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## Intake of dietary carbohydrates in early adulthood and adolescence and breast density among young women

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### Abstract

**Purpose**—Carbohydrate intake increases postprandial insulin secretion and may affect breast density, a strong risk factor for breast cancer, early in life. We examined associations of adolescent and early adulthood intakes of total carbohydrates, glycemic index/load, fiber, and simple sugars with breast density among 182 young women.

**Methods**—Diet was assessed using three 24-h recalls at each of five Dietary Intervention Study in Children (DISC) clinic visits when participants were age 10–19 years and at the DISC06 Follow-Up Study clinic visit when participants were age 25–29 years. Associations between energy-adjusted carbohydrates and MRI-measured percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) at 25–29 years were quantified using multivariable-adjusted mixed-effects linear models.

**Results**—Adolescent sucrose intakes and premenarcheal total carbohydrates intakes were modestly associated with higher %DBV (mean %DBV<sub>Q1 vs Q4</sub>, 16.6 vs 23.5% for sucrose; and 17.2 vs 22.3% for premenarcheal total carbohydrates, all  $P_{\text{trend}} < 0.02$ ), but not with ADBV. However, adolescent intakes of fiber and fructose were not associated with %DBV and ADBV. Early adulthood intakes of total carbohydrates, glycemic index/load, fiber, and simple sugars were not associated with %DBV and ADBV.

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**Conclusions**—Insulinemic carbohydrate diet during puberty may be associated with adulthood breast density, but our findings need replication in larger studies. *Clinical Trials Registration* [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00458588) Identifier, [NCT00458588](https://clinicaltrials.gov/ct2/show/study/NCT00458588) April 9, 2007; [NCT00000459](https://clinicaltrials.gov/ct2/show/study/NCT00000459) October 27, 1999

## Keywords

Carbohydrate; Fiber; Glycemic index; Glycemic load; Fructose; Sucrose; Breast density; Absolute dense; breast volume; Absolute non-dense breast volume; Young women; Timing of exposure; Breast cancer

## Introduction

Dietary carbohydrates, particularly those rapidly metabolized in the body, are well known to elevate blood glucose level and insulin secretion [1], which may stimulate breast carcinogenesis by increasing mitosis or oxidative stress, suppressing apoptosis, and causing an imbalance in bioavailable sex steroids via a decrease in sex-hormone-binding globulin [2–5]. The glycemic index (GI) or glycemic load (GL) ranks carbohydrate-containing foods according to their effect on postprandial blood glucose level [6]. Meta-analyses of cohort studies reported that women with high GI or GL dietary patterns in mid-life or older are at a 5–6% increased risk of breast cancer, compared to women with low GI or GL dietary patterns [7, 8].

Growing evidence suggests that breasts have unique developmental features, resulting in life-cycle-specific risk windows [9–11]. The rudimentary ductal architecture of the breasts undergoes rapid proliferation and expansion during pubertal development, achieving terminal differentiation during a first full-term pregnancy and lactation [9, 12, 13]. Earlier-age pubertal events [14, 15] and later-age first pregnancies [16] are risk factors for breast cancer. Exposure to ionizing radiation [17] at younger ages before pregnancy has been reported to be associated with an increased risk of breast cancer. Collectively, the evidence indicates that breasts are particularly susceptible to stimuli during pubertal development [18]. Insulinaemic carbohydrate diets in early life may influence breast density, a measure of the relative amount of glandular and stromal tissue in the breasts, and an established risk factor for breast cancer that tracks over time [19–21].

However, the impact of dietary carbohydrates early in life on the development of breast density remains unclear. In three out of four studies that examined early-life diet and breast density [22–25], neither fiber [22] nor high-carbohydrate-diets [23, 24] were associated with breast density. However, these studies may be subject to misclassification of dietary intake due to their use of distant dietary recalls [22–24]. Conversely, a recent prospective cohort study of adolescents found that frequent consumption of sweetened, milk-based drinks is associated with greater dense breast tissue [25], supporting the long-term effect of diet on breast tissue composition.

The aim of our study is to clarify the potential impact of early-life insulin-related carbohydrate diets on breast tissues, as measured by breast density, using prospectively collected early-life dietary data from the dietary intervention study in children (DISC) and DISC06 Follow-Up Study.

We investigated the associations of total carbohydrate, GI, GL, fiber, and individual sugar intakes during early adulthood and adolescence with breast density measured at 25–29 years. We also explored whether associations differed by diet before and after menarche [14, 26–28].

