline questionnaire and, 10 d after enrollment, the NCI's 143-item Diet History Questionnaire II (DHQII). Participants were also randomly assigned, with a 50% probability, to receive and consented to using either a premium subscription to FertilityFriend.com (June 2013 to March 2019) or Kindara.com (June 2019 to present), fertility awareness mobile phone applications for recording menstrual cycle information and pregnancies. The baseline questionnaire was completed by 11,659 women from June 2013 through June 2020 (Figure 1). We restricted our analytic population to women who conceived during 12 mo of follow-up ($n = 6325$). We excluded those who did not fill out the FFQ (72% completion), with estimated energy intake <600 or >3800 kcal/d ($n = 96$), or who completed the FFQ ≥6 wk into their pregnancy or after experiencing an SAB ($n = 219$) for a final analytic sample of 4246 women.

In both cohorts, women completed baseline questionnaires to ascertain information on demographic, lifestyle, reproductive factors, and medical history. Female participants completed bimonthly follow-up questionnaires to ascertain self-reported pregnancy status for ≤12 mo, or until reported conception. Women who reported conception were invited to complete a questionnaire in early (<12 wk of gestation) pregnancy. In PRESTO, participants were invited to complete an additional questionnaire in late pregnancy (∼32 wk of gestation). In SF, women provided their Civil Personal Registration (CPR) number, a 10-digit unique identifier assigned to all Denmark residents, which permitted linkage to pregnancy outcome information in the Danish National Registry of Patients (23).

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

Exposure assessment

We estimated intake of food groups and macro- and micronutrients using the nutrient composition of all food items in each cohort. In SF, we used the Danish Nutrient Database (24), and in PRESTO, we used the NCI's Diet*Calc software, which uses data from the US NHANES 24-h dietary recall data from years 2001–2002, 2003–2004, and 2005–2006. We estimated glycemic load and intake of total carbohydrates, dietary fiber, and added sugars in both cohorts. In PRESTO, we estimated soluble fiber and insoluble fiber (data not available in SF). Nutrients, including total carbohydrates, fiber, and added sugars, have been previously evaluated for validity within each population (21, 22, 24–26). The SF-FFQ was evaluated for validity against a 4-d food record in Denmark in 100 study participants, with deattenuated Pearson correlation coefficients for total carbohydrates, dietary fiber, and added sugars of 0.70, 0.70, and 0.47, respectively (21). The DHQ (a prior version of the FFQ used in PRESTO) was evaluated for validity against repeated 24-h dietary recalls in the United States, with deattenuated Pearson correlation coefficients for total carbohydrates, fiber, and added sugars of 0.69, 0.77, and 0.79, respectively (25). In SF, glycemic load was calculated using published GI values for each SF-FFQ food item (27, 28). If published GI values did not exist, GI values for similar foods were chosen based on nutritional content. In PRESTO, glycemic load was calculated using published GI values for each DHQII food and, if published GI values did not exist, decision criteria were used to assign GI values (27, 29). Serving-size-specific glycemic load values were calculated for each food item (29). We adjusted nutrient intakes for total energy using the nutrient residual method, standardizing to 2000 kcal in both cohorts (30).

Assessment of SAB

In both cohorts, we used data from self-administered questionnaires to identify SAB, defined as pregnancy loss before 20 wk of gestation. On each follow-up questionnaire, women reported the first day of their last menstrual period and if they were currently pregnant. If a woman was not pregnant, we asked if she had experienced a pregnancy loss since her last questionnaire. If a woman reported being currently pregnant, she

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Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
Address correspondence to SKW (e-mail: sydney.kaye.willis@gmail.com).
Abbreviations used: aHEI-P, alternative Healthy Eating Index modified for pregnant populations; CPR, Civil Personal Registration; DDGI, Danish Dietary Guidelines; DHQII, Diet History Questionnaire II; DMBR, Danish Medical Birth Register; DNRP, Danish National Registry of Patients; HEI-2010, Healthy Eating Index-2010; MET, metabolic equivalent; PCOS, polycystic ovary syndrome; PRESTO, Pregnancy Study Online; SAB, spontaneous abortion; SF, SnartForaeldre.dk; SF-FFQ, SnartForaeldre.dk food frequency questionnaire.

