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Dietary Energy Density is Positively Associated with Breast Density among Young Women

Jessica A. Jones, PhD,

Dietetic Intern, The Pennsylvania State University, 110 Chandlee Laboratory, University Park, PA 16802, Phone: 814-335-1101, jal5150@psu.edu, Fax: 717-260-4400

Nutrition Scientist (Contractor through System One, Inc.), The Hershey Company, 1025 Reese Avenue, Hershey, PA 17033

Graduate Research Assistant, The Pennsylvania State University, 110 Chandlee Laboratory, University Park, PA 16802

Terryl J. Hartman, PhD, MPH, RD,

Professor, Department of Epidemiology, Rollins School of Public Health & Winship Cancer Institute, Emory University, 1518 Clifton Road NE, CNR #3035, Atlanta, GA 30322, Phone: 404-727-8713, Fax: 404-727-8737, tjhartm@emory.edu

Professor, Department of Nutritional Sciences, The Pennsylvania State University, 110 Chandlee Laboratory, University Park, PA 16802

Catherine J. Klifa,

Consultant, Dangeard Group, 580 West Remington Drive, Sunnyvale, CA 94087, Phone: 415-779-5905, Catherine@klifa.net

Donna L. Coffman, PhD,

Research Associate Professor, The Methodology Center, The Pennsylvania State University, 400 Calder Square II, State College, PA 16801, Phone: 814-863-9724, Dcoffman@psu.edu

Diane C. Mitchell, MS, RD,

Senior Research Scientist, Director, Diet Assessment Center, Department of Nutritional Sciences, Pennsylvania State University, University Park, PA 16802, Phone: 814-863-5955, Fax:, dcm1@psu.edu

Jacqueline A. Vernarelli, PhD,

Research Associate, Department of Nutritional Sciences, The Pennsylvania State University, 110 Chandlee Laboratory, University Park, PA 16802, Phone: 814-863-3930, Fax: 814-865-5870, jvern@psu.edu

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Correspondence to: Jessica A. Jones.

*Position when the work was completed

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Linda Snetselaar, PhD, RD, LD,

Professor and Chair, Preventive Nutrition Education, Department of Epidemiology, Associate Head for Admissions and Curriculum, Department of Epidemiology, Director, Nutrition Center, Co-Director, Preventive Intervention Center, The University of Iowa, College of Public Health, 105 River Street, Iowa City, Iowa 52242, Phone: 319-384-1553, linda-snetselaar@uiowa.edu

Linda Van Horn, PhD, RD,

Associate Dean for Faculty Development, Professor in Preventative Medicine, Northwestern University, 680 N Lake Shore Drive, Suite 1400, Chicago IL 60611, Phone: 312-908-8938, lvanhorn@northwestern.edu

Victor J. Stevens, PhD,

Senior Investigator, Behavioral Psychology, Kaiser Permanente Center for Health Research, 3800 N. Interstate Ave., Portland, OR 97227, Phone: (503) 335-6751, Fax: (503) 335-2424, Victor.J.Stevens@kpchr.org

Alan Robson, MD,

Senior Vice President, Medical Director, Children's Hospital, 200 Henry Clay Avenue, New Orleans, LA 70118, Phone: 504-896-9400, Fax: 504-896-9707, arobson@chnola.org

John Himes, PhD,

Professor, School of Public Health, Division of Epidemiology and Community Health, University of Minnesota, 1300 South Second Street, Suite 300, Minneapolis, Minnesota, Phone: 612-624-8210, Fax: 612-624-9328, himes001@umn.edu

John Shepherd, PhD, CCD, and

Associate Professor, Radiology and Biomedical Imaging, University of California, San Francisco School of Medicine, 400 Parnassus Ave, UC Clinics, San Francisco, CA 94143, Phone: +1-415-891-7437, john.shepherd@ucsf.edu, Fax: +1 415-476-8723

Visiting Professor, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden, Sweden Cell: +460736750652

Joanne F. Dorgan, PhD, MPH

Professor, Department of Epidemiology and Public Health, Howard Hall, Rm. 102E, 660 W. Redwood St., Baltimore, MD 21201, Phone: 410-706-1602, Fax: 410-706-8013, jdorgan@epi.umaryland.edu

Associate Professor, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111

Abstract

Background—Breast density is an established predictor of breast cancer risk, and there is considerable interest in associations of modifiable lifestyle factors, such as diet, with breast density.

Objective—To determine if dietary energy density (ED) is associated with percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) in young women.