## Method

### Study design and study population

DISC was a multicenter, randomized controlled clinical trial to evaluate the efficacy and safety of a lipid-lowering diet in children [29, 30]. Between 1988 and 1990, a total of 663 healthy, pre-pubertal, 8- to 10-year-old children (301 girls and 362 boys) with elevated low-density lipoprotein cholesterol were recruited from six clinical centers. Children were randomized to a lower-fat diet intervention or a usual-care control group at baseline and continued on the trial until 1997 [30]. All 301 girls in the DISC were invited to participate in the DISC06 Follow-Up Study to evaluate the longer term effect of the diet intervention on breast cancer-related biomarkers. Of those, 260 attended the DISC06 Follow-Up clinic visit between 2006 and 2008 when they were aged 25–29 years [31]. The institutional review boards from all six participating clinical centers and the coordinating center approved the original and follow-up DISC protocols. The Fox Chase Cancer Center institutional review board also approved the DISC06 Follow-Up Study protocol. We obtained assent from participants and informed consent from their parents or guardians prior to the DISC. Informed consent from participants was also obtained before the DISC06 Follow-Up Study.

Of 260 women in the DISC06 Follow-Up Study, we excluded those who were pregnant or breastfeeding within 12 weeks prior to the DISC06 follow-up visit ( $N=30$ ), had breast augmentation or reduction surgery ( $N=16$ ), or had unacceptable or missing breast density data ( $N=32$ ). Consequently, the present study included 182 women with breast density data measured during the DISC06 Follow-Up Study and any dietary data collected during the DISC trial (beginning at age 10 years) or DISC06 Follow-Up Study—172 women had both adolescent and adulthood dietary data; 4 had only adolescent and 6 had only adulthood dietary data. None of the participants had a history of breast cancer.

### Data collection

Data were collected following a standardized protocol at baseline and thereafter at year 1, 3, 5, and last follow-up clinic visits in DISC and at the DISC06 Follow-Up Study visit. Information on demographics, lifestyle, medication use, and reproductive and medical history were obtained via self-administered questionnaires. Leisure time physical activity was assessed by an interviewer-administered questionnaire. Trained staff measured the height and weight of the study participants [32] and body mass index (BMI) was calculated as weight/height<sup>2</sup> (kg/m<sup>2</sup>). To account for age-specific growth changes during childhood and adolescence, BMI during the DISC trial was expressed as a BMI  $z$  score relative to the Centers for Disease Control and Prevention 2000 Growth Charts [33]. During the DISC trial onset of menses was queried annually until menarche [34]. Whole-body fat percentage in early adulthood was measured using dual-energy X-ray absorptiometry (DEXA) at a clinic visit during the DISC06 Follow-Up Study [32].

## Dietary assessment

Usual diet was assessed at baseline, years 1, 3, and 5, and the last follow-up visit during DISC and at the DISC06 follow-up visit using three 24-h dietary recalls over 2 weeks [35, 36]. Trained dietitians collected recalls via face-to-face interviews during the clinic visit and two additional subsequent phone call interviews. Of three recalls, two were obtained on two non-consecutive weekdays and one was obtained on a weekend day. Nutrient analysis was performed to estimate nutrient intakes from recalls. Analyses were performed during the DISC trial at the University of Minnesota Nutrition Coordinating Center using version 20 of their database, and during the DISC06 Follow-Up Study at DISC clinical centers using the University of Minnesota's Nutrition Data System for Research 2007. Nutrient estimates from three recalls were averaged to quantify usual dietary intake. Dietary estimates from recalls with an implausible caloric intake ( $< 600$  or  $> 3,500$  kcal/day) [37] were considered to be inaccurate and excluded. All nutrients were energy-adjusted using the residual method [38].

Overall dietary GI and GL were calculated using information on individual foods consumed, which is currently available only in the DISC06 Follow-Up Study. GI is a value assigned to carbohydrate-containing foods based on their relative effects on blood glucose level, compared to those of a reference food (white bread) [39]. Using the GI values of individual foods from published reports [39], overall dietary GL was computed by summing the product of the GI of each carbohydrate-containing food with carbohydrate content (g/servings) and intake frequency of the food [40]. Overall dietary GI was computed by dividing the overall dietary GL by the total amount of carbohydrate consumption [41].

## Breast density measurements

Breast density was measured at the DISC06 Follow-Up Study visit by non-contrast magnetic resonance imaging (MRI). The breast image acquisition protocol followed the American College of Radiology Guidelines [31]. In brief, the breasts were scanned using a whole-body 1.5 T or higher field-strength MRI scanner with a dedicated breast imaging radiofrequency coil. A three-dimensional T1-weighted, fast gradient echo pulse sequence was performed using a 32–40 cm field of view for bilateral coverage for transaxial and coronal orientation, with and without fat suppression. To reduce data acquisition variability across clinical sites, MRI technologists were trained to recognize and correct MRI image failure due to incomplete fat suppression, motion artifacts, and inadequate breast coverage. The breast MRI image quality at each DISC clinical center was also certified by obtaining acceptable images from three volunteers prior to the DISC06 Follow-Up Study.