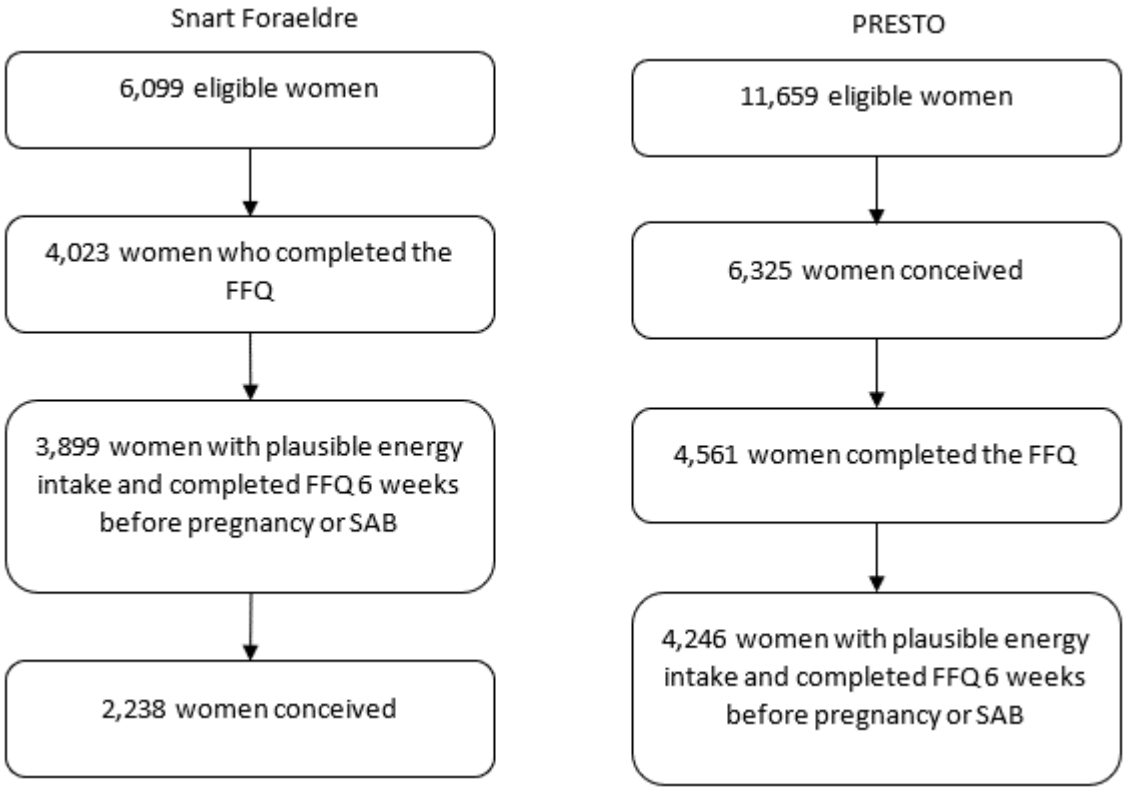

FIGURE 1 Exclusion criteria for Snart Foraeldre and PRESTO participants. PRESTO, Pregnancy Study Online; SAB, spontaneous abortion.

was directed to the early pregnancy questionnaire, where she reported any intervening pregnancy losses since her last follow-up questionnaire, the date of first positive pregnancy test, and her pregnancy due date. Women who reported a loss on any questionnaire were asked how many weeks the pregnancy lasted, and on what date the pregnancy ended.