Design—A cross-sectional analysis was conducted with women who participated in the Dietary Intervention Study in Children Follow-Up Study (DISC06). %DBV and ADBV were measured by

magnetic resonance imaging (MRI). Diet was assessed by three 24-hour recalls. Dietary ED (kcal/g) was calculated using three methods: (1) food only, (2) food and caloric beverages, and (3) food and all beverages.

Participants/setting—172 women (25–29 years) who were enrolled in the DISC06 study.

Subjects who reported breast augmentation or reduction surgery or were pregnant or lactating within three months before breast density assessment were excluded.

Main outcome measures—ADBV and %DBV.

Statistical analyses performed—Multivariable linear mixed effects models were used. Final models were adjusted for race, smoking status, education, parity, duration of sex hormone use, whole body percent fat, childhood BMI z-score, and energy from beverages.

Results—After adjustment, each 1 kcal/g unit increase in food-only ED was associated with a 25.9% (95% confidence interval = 6.2 to 56.8%) increase in %DBV ($p=0.01$). Childhood BMI z-score modified the association between food-only ED and %DBV such that a significant positive association was observed only in women who were heavier as children. Food-only ED was not associated with ADBV in all women, but a borderline significant positive association was observed in women who had higher childhood BMI z-scores.

Conclusions—This is the first report to suggest a potential role for dietary ED in breast density; the effects of long-term exposure to high ED diets on breast cancer risk remain unknown.

Keywords

Premenopausal Women; Breast Density; Breast Cancer; Dietary Energy Density; Diet

INTRODUCTION

Breast density, quantified as the amount of fibroglandular tissue relative to total breast tissue, is one of the strongest risk factors for breast cancer. Women with high breast densities (greater than 75%) have a 4-fold increase in breast cancer risk¹. Consequently, breast density is considered by some to be an intermediate phenotype along the breast cancer continuum². Breast density is modifiable^{2–5} and diet may be a contributing factor^{6–8}. Most research to date regarding dietary influences on breast density has focused on single foods or nutrients^{7, 9–11}. Few studies have addressed the effects of overall diet on breast density, despite the fact that it may more aptly account for the complex interactions among foods consumed as components of diets^{12–14}.

Dietary energy density (ED) is a measure of diet quality that estimates the amount of energy per gram of food (kcal/g) consumed. Dietary ED can be calculated for food only, food and caloric beverages, and food and all beverages¹⁵. Diets high in water and fiber have lower ED due to relatively large total gram weights and proportionately less energy contributions to the diet. In contrast, diets high in fat have relatively higher ED. While the data remains somewhat mixed^{16, 17}, energy-dense diets have been positively associated with body weight in both children and adults¹⁸ and may be contributing to obesity-related chronic disease incidence. While there is no consensus on the most appropriate way to measure dietary ED¹⁹, a recent comprehensive review suggested that ED from food alone provides the most

robust associations and that including energy from caloric beverages as a covariate in models aids in accounting for caloric beverages without attenuating the ED value by the addition of large gram weights contributed by liquids²⁰. Food-only ED estimates have the strongest associations with weight status in both adults and children^{17, 21}.

Diet could potentially influence breast cancer risk through influences on breast density, but we are not aware of any studies that have evaluated the association of dietary ED with breast density. High ED diets are frequently high in fat, which has been positively associated with BD in some^{10, 22–25} but not all studies^{26, 27}. High ED diets also tend to be lower in fiber, which also could influence breast density^{23, 24}. Mechanisms underlying these associations are not fully understood, but dietary influences on hormones and growth factors could contribute^{28, 29}.

We used data from the Dietary Intervention Study in Children Follow-Up Study (DISC06) to test the hypothesis that low ED diets that are higher in fruits, vegetables, and lower in fat are inversely associated with percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) in young women. In previous analyses from this study, we observed a strong inverse association between childhood adiposity and breast density that was independent of adult adiposity³⁰. Therefore, in the current analysis, we evaluated effect modification of the association of ED with young adult BD by childhood BMI z-score.