All MRI images were sent to the University of California San Francisco (Dr. Klifa) to identify chest wall-breast tissue boundaries and skin surfaces and separated the breast fibroglandular and fatty tissue using an automated segmentation method, based on fuzzy *C*-means clustering (FCM) [42]. Manual delineation was used if automated FCM methods could not be used. Total breast volume and absolute dense breast fibroglandular volume (ADBV) were computed separately for each breast and an average was obtained for analysis. Percent dense breast volume (%DBV) was estimated as the percentage of ADBV over total

breast volume. Absolute non-dense breast volume (ANDBV) was calculated by subtracting the ADBV from the total breast volume.

### Statistical analysis

Carbohydrate intake in early adulthood and adolescence was assessed separately. Early adulthood intake was estimated using 24-h dietary recalls obtained at age 25–29 years in the DISC06 Follow-Up Study. Long-term adolescent intake was estimated by averaging intake estimated from 24-h recalls collected from age 10 to 19 years following the age definition of adolescence from the World Health Organization [43]. To evaluate intake consumed at distinct pubertal stages [14, 26–28], pre- and post-menarcheal intakes were estimated separately by obtaining an average intake from age 10 years to the onset of menarche, and by calculating an average intake thereafter to the last DISC trial visit, respectively.

%DBV, ADBV, and ANDBV were log-transformed to obtain approximate normality; we mainly present associations with %DBV and ADBV, because of their strong associations with breast cancer [19]. Twenty-five multiple imputed datasets were created to impute the missing values for whole-body fat percentage ( $n = 6$ ) using estimated values from a prediction model that included adult BMI, a strong predictor of whole-body fat percentage (correlation  $r = 0.83$ ), as an independent variable. To assess the association between dietary carbohydrates and breast density measurements in each imputed dataset, a linear mixed-effects regression model with robust standard errors was used. The geometric means and the 95% confidence intervals of breast density measurements across the quartiles of each dietary carbohydrate were calculated. The regression model was adjusted for the following potential confounding factors associated with breast density and breast cancer [32, 44, 45] as fixed effects: race, education, childhood BMI  $z$  score at baseline, adult whole-body fat percentage, duration of hormone use, number of live births, smoking status, treatment assignment, and total energy and alcohol intake. The clinic location was included as a random effect [43]. Tests for trends were conducted, modelling the quartile median for dietary intake as a continuous term. Tests for interaction by intervention assignment were conducted by including the cross-product terms between the intervention assignment and carbohydrate intakes. The results from each imputed dataset were pooled using Rubin's rule [46].

We conducted sensitivity analyses restricted to nulliparous women or additionally adjusting for protein and fat intake. To examine associations independent of dietary behavior at other life periods, adolescent and adulthood carbohydrate intakes were also simultaneously adjusted for in separate models. Analysis was conducted using STATA (version 13.0) (College Station, Texas, USA). All statistical tests were two-sided and conducted at the 0.05 significance level.

## Results

The characteristics of 182 females in this study in early adulthood are shown in Table 1. At the DISC06 follow-up visit, the mean age of the study participants was 27.1 years and their mean BMI was 25.4 kg/m<sup>2</sup>. The majority of women were White (90%), nulliparous (71%), well-educated (90% had obtained a college degree), and were ever users of hormonal contraceptives (94%). The mean dietary intake in early adulthood was 214.9 g/day for total

carbohydrates, 15.2 g/day for fiber, 36.7 g/day for sucrose, and 19.4 g/day for fructose. The mean dietary intake in adolescence at age 10–18 years was 228.9 g/day for total carbohydrates, 10.7 g/day for fiber, 44.0 g/day for sucrose, and 25.3 g/day for fructose. The median and interquartile range for %DBV, ADBV, and ANDBV were 24.5% (9.7–41.2%), 93.0 cm<sup>3</sup> (50.0–140.3 cm<sup>3</sup>), and 298.5 cm<sup>3</sup> (157.8–485.3 cm<sup>3</sup>), respectively.

### Early adulthood intakes and breast density measures

Early adult intake of total carbohydrates was not significantly associated with %DBV and ADBV ( $P_{\text{trend}} = 0.20$ ) (Table 2) in the multivariable-adjusted model. Similarly GI, GL and specific carbohydrate types (e.g., fiber, sucrose, and fructose) in early adulthood were not significantly associated with %DBV and ADBV ( $P_{\text{trend}} = 0.07$ ).

### Adolescent intake and breast density measures

When associations with adolescent intake were evaluated (Table 3), we observed a significant positive association between sucrose and %DBV, although a pattern of increasing density across increasing quartiles of intake was not evident (multivariable-adjusted mean %DBV<sub>Q1,Q2,Q3,Q4</sub> = 16.6, 19.5, 16.4, 23.5%,  $P_{\text{trend}} < 0.001$ ). Intakes of total carbohydrates, fiber, and fructose were not associated with %DBV. There was no association between ADBV and adolescent intake of total carbohydrates, fiber, fructose, and sucrose.