In SF, we linked participant CPR numbers to the Danish National Registry of Patients (DNRP) and the Danish Medical Birth Register (DMBR). The DNRP provides information on inpatient and outpatient diagnoses and services, including labor and delivery, SAB, induced abortion, and week of gestation at pregnancy loss for losses less than week 20 of gestation. The DMBR contains information about live births and stillbirths after 22 wk of gestation, which is the clinical cut-point used for abortions and births in Denmark. We used ICD 10th edition codes O03x, O020, O021, and O022 for SAB (including blighted ovum, missed abortion, and pregnancy of unknown location), O04-O05 for induced abortion, O00x for ectopic pregnancy, and O01 for molar pregnancy. The positive predictive value of SAB diagnosis (ICD-10 O03 and O021) in the DNRP is 97.4% (31). If SAB was identified by self-report and the registry data were 21 d before or after the self-reported date, we prioritized the registry data. Registry data were available through the end of 2018; women with self-reported conception after August 13, 2018 (20 wk before December 31, 2018) with no registered outcome in the DNRP or the DMBR, were censored at their week of gestation at last contact.

In PRESTO, we obtained additional information on pregnancy losses using a late pregnancy questionnaire sent to participants at 32 wk of gestation. We asked women if they were still pregnant and, if not, why they were no longer pregnant (response options: miscarriage or chemical pregnancy, induced or therapeutic abortion, ectopic pregnancy, blighted ovum, stillbirth, already had baby). We attempted to identify outcome information on women lost to follow-up by contacting them via e-mail or phone and searching on social media or for online baby registries. If we were able to contact a participant, we asked for information on her pregnancy status, including whether she experienced a pregnancy loss, the date of loss, and the number of weeks of gestation at loss. We used data from FertilityFriend.com and Kindara.com to identify pregnancies and SABs that were not reported on study questionnaires, based on reporting within the respective applications. We also identified women who did not experience a pregnancy loss by linking participant data to birth registries in states with a high proportion of participants (California, Florida, Massachusetts, Michigan, Ohio, Pennsylvania, and Texas). If we identified a live birth in the registry with a date of birth corresponding to a last menstrual period date during the study period, we assumed there was no pregnancy loss. We censored women with induced abortion or ectopic pregnancy from the analytic dataset at the date of pregnancy loss ($n = 25$).

We estimated gestational weeks at pregnancy loss based on the reported number of weeks the pregnancy lasted. When we had data from both the registry and self-report, we prioritized the registry data. We used multiple imputation to impute the gestational week at loss if gestational week at loss was missing.

Covariate assessment

At baseline, we collected covariate information on age, weight, height, racial and ethnic groups, education, income, smoking status, alcohol intake, physical activity, parity, gravidity, last form of contraception, and multivitamin use. BMI was measured in kg/m^2. In SF, total metabolic equivalents (METs) were calculated from the International Physical Activity Questionnaire short-form by summing MET-hours from walking, moderate physical activity, and vigorous physical activity (32). 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 (33). We adjusted for overall diet quality using the Danish Dietary Guidelines Index (DDGI) in SF, which considers intake of 6 dietary components (fruit and vegetables, fish, red and processed meat, saturated fat, added sugar, and whole grains) (34) and the Healthy Eating Index 2010 (HEI-2010) in PRESTO, which considers intake of 12 dietary 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], adjusting for total energy intake (35, 36).

To avoid overadjustment by diet quality scores, we calculated an adjusted diet quality measure by removing the proportion of the diet

quality score contributed by whole grains and added sugars for the glycemic load–SAB and carbohydrate-SAB associations; the proportion of the score contributed by whole grains for the fiber-SAB association; and the proportion of the score contributed by added sugars for the added sugars–SAB association. All other potential confounders were identical, except for racial and ethnic groups (not ascertained in SF), education, income, and marital status, which were ascertained differently across studies.

Data analysis

We used Cox proportional hazards regression models with gestational weeks as the time scale to estimate HRs and 95% CIs. We used the exact option to account for tied event times. We began follow-up from the week of gestation at first positive pregnancy test (when data were available) or at 4 wk of gestation otherwise (i.e., median value for observed data). We ended follow-up at *1*) the week in gestation of SAB, induced abortion, or ectopic pregnancy for women who experienced these outcomes, *2*) the week in gestation at last contact, for women who were lost to follow-up, or *3*) 20 wk of gestation for women who did not experience a pregnancy loss. We used an Andersen–Gill data structure with 1 observation per gestational week to account for left truncation from differential timing of pregnancy recognition. We assigned women 0.5 wk of follow-up time during the week participants experienced SAB under the assumption that, on average, losses occurred halfway through the week.