Because breasts' susceptibility to stimuli might differ during pubertal development [14, 26–28], we further explored associations with diet consumed before and after the onset of menarche (Table 3). Premenarcheal intake of total carbohydrates was modestly positively associated with %DBV (multivariable-adjusted mean %DBV<sub>Q1,Q2,Q3,Q4</sub> = 17.2, 16.6, 18.4, 22.3%,  $P_{\text{trend}} = 0.02$ ) but not with ADBV. Premenarcheal intakes of fiber, fructose, and sucrose were not associated with %DBV or ADBV. None of the post-menarcheal carbohydrate intakes were associated with %DBV or ADBV.

### Additional analyses

Associations with ANDBV, which is another component of %DBV, are presented in Supplementary Tables 1 and 2. Early adulthood total carbohydrate ( $P_{\text{trend}} = 0.01$ ) and fiber ( $P_{\text{trend}} = 0.04$ ) intakes were significantly positively associated with ANDBV, whereas simple sugars, GI, and GL were not associated. Adolescent intake of fructose was significantly positively, while sucrose was significantly inversely associated with ANDBV (all  $P_{\text{trend}} < 0.04$ ). There were no associations between ANDBV and adolescent intakes of total carbohydrate and fiber. Pre- and post-menarcheal intakes of total carbohydrates, fiber, fructose, and sucrose were not associated with ANDBV.

Repeating all analyses with only nulliparous women or additionally adjusting for protein or fat intake did not substantially change our main results (data not shown). Similarly, mutual adjustment for adulthood and adolescent intakes did not change our findings substantially (data not shown). Intervention assignment also did not modify any of our results (data not shown).

## Discussion

In this analysis of carbohydrates consumed during early-life, early adulthood intakes of total carbohydrates, GI, GL, fiber, sucrose, and fructose were not significantly associated with %DBV. Intakes of sucrose during adolescence and total carbohydrates during the premenarcheal period were modestly positively associated with %DBV, while fiber and fructose intakes were not associated with %DBV during any period of adolescence. There were no associations between ADBV and any carbohydrates evaluated in either early adulthood or adolescence.

Our study examined several dietary carbohydrates that may have varied insulin responses. Total carbohydrates, which have been frequently studied, represent the total amount of any carbohydrate consumed in the diet. GI measures a food's relative postprandial blood glucose spike and has been used as the gold standards for indicating the overall postprandial insulinemic quality of carbohydrates in the diet. GL, a product of a food's GI by the carbohydrate content consumed, represents both the quantity and insulinemic quality of carbohydrates [39]. Fiber, abundant in fruits, vegetables, whole grains, legumes and nuts, is a type of non-digestible complex carbohydrate. Fiber has been the subject of much research due to its effects on inhibiting glucose absorption [47] as well as increasing fecal excretion of estrogens [48–50] via accelerating intestinal transit time. Fructose and sucrose, frequently added to candy, desserts, soft drinks, and fruit drinks, are easily broken down during digestion, resulting in large fluctuations in blood glucose levels.

To date, six cross-sectional studies [51–56] and three longitudinal studies [57–59] of women in mid-life or older (> 40 years) have examined the associations between adult intake of carbohydrates and breast density [51–59]. Of these, seven examined breast density associations with total carbohydrates [51–54, 57–59] and six with fiber [51–54, 56, 58]. Our finding of no cross-sectional association between total carbohydrates and breast density among young women is consistent with the main results of all seven studies of carbohydrates [51–54, 57–59], although sub-group analyses of two studies found some significant, but inconsistent results [51, 59]. For example, a cross-sectional study in Japan [51] observed a 6% lower breast density among women in the highest quartile of carbohydrate intake, compared to those in the lowest quartile, in a subset of 253 postmenopausal women. But a longitudinal study in Italy [59] reported that women in the highest quartile of carbohydrates intake were at 2.7 fold increased odds of having Wolfe's defined high breast density (P2 + DY) in a subset of 875 lean women with BMI < 25 kg/m<sup>2</sup>. Similarly, adult fiber intakes were not associated with breast density in the majority of previous studies [51–54, 58], though a case control study in Canada observed a 7.9% decrease in breast density comparing women in the extreme quartiles of fiber intake among 645 controls [56]. Evidence for the association between breast density and GI and GL [59] or individual sugars consumed during adulthood [55, 57, 59] is sparse and the results have been inconsistent. While we did not observe any cross-sectional associations with GI and GL in young women, a longitudinal study of mostly postmenopausal women (*N* = 1,668) found a significant positive association with GL but not with GI [59]; women in the highest quartile of GL were at 1.73 times increased odds of having Wolfe's high breast density, compared to those in the lowest [59]. For simple sugars or food groups containing high



amount of simple sugars, a longitudinal study ( $N=1,668$ ) [59] found that women who consumed  $> 130.4$  g/day of simple sugar were at 1.71-fold increased odds of having Wolfe's high breast density, compared to those who consumed  $< 69.4$  g/day of simple sugar, but evidence from other studies is weak; another longitudinal study ( $N=2,000$ ) found no association with sugars [57] and a cross-sectional study ( $N=1,553$ ) reported a weak 2.5% increase in breast density with sweet foods or sugar-sweetened beverages, comparing women in the extreme quartiles of each food group [55].

Although we did not find an association between current dietary intake and breast density, we further examined adolescent diet because breasts undergo dynamic structural changes throughout a woman's life, including puberty [9, 12, 13], which may change breasts' susceptibility to diet. Three studies have evaluated the association between adulthood breast density and childhood [24] or adolescent [22, 23] consumption of carbohydrates and fiber [22–24]. Our finding that there was no association between early adult breast density and adolescent fiber intake is consistent with these studies [22, 23]. Previous studies of the association between breast density and carbohydrate intake are mixed. Snack and dessert consumption at age 12–13 [23] and bread or biscuit consumption at age four [24], all of which are foods containing rapidly absorbable carbohydrates, were not associated with breast density. But these studies retrospectively assessed childhood or adolescent diet 30–50 years later [22–24], which is susceptible to measurement error that can attenuate associations. A recent longitudinal cohort study of girls [25] found that frequent consumption of sweetened milk, of which sugar is a primary component, was prospectively associated with higher %DBV at Tanner stage 4, which tends to persist until the first pregnancy or later [60]. Consistent with the results of the longitudinal study, we observed mean differences in %DBV of approximately 5% across extreme quartiles of sucrose and total carbohydrate intakes during adolescence, which is similar to mean differences in %DBV observed with parity, an established risk factor for breast cancer [45]. Thus, our results may support a modest effect of early-life diet on breast tissues, but additional studies are needed to determine whether they can be translated to breast cancer risk.

Growing evidence supports independent effects of dense breast tissues and non-dense fatty breast tissues, which are individual components of %DBV, on breast cancer risk [19]. Examining differential associations with ADBV and ANDBV may provide insights into which dietary factors affect %DBV and potentially breast cancer risk. Of carbohydrates associated with %DBV, we observed that adolescent sucrose intake is significantly inversely associated with ANDBV, but not with ADBV, which might suggest a greater influence of sucrose on non-dense fatty breast tissue than dense breast tissue. However, cautious interpretation is needed because of possible residual confounding by BMI despite adjustment for DEXA-measured body fat percent in our analyses.

A strength of our study is the prospective design with data collection conducted over 20 years of follow-up, particularly during the participants' transition from adolescence to early adulthood. Trained dietitians assessed the diet on two non-consecutive weekdays and on a weekend day using 24-h dietary recalls, providing a valid estimate of usual diet intake for population research [61]. We also prospectively assessed adolescent diet on five occasions between ages 10 and 18 years [62], which minimizes recall bias. It also allowed us to

calculate average intake during adolescence, which better reflects long-term dietary intake during adolescence as well as reduces random measurement errors inherent to diet assessment on a single occasion. Thus, we may have been more able to accurately assess adolescent diet and capture the health effects of long-term carbohydrate intake during adolescence and at specific pubertal stages. In addition, with comprehensive dietary data in our study, we were able to test whether the presence of other nutrients (e.g., proteins and fat) also affect our results [63]. Multivariable-adjusted models controlled for adolescent and adulthood risk factors for breast density and breast cancer. We were able to adjust for DEXA-measured adiposity, the gold standard for assessment of adiposity, which is strongly correlated with breast density. A further strength of this study includes the quantitative assessment of volumetric breast density in mostly nulliparous young women at ages 25–29.

Our study also has weaknesses. We were unable to take into account physical structures of foods (e.g., ripeness), the degree and type of food processing, and meal composition (individual foods or mixed dishes), which might affect the glycemic response to carbohydrates [64]. The absence of food group analyses is another limitation of our study, particularly in relation to our finding for total carbohydrates, which are found in a variety of foods, some healthier than others. Seasonal variation in carbohydrate intakes, though it has been reported to be relatively small [65, 66], could not be taken into account when estimating usual intake. Compared to many prior studies, we measured breast density by MRI, whose absolute values are approximately 1.5 times lower than mammographic breast density, as observed in our study [67]. Even so, MRI-measured breast density is highly correlated with mammographic breast density ( $r = 0.75$ ) [68, 69], and women with high breast density measured by MRI and mammography were at a similar increased breast cancer risk [70]. Very lean or very obese girls (weight-for-height ratios:  $> 90$ th or  $< 5$ th percentile) were not included in the DISC trial, though our study participants had a wide range of adiposity and physical activity level. The participants had elevated LDL-C at baseline, possibly limiting the generalizability of our results; however, based on current National Cholesterol Education Program criteria only half of DISC participants now would be classified as having high LDL-C levels at baseline [71] and only 8% had elevated LDL-C at the DISC06 follow-up visit. Although one measurement of breast density at age 25–29 years in our study does not account for density changes that might occur with aging and lifestyle modification, breast density measurements taken 10 years apart are reported to be highly correlated ( $r > 0.80$ ) [20, 21], supporting the use of breast density as a biomarker to identify young women at higher risk of breast cancer. Our sample size was small for stratified analyses particularly by adiposity and physical activity, which might modulate adverse metabolic effects of carbohydrates [72]. Finally, though our results are subject to multiple testing issues, we cautiously interpreted results in relation to a priori hypotheses that considered biological relevance and prior evidence.