Final models were adjusted for age (<25, 25–29, 30–34, ≥35 y), BMI (<18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥35), energy intake, current smoker (yes compared with no), alcohol (drinks per week), MET-hours per week, oral contraceptives as last form of birth control (yes compared with no), daily use of prenatal supplementation or multivitamins (yes compared with no), education (<12, 12–15, 16, >16 y), income (<25, 25–39, 40–64, or ≥65 K DKK/mo in SF; and <50,000, 50,000–99,999, 100,000–149,999, or ≥150,000 US$/y in PRESTO), and adjusted dietary quality (DDGI or HEI-2010). PRESTO models were additionally adjusted for racial and ethnic groups (non-Hispanic White compared with other). Because we measured diet during preconception, we controlled for covariates collected at baseline rather than in early pregnancy to ensure that covariates were not on the causal pathway between diet and SAB.

We assessed the extent to which the associations of glycemic load and intake of carbohydrates, dietary fiber, and added sugars with SAB varied by BMI (<25 compared with ≥25), because adiposity can modify these associations (11). We restricted analyses to individuals without a history of PCOS or type 2 diabetes, because both of these conditions are associated with insulin resistance and can mediate the association between glycemic load and SAB risk (5, 9, 10). We restricted analyses to the first 8 wk of gestation, to assess whether dietary factors had a greater effect on early losses (<8 wk of gestation), because early losses could have different risk factors than later losses (37). Lastly, to reduce exposure misclassification, we restricted analyses to those who filled out the dietary questionnaires within 90 d of estimated conception (defined as 14 d after the date of last menstrual period), because we expected that these individuals' diet at baseline would most closely represent their diet at conception.

We used multiple imputation to impute missing data on covariates and gestational age at loss (38). We generated 20 imputed datasets, and combined coefficients and SEs across imputed datasets within each cohort (39). Gestational week at SAB was missing for <1% of women in SF and for 5% of women in PRESTO. Missingness for covariates ranged from 1% (BMI and education) to 5% (income) in SF, and from <1% (physical activity) to 3% (income) in PRESTO. There were no missing values for age or total energy intake.

Results

In this study population, 15% of SF participants and 22% of PRESTO participants experienced SAB. In both cohorts, the median gestational week at SAB was 6 (IQR: 5–7 in SF and 5–9 in PRESTO). The median glycemic load across cohorts was similar (SF: 115, IQR: 104–125; PRESTO: 118, IQR: 103–134), but mean carbohydrate and dietary fiber intakes were slightly higher in SF (SF: 235 g/d, IQR: 218–253 g/d; PRESTO: 225 g/d, IQR: 201–250 g/d; and SF: 24 g/d, IQR: 20–27 g/d; PRESTO: 21 g/d, IQR: 17–25 g/d, respectively). Mean intake of added sugars was higher in PRESTO than in SF (SF: 29 g/d, IQR: 21–40 g/d; PRESTO: 46 g/d, IQR: 34–64 g/d).

In SF, the top food contributor to glycemic load and dietary fiber was rye bread, and the top contributor to added sugars was sugar-sweetened beverages; in PRESTO, the top contributor to both glycemic load and added sugars was sugar-sweetened beverages, and the top contributor to dietary fiber was vegetables. In both cohorts, high glycemic load was positively associated with sugar-sweetened beverage intake, ≤12 y of education, and parity, and inversely associated with alcohol intake (**Table 1**). In SF, high glycemic load intake was inversely associated with PCOS diagnosis whereas in PRESTO, high glycemic load intake was positively associated with PCOS diagnosis.