In summary, it is increasingly emphasized that diet may have a greater and prolonged impact on immature and proliferating breast cells during times of rapid breast growth and development [9, 12, 13, 18]. In our study, there was no evidence for associations of breast density with intakes of any dietary carbohydrates during early adulthood. However, we found modest, positive associations of %DBV with adolescent intake of sucrose and premenarcheal intake of total carbohydrates. Larger prospective studies and food group

analyses are warranted to confirm the long-term effects of carbohydrate composition of adolescent diets on adult breast density.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

<b>ADBV</b>	Absolute dense breast volume
<b>ANDBV</b>	Absolute non-dense breast volume
<b>BMI</b>	Body mass index
<b>BRC</b>	Breast cancer
<b>DEXA</b>	Dual-energy X-ray absorptiometry
<b>DISC</b>	Dietary intervention study in children
<b>DISC06</b>	Dietary intervention study in children 2006 Follow-Up Study
<b>IQR</b>	Interquartile range
<b>MRI</b>	Magnetic resonance imaging
<b>%DBV</b>	Percent dense breast volume

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Table 1

Study population characteristics at the DISC06 follow-up visit ( $N = 182$ )

Characteristics	<i>N</i>	Mean $\pm$ SD
Age (years)	182	27.2 $\pm$ 1.0
BMI (kg/m <sup>2</sup> )	182	25.4 $\pm$ 5.4
BMI- <i>z</i> score <sup>a</sup>	182	0.23 $\pm$ 0.90
Physical activity (Mets-h/week)	182	310.1 $\pm$ 55.5
Age at menarche (years)	182	12.9 $\pm$ 1.3
Duration of hormonal contraceptive use (years) <sup>b</sup>	171	5.6 $\pm$ 3.5
Dietary intake		
During DISC06 follow-up visit <sup>c</sup>		
Total energy intake (kcal/day)	176	1,731.3 $\pm$ 469.9
Total carbohydrates (g/day)	176	214.9 $\pm$ 36.4
Glycemic index (units/day)	176	86.9 $\pm$ 6.6
Glycemic load (units/day)	176	174.5 $\pm$ 60.9
Fiber(g/day)	176	15.2 $\pm$ 6.4
Fructose (g/day)	176	19.4 $\pm$ 12.5
Sucrose (g/day)	176	36.7 $\pm$ 16.8
During DISC trial <sup>b</sup>		
Total energy intake (kcal/day)	178	1,612.3 $\pm$ 348.9
Total carbohydrates (g/day)	178	228.9 $\pm$ 20.5
Fiber(g/day)	178	10.7 $\pm$ 2.5
Fructose (g/day)	178	25.3 $\pm$ 8.5
Sucrose (g/day)	178	44.0 $\pm$ 11.4
Race		
	<i>N</i>	Percentage (%)
White	164	90
Non-white	18	10
Education		



Some college	44	24
Bachelor's degree	95	52
Graduate degree	25	14
Other <sup>d</sup>	18	10
Number of live births		
0	129	71
> 1	53	29
Family history of breast cancer		
No	171	96
Yes	7	4
Hormonal contraceptive use		
Never	11	6
Former	66	36
Current	105	58
Smoking status		
Never	100	55
Former	38	21
Current	44	24
Alcohol consumption		
Never/former	16	9
Current, < 3 per week	71	39
Current, 3-6 per week	33	18
Current, 6-10 per week	40	22
Current, > 10 per week	22	12
	N	Percentage (%)
<hr/>		
Treatment assignment		
Intervention	87	48
Usual care	95	52
	N	Median (IQR)
<hr/>		
Breast density measures		

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Percent dense breast volume (%)	182	24.5 (9.7–41.2)
Absolute dense breast volume (cm <sup>3</sup> )	182	93.0 (50.0–140.3)
Absolute non-dense breast volume (cm <sup>3</sup> )	182	298.5 (157.8–485.3)

*SD* standard deviation, *BMI* body mass index, *IQR* interquartile range

<sup>a</sup> BMI-*z* score at baseline during the DISC trial

<sup>b</sup> Mean duration of hormonal use was calculated among past and current hormone users

<sup>c</sup> Nutrients are energy-adjusted

<sup>d</sup> Other education includes education until 8–11 years, completion of high school and vocational or technical school

**Table 2**

Multivariable adjusted geometric mean and 95% confidence interval (95% CI) of percent dense breast volume (%DBV) (%) and absolute dense breast volume (ADBV) (cm<sup>3</sup>) according to quartiles of intakes of carbohydrates during early adulthood