Across both cohorts, there was no appreciable association between glycemic load, carbohydrate quality, dietary fiber, or added sugar intake and SAB (**Table 2**). In SF, compared with daily mean glycemic load <110, the HR for women with daily mean glycemic load ≥130 was 0.76 (95% CI: 0.52, 1.10), whereas it was 1.01 (95% CI: 0.86, 1.19) in PRESTO. Similarly, compared with women consuming ≤224 g/d carbohydrate, women who consumed ≥262 g/d carbohydrates had an HR of 0.86 (95% CI: 0.60, 1.24) in SF and 1.09 (95% CI: 0.91, 1.31) in PRESTO. Dietary fiber intake was not consistently associated with SAB risk in either cohort. We observed no meaningful association between insoluble or soluble fiber and risk of SAB in PRESTO (data not available in SF). Compared with women consuming ≤27 g/d added sugars, women who consumed ≥52 g/d had an HR of 0.78 (95% CI: 0.54, 1.14) in SF and 0.96 (95% CI: 0.79, 1.17) in PRESTO.

In both cohorts, when stratified by BMI (**Supplemental Table 1**), restricting to those with early losses (<8 wk of gestation) (**Supplemental Table 2**) or those without a history of PCOS or diabetes (**Supplemental Table 3**), or restricting to individuals who conceived within 90 d of completing the FFQ (i.e., those for whom reported diet likely represented their diet during early pregnancy) (**Supplemental Table 4**), glycemic load, total carbohydrates, dietary fiber, and added sugars were not appreciably associated with SAB.

Discussion

We observed that dietary intakes with high glycemic load, carbohydrates, and added sugars were not consistently associated with risk of SAB in parallel analyses of 2 preconception cohort studies of women, in North America and Denmark. In the Danish study population, there was some evidence for inverse association between glycemic load and SAB in individuals with BMI ≥25, but little association in the North American cohort. In addition, there was little association between dietary fiber intake and SAB in either cohort. Similarly, we observed no consistent association when restricting to individuals who conceived within 90 d of completing the FFQ (those for whom reported diet was likely an accurate representation of diet during early pregnancy).

Results of the present study do not agree with the literature on dietary patterns and SAB risk from 2 case-control studies, which indicate that a diet low in glycemic load and added sugars

TABLE 1 Preconception characteristics of participants in 2 prospective preconception cohorts by daily average glycemic load[1]

	Snart Foraeldre ($n = 2238$)				PRESTO ($n = 4465$)			
	Daily average glycemic load				Daily average glycemic load			
	<110	110–119	120–129	≥130	<110	110–119	120–129	≥130
Number of women	838	574	491	335	1596	793	720	1356
Age, y (mean ± SD)	29.7 ± 3.6	29.5 ± 3.6	29.2 ± 3.4	29.4 ± 3.7	30.4 ± 3.6	30.0 ± 3.7	29.7 ± 3.7	29.5 ± 3.9
BMI, kg/m^2 (mean ± SD)	24.5 ± 4.6	23.6 ± 4.9	23.9 ± 4.6	23.8 ± 4.9	25.8 ± 5.8	26.2 ± 6.3	26.5 ± 6.1	27.7 ± 7.3
Energy intake, kcal/d (mean ± SD)	1936 ± 559	1964 ± 571	1949 ± 494	1796 ± 459	1564 ± 515	1560 ± 499	1565 ± 483	1569 ± 545
Baseline sugar-sweetened beverages, drinks/wk (mean ± SD)	0.4 ± 0.8	0.8 ± 1.1	0.8 ± 1.6	1.9 ± 1.7	0.4 ± 1.1	0.6 ± 1.2	0.9 ± 1.8	2.3 ± 4.7
Baseline MET-h physical activity/wk (mean ± SD)	61.8 ± 72.6	61.7 ± 72.6	59.9 ± 71.8	65.3 ± 74.0	37.0 ± 24.4	36.3 ± 23.4	34.5 ± 24.2	32.4 ± 24.6
Danish Dietary Guidelines Index (mean ± SD)	4.0 ± 0.9	4.2 ± 0.9	4.3 ± 0.9	4.1 ± 0.9	—	—	—	—
Healthy Eating Index-2010 score (mean ± SD)	—	—	—	—	68.7 ± 9.7	68.6 ± 9.7	66.8 ± 9.9	62.0 ± 11.4
Baseline alcohol intake, drinks/wk (mean ± SD)	2.7 ± 3.6	2.5 ± 3.3	2.1 ± 3.6	1.8 ± 3.3	4.2 ± 4.9	3.2 ± 3.8	2.6 ± 3.2	2.1 ± 3.5
Current smoker, %	13.0	8.6	10.3	8.3	2.5	2.2	3.0	6.2
Parous, %	31.6	37.9	36.9	40.5	25.6	32.9	34.8	39.3
Last birth control method hormonal, %	58.7	56.0	61.4	59.1	32.4	33.9	41.9	44.0
Baseline daily use of multivitamins, %	90.4	89.0	90.6	87.0	88.1	86.0	86.7	82.6
White/non-Hispanic, %	—	—	—	—	87.9	88.6	87.2	87.0
Education ≤12 y, %	3.7	4.0	6.0	6.3	1.9	1.4	1.8	4.4
Income <US$50,000/y, %	11.9	11.8	10.4	10.4	9.1	11.3	14.6	21.3
Diabetes diagnosis, %	0.9	0.9	0.3	0.0	0.8	1.1	1.1	1.2
Polycystic ovarian syndrome diagnosis, %	5.2	3.0	2.4	1.8	4.9	4.7	4.5	7.1