Quartiles of intake	Early adulthood (N = 176)		
	Median intake	%DBV mean (95% CI)	ADBV mean (95% CI)
Total carbohydrates, g/day			
Q1	176.2	23.6 (20.3–27.4)	86.3 (78.7–94.5)
Q2	204.2	15.4 (12.6–18.9)	62.4 (53.5–72.8)
Q3	228.9	17.5 (14.4–21.3)	80.1 (58.0–110.8)
Q4	249.2	19.2 (14.8–24.8)	86.9 (59.4–127.0)
<i>P</i> <sub>trend</sub> <sup>a</sup>		0.20	0.71
Glycemic index			
Q1	79.0	19.3 (16.1–23.1)	82.2 (70.4–96.1)
Q2	84.7	18.7 (15.2–23.0)	80.1 (69.2–92.7)
Q3	89.1	18.5 (15.8–21.7)	79.3 (59.4–106.0)
Q4	95.0	18.3 (14.1–23.6)	71.7 (53.7–95.7)
<i>P</i> <sub>trend</sub> <sup>a</sup>		0.80	0.48
Glycemic load			
Q1	142.7	22.9 (18.0–29.2)	85.6 (71.9–102.0)
Q2	164.8	15.1 (12.7–18.0)	63.3 (55.0–72.8)
Q3	183.3	18.6 (17.4–20.0)	87.5 (76.0–100.7)
Q4	209.7	18.9 (15.3–23.2)	79.1 (57.1–110.0)
<i>P</i> <sub>trend</sub> <sup>a</sup>		0.56	0.93
Fiber, g/day			
Q1	9.0	19.7 (14.2–27.5)	73.2 (53.3–100.4)
Q2	12.3	19.1 (15.2–23.9)	77.9 (66.9–90.6)
Q3	15.8	19.2 (18.3–20.2)	79.7 (71.6–88.6)
Q4	22.3	16.9 (15.3–18.6)	82.5 (65.9–103.4)
<i>P</i> <sub>trend</sub> <sup>a</sup>		0.17	0.48
Fructose, g/day			
Q1	8.2	21.3 (17.7–25.5)	90.4 (72.5–112.8)
Q2	14.1	19.6 (16.5–23.4)	80.9 (72.6–90.2)
Q3	19.6	16.4 (13.5–19.9)	72.3 (51.1–102.2)
Q4	30.4	17.8 (14.8–21.4)	70.8 (57.1–87.8)
<i>P</i> <sub>trend</sub> <sup>a</sup>		0.07	0.09
Sucrose, g/day			
Q1	19.1	18.1 (15.7–21.0)	80.6 (75.5–85.9)
Q2	29.2	19.9 (15.7–25.4)	71.6 (54.5–94.0)
Q3	40.8	16.4 (12.2–22.1)	70.2 (46.8–105.3)
Q4	57.0	20.5 (17.3–24.3)	92.6 (79.4–108.1)

Quartiles of intake	Early adulthood ( <i>N</i> = 176)		
	Median intake	%DBV mean (95% CI)	ADBV mean (95% CI)
$P_{trend}^a$		0.66	0.19

Geometric means and 95% CI are estimated from linear mixed effects models including clinic as a random effect and including treatment group (diet intervention group and usual care-control group), childhood BMI *z* score at baseline, current adult percent body fat from DXA (%), continuous), number of live births (0 and > 0), duration of hormone use (years, continuous), race (White and non-White), education (bachelor's degree, graduate school and other), status of smoking (never, former and current), alcohol consumption (never/former, < 3 drinks/week, 3–<6 drinks/week, 6–<10 drinks/week, > 10 drinks/ week), and total energy intake (kcal/day, continuous) as fixed effects

<sup>a</sup> *P*test for trend was conducted by modelling the quartile medians of each dietary intake as a continuous term in linear mixed effects models and calculating the Wald test statistic

**Table 3**

Multivariable adjusted geometric mean and 95% confidence interval (95% CI) of percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) (cm<sup>3</sup>) according to quartiles of intakes of carbohydrates during adolescence

Quartiles of intake	By menarcheal status									
	Adolescence (N = 178)					After menarche (N = 163)				
	Before menarche (N = 161)		After menarche (N = 163)			Before menarche (N = 161)		After menarche (N = 163)		
Total carbohydrates, g/day	Median intake	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes
Q1	203.1	17.0 (13.421.7)	80.3 (60.8105.9)	189.2	17.2 (13.621.8)	74.8 (54.7102.5)	206.5	19.0 (15.023.9)	85.7 (70.3104.5)	206.5
Q2	217.9	20.3 (18.022.9)	80.7 (77.184.4)	213.4	16.7 (13.420.8)	71.8 (56.092.2)	228.5	18.6 (16.321.2)	82.1 (70.995.0)	228.5
Q3	232.4	18.2 (15.121.8)	71.6 (55.592.5)	228.1	18.4 (15.222.2)	71.2 (52.197.3)	246.0	19.8 (17.023.0)	74.0 (58.394.0)	246.0
Q4	245.7	19.9 (17.422.8)	84.4 (68.3104.4)	244.3	22.3 (20.124.8)	95.6 (80.6113.3)	267.9	16.6 (14.119.4)	73.0 (55.396.4)	267.9
<i>P</i> <sub>trend</sub> <sup>a</sup>		0.36	0.96		0.02	0.19		0.41	0.39	
Fiber, g/day	Median intake	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes
Q1	8.2	19.2 (16.622.2)	80.7 (67.896.2)	7.4	17.2 (15.519.1)	73.6 (64.584.1)	7.9	21.3 (16.327.9)	82.8 (64.8105.6)	7.9
Q2	9.7	19.4 (16.323.2)	81.2 (66.0100.0)	9.2	17.0 (12.922.3)	71.7 (53.995.5)	9.6	18.0 (15.221.3)	77.2 (67.288.7)	9.6
Q3	10.9	20.3 (17.823.1)	81.8 (66.8100.1)	10.6	20.7 (17.025.1)	79.7 (67.494.3)	11.3	19.2 (14.625.1)	84.3 (63.3112.2)	11.3
Q4	12.9	16.4 (14.119.0)	72.8 (57.192.7)	13.0	19.5 (15.125.1)	86.9 (65.6115.0)	14.3	15.6 (12.918.9)	70.6 (53.094.1)	14.3
<i>P</i> <sub>trend</sub> <sup>a</sup>		0.20	0.43		0.34	0.15		0.18	0.41	
Fructose, g/day	Median intake	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes
Q1	16.1	21.1 (17.325.7)	88.3 (72.1108.3)	12.6	21.5 (18.824.6)	91.1 (74.5111.5)	14.9	21.1 (17.3-25.6)	91.9 (72.8116.1)	14.9
Q2	21.9	19.5 (16.722.8)	76.6 (69.484.6)	18.1	20.0 (16.124.8)	80.2 (63.5101.3)	24.0	19.0 (16.721.8)	80.9 (73.389.3)	24.0
Q3	26.2	16.1 (12.720.3)	69.4 (55.486.8)	23.4	14.7 (11.918.2)	64.0 (45.989.4)	30.2	15.5 (11.720.6)	61.6 (41.990.7)	30.2
Q4	32.7	18.9 (16.321.8)	83.3 (65.4106.2)	35.3	18.5 (14.923.0)	77.8 (65.592.3)	39.9	18.6 (17.120.2)	83.3 (65.4106.2)	39.9
<i>P</i> <sub>trend</sub> <sup>a</sup>		0.19	0.61		0.22	0.22		0.23	0.46	
Sucrose, g/day	Median intake	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes
Q1	34.1	16.6 (14.718.8)	81.9 (69.396.7)	31.2	18.3 (16.120.9)	83.5 (67.1104.0)	30.3	18.4 (14.124.1)	80.4 (62.9102.7)	30.3
Q2	41.2	19.5 (15.624.4)	78.7 (61.8100.3)	40.9	18.4 (15.122.6)	77.5 (63.195.2)	38.2	15.2 (11.520.0)	73.3 (53.4100.6)	38.2
Q3	46.5	16.4 (13.320.1)	64.8 (43.397.0)	50.0	17.5 (15.120.2)	69.6 (52.791.9)	46.0	19.4 (15.923.7)	79.4 (61.1103.1)	46.0

Quartiles of intake	By menarcheal status					
	Adolescence (N = 178)			After menarche (N = 163)		
	Median intake	%DBV mean (95% CI)	ADBV mean (95% CI)	Median intakes	%DBV mean (95% CI)	ADBV mean (95% CI)
Q4	55.3	23.5 (20.427.2)	93.9 (74.8118.0)	60.0	20.0 (18.022.0)	80.9 (70.892.5)
<i>P<sub>trend</sub></i> <sup>a</sup>		< 0.001	0.50		0.19	0.18
				55.5	21.5 (18.624.7)	81.7 (68.098.0)
					0.09	0.77

Geometric means and 95% CI are estimated from linear mixed effects models including clinic as a random effect and including treatment group (diet intervention group and usual care-control group), childhood BMI z score at baseline, current adult percent body fat from DXA (% continuous), number of live births (0 and > 0), duration of hormone use (years, continuous), race (White and non-White), education (bachelor's degree, graduate school and other), status of smoking (never, former and current), alcohol consumption (never/former, < 3 drinks/week, 3-6 drinks/week, 6-10 drinks/week, > 10 drinks/week), and total energy intake (kcal/day, continuous) as fixed effects

<sup>a</sup> *P*-test for trend was conducted by modeling the quartile medians of each dietary intake as a continuous term in linear mixed effects models and calculating the Wald test statistic