[1] All covariates, except age, are age adjusted to cohort at baseline. MET-h, metabolic equivalent hours.

TABLE 2 Association between preconception-reported glycemic load, total carbohydrates, dietary fiber, and added sugar and spontaneous abortion[1]

	Snart Foraeldre						PRESTO					
			Unadjusted		Adjusted[2]				Unadjusted		Adjusted[2]	
	No. of SAB	No. of women	HR	95% CI	HR	95% CI	No. of SAB	No. of women	HR	95% CI	HR	95% CI
Daily average glycemic load												
<110	127	838	1.00	Ref	1.00	Ref	364	1596	1.00	Ref	1.00	Ref
110–119	87	574	1.00	0.76, 1.32	1.01	0.77, 1.33	170	793	0.94	0.78, 1.12	0.94	0.79, 1.13
120–129	70	491	0.93	0.69, 1.24	0.91	0.68, 1.23	142	720	0.86	0.71, 1.04	0.87	0.72, 1.06
≥130	40	335	0.79	0.55, 1.12	0.76	0.52, 1.10	306	1356	1.02	0.88, 1.19	1.01	0.86, 1.19
Total carbohydrates, g/d												
≤224	122	790	1.00	Ref	1.00	Ref	503	2220	1.00	Ref	1.00	Ref
225–238	63	454	0.91	0.67, 1.24	0.89	0.65, 1.21	143	696	0.89	0.74, 1.07	0.90	0.75, 1.09
239–261	91	640	0.92	0.70, 1.21	0.89	0.67, 1.19	159	809	0.87	0.73, 1.05	0.89	0.74, 1.07
≥262	48	354	0.88	0.63, 1.23	0.86	0.60, 1.24	177	740	1.09	0.92, 1.30	1.09	0.91, 1.31
Fiber, g/d												
≤16	34	210	1.00	Ref	1.00	Ref	246	1095	1.00	Ref	1.00	Ref
17–20	59	462	0.76	0.50, 1.15	0.81	0.52, 1.25	260	1142	0.99	0.83, 1.18	1.02	0.85, 1.22
21–24	88	670	0.75	0.51, 1.12	0.81	0.53, 1.24	254	1036	1.09	0.91, 1.30	1.12	0.93, 1.35
≥25[3]	143	896	0.96	0.66, 1.39	1.08	0.70, 1.66	222	1192	0.80	0.67, 0.96	0.82	0.67, 1.00
Soluble fiber, g/d												
≤4	—	—	—	—	—	—	236	1062	1.00	Ref	1.00	Ref
5–6	—	—	—	—	—	—	317	1320	1.08	0.91, 1.28	1.11	0.93, 1.32
7–8	—	—	—	—	—	—	219	1005	0.97	0.81, 1.17	1.00	0.82, 1.20
≥9	—	—	—	—	—	—	210	1078	0.86	0.71, 1.03	0.85	0.70, 1.04
Insoluble fiber, g/d												
≤10	—	—	—	—	—	—	245	1104	1.00	Ref	1.00	Ref
11–13	—	—	—	—	—	—	285	1221	1.04	0.88, 1.24	1.07	0.90, 1.27
14–17	—	—	—	—	—	—	218	1033	0.92	0.77, 1.11	0.96	0.79, 1.16
≥18	—	—	—	—	—	—	234	1107	0.93	0.78, 1.11	0.97	0.79, 1.18
Added sugar, g/d												
≤27[3]	171	1027	1.00	Ref	1.00	Ref	162	701	1.00	Ref	1.00	Ref
28–39	82	678	0.71	0.55, 0.93	0.71	0.54, 0.93	239	1113	0.90	0.74, 1.10	0.92	0.75, 1.13
40–51	34	262	0.77	0.53, 1.11	0.75	0.52, 1.09	221	1023	0.94	0.77, 1.15	0.96	0.78, 1.17
≥52	37	271	0.82	0.58, 1.17	0.78	0.54, 1.14	360	1628	0.98	0.81, 1.17	0.96	0.79, 1.17

[1] Ref, reference; SAB, spontaneous abortion.

[2] Adjusted for age (<25, 25–29, 30–34, ≥35 y), BMI (<18.5, 18.6–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2), energy (kcal/d), current smoker at pregnancy (yes vs. no), alcohol (drinks per week), metabolic equivalent hours per week, oral contraceptives as last form of birth control (yes vs. no), prenatal supplementation or multivitamin (yes vs. no), White/non-Hispanic (yes vs. no), education (<12, 12–15, 16, >16 y), income (<50,000, 50,000–99,000, 100,000–149,000, ≥150,000 US$/y), altered Danish Dietary Guidelines/Healthy Eating Index-2010 score.

[3] Daily recommended values.

is associated with lower risk of SAB. However, these studies could have suffered from selection bias (from using controls who had a term birth) and recall bias (because they required women to recall first trimester dietary patterns), and did not use a dietary questionnaire evaluated for validity (16, 17).

The present results are more consistent with available prospective cohort data, which have shown no strong association between preconception dietary pattern and risk of SAB, although it is possible for individual food groups to be positively or inversely associated with SAB whereas the overall dietary pattern is null. An analysis of NHS II data found that, among the HEI-2010, alternative Mediterranean diet, and the Fertility Diet score, only the Fertility Diet score was associated with lower risk of SAB, when restricted to pregnancies in the year immediately following dietary assessment (18). Although 1 component of the Fertility Diet score is glycemic load, the authors did not specifically examine if glycemic load was independently associated with SAB. As in the present study, the NHS II used a dietary questionnaire evaluated for validity and attempted to capture dietary consumption before conception. However, for the primary analysis, the NHS II study used dietary data collected ≤4 y before the pregnancy occurred and found no appreciable association between dietary patterns and SAB risk. Because dietary habits could have changed in this timespan, this might have resulted in misclassification of diet, which would be expected to bias results toward the null. A prior prospective cohort study including couples planning their first pregnancy used three 24-h dietary recalls to classify adherence to the aHEI-P (19). Although numbers were small (only 11 pregnancies ended in loss), they observed that greater adherence to the aHEI-P (greater overall diet quality) was associated with reduced risk of pregnancy loss. The present study adds to this literature by specifically examining dietary components including glycemic load, dietary fiber, carbohydrates, and added sugar, to identify which, if any, are associated with SAB risk. In the present study, it is possible that dietary intake before conception is not the etiologically relevant time period for assessing the association between dietary pattern and risk of SAB.

To our knowledge, this is the first study to examine associations between glycemic load and SAB in a group of pregnancy planners that were not specifically selected based on known conditions that impair glycemic control. Two prior studies have examined the association between glycemic control and SAB in pregnant women with insulin-dependent diabetes. In a prospective US cohort study, women with insulin-dependent diabetes were followed throughout pregnancy to examine the effect of glucose control, measured using glycosylated hemoglobin concentration, on pregnancy outcomes, including SAB (5, 6). Poor diabetes control during the first trimester, specifically in the time proximal to conception, was associated with risk of SAB, compared with poor glycemic control later in the first trimester, more proximal to the abortion event. A second prospective cohort study found that, whereas women with insulin-dependent diabetes with good glycemic control had no greater risk of SAB than women without insulin-dependent diabetes, women with diabetes and poor glycemic control had greater risk of pregnancy loss (40). These findings suggest that glycemic control, and not necessarily diabetes, in the early periconceptional period is the relevant exposure and exposure window to identify potential mechanisms for the association between glycemic response and SAB.

Although the FFQ is an instrument, evaluated for validity, well suited to capture long-term dietary data, dietary intake was likely still misclassified (41). Validation studies have raised questions of the appropriateness of using GI to estimate glycemic response after mixed meals (42, 43). Error in capturing GI introduces error in glycemic load, but the magnitude is likely similar to that of measurements of other standard nutrients (29). Additionally, dietary quality, specifically for total carbohydrate intake, likely varied considerably across the cohorts. As an example, the top contributor to glycemic load in SF was rye bread whereas in PRESTO the top contributor was sugar-sweetened beverages, which differ greatly in nutritional quality. The observed findings and dietary categories used might not be comparable across cohorts. Differences in diet quality and population preferences across cohorts could help explain slightly different findings in the observed association between glycemic load and SAB.

Although we were unable to assess the association between early pregnancy glycemic load and SAB risk, because diet was assessed during the preconception period and the FFQ was not repeated in early pregnancy, 1 prior study found that glycemic response close to conception was more strongly associated with SAB risk than glycemic response closer to the abortive event (5). By assessing diet during the preconception period, we could be missing the most etiologically relevant exposure window for examining the exposure and outcome relation, because a long interval could elapse between filling out the FFQ and conception. However, we found no meaningful association between these dietary factors and SAB in our sensitivity analysis that restricted to participants who completed the FFQ within 90 d before conception. It is also possible that the observed findings could be an artifact of collider bias (44). Within the same cohort in a prior analysis, we observed a strong association between glycemic load and reduced fecundability. In the present study, because we examined the association between glycemic load and SAB, we conditioned, by definition, on women who conceived. It is possible that the women most susceptible to the adverse effects of a diet with a high glycemic load are being excluded from the sample because they have greater difficulty conceiving. This phenomenon could lead to a spurious inverse association similar to that observed in the present analysis.

The majority of SF (95%) and PRESTO (96%) participants reported using home pregnancy tests to detect pregnancy, and the median gestational week of first positive pregnancy test was 4 wk in both cohorts, thereby indicating that we captured many early losses (<8 wk of gestation). Nevertheless, it is still likely that we underascertained very early SAB (<6 wk of gestation). In a cohort of this size, it is not feasible to collect daily urine specimens to measure human chorionic gonadotropin, which allows for identification of pregnancy soon after implantation. Therefore, we could not identify losses that occurred before pregnancy was clinically recognized (via home pregnancy test or in a clinical setting). Although we controlled for a range of covariates, our results could have been affected by unmeasured confounding.

In conclusion, diets high in glycemic load, carbohydrates, dietary fiber, and added sugars were not clearly associated with risk of SAB in Danish or North American pregnant women without conditions known to affect insulin sensitivity. However, evaluating these dietary measures in the months before conception, as examined in the present study, might not be the most relevant period in which to measure dietary quality and exposure.

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The authors' responsibilities were as follows—EEH, KJR, EMM, KLT, LAW: designed the research; SKW, EEH, AKW, KJR, EMM, LAW: conducted the research; SKW: analyzed the data; SKW, AKW, LAW: coded the outcome and covariate data; SKW: took the lead in writing the manuscript and has primary responsibility for the final content; and all authors: read, contributed to, and approved the final manuscript.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

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