METHODS

Design

The Dietary Intervention Study in Children (DISC) was a multicenter, randomized, controlled clinical trial sponsored by the National Heart, Lung, and Blood Institute and designed to test a dietary intervention intended to reduce low-density lipoprotein cholesterol levels (LDL-C) in children. Complete details regarding trial design and primary results have been described previously^{31–37}. Briefly, a total of 663 healthy, pre-pubertal, 8–10 year-old children with elevated LDL-C, including 301 girls, were recruited from six clinical centers between 1988–1990 and randomly assigned to a behavioral dietary intervention or usual-care control group. The intervention, which promoted a diet lower in total and saturated fat and higher in fiber, continued for a median of 7 years. In 2006–2008 when participants were 25 to 29 years old, the DISC06 Follow-Up Study was conducted to evaluate the longer-term effects of the diet intervention on biomarkers associated with breast cancer risk in DISC female participants. Assent was obtained from original DISC participants and informed consent was obtained from their parents or guardians prior to randomization. Informed consent was obtained again from participants prior to DISC06 follow-up visits. All DISC protocols were approved by Institutional Review Boards at the involved centers.

Participants

All 301 female DISC participants were invited to participate in the DISC06 Follow-Up Study and 260 attended data collection visits at one of the six DISC clinic sites in Baltimore, MD; Iowa City, IA; New Orleans, LA; Chicago, IL; Newark, NJ; and Portland, OR. Women who were pregnant or breastfeeding during or within 12 weeks before the follow-up visit

(n=30), as well as those who had breast augmentation or reduction surgery (n=16), were not eligible for the current analysis, leaving a total of 214 women. Of these, 38 had technically unacceptable or missing breast density or whole body percent fat measures, and four additional women were missing dietary assessments, resulting in a final analytical sample of 172 women.

Data Collection

All data for DISC06 were collected at a single visit at one of the six DISC clinics between 2006 and 2008. Visits were scheduled to take place in the luteal phase of the menstrual cycle whenever possible, and 85% of visits took place within 14 days of onset of next menses. During the visit, participants provided a fasting blood sample and completed questionnaires about demographics, medical and reproductive history, hormone use, health behaviors and family history of breast cancer. Height was measured at baseline DISC visits using a stadiometer and weight was measured on an electronic or beam balance scale. Each measurement was made twice on each participant. A third measurement was taken if the first two measurements were not within allowable tolerances (0.5 cm for height and 0.2 kg for weight) and the two closest values were averaged. Body mass index (BMI) was calculated as $\text{weight(kg)}/\text{height(m}^2\text{)}$ and expressed as a z-score relative to CDC 2000 Growth Charts³⁸ to account for changes in BMI with age in childhood and adolescence. Height and weight were measured at DISC06 follow-up visits using the same protocol; a young adult BMI <18.5 was considered underweight, 18.5–24.9 was considered normal weight, 25.0–29.9 was considered overweight, and a BMI >30 was considered obese¹⁶.

Total adiposity at DISC06 follow-up visits was characterized by percent whole body fat mass estimated by the ratio of whole body fat mass to whole body total mass measured by dual-energy X-ray absorptiometry (DXA) using clinical protocols as described previously³². Briefly, DXA scans were acquired at default scan speeds on Hologic (Hologic, Inc. Bedford, MA) and GE Lunar (General Electric/Lunar, Madison, WI) systems. All DXA image data were processed using the manufacturers' software at the University of California at San Francisco (UCSF) under the direction of one of the investigators. Different systems were cross-calibrated using a set of static calibration objects (phantoms) and equations derived by UCSF. Device-specific phantoms were scanned routinely throughout the course of the study to allow correction for any calibration drifts. To insure accuracy and uniformity of data acquisition, all DXA personnel at DISC clinical centers were trained by UCSF personnel. Additionally, a clinical center was not certified to recruit study participants until test data on 5 volunteers met UCSF's quality assurance standards.

Breast density was measured by non-contrast magnetic resonance imaging (MRI) as described previously³². Briefly, scanning was performed following a standard protocol using a whole-body 1.5 Tesla or higher field strength MRI scanner with a dedicated breast imaging radiofrequency coil. Images were obtained both with and without fat-suppression and in both the transaxial and coronal orientations. All MRI image data were processed at UCSF using customized software to identify the chest wall-breast tissue boundary and skin surface, and to separate breast fibroglandular and fatty tissue³⁹. Fat suppressed images were used except when incorrect or failed segmentation occurred due to poor fat-suppression. In

problematic cases, manual delineation was used. To insure accuracy and uniformity of data acquisition at the different clinical centers, MRI technologists at the sites were individually trained and acceptable image quality on 3 volunteers was required for site certification.

Total breast volume and ADBV, which reflects the amount of breast fibroglandular tissue, were computed separately for each breast. Percentage DBV was then calculated by dividing ADBV by total breast volume and multiplying by 100. Breast density measurements on left and right breasts are highly correlated^{40, 41}; in our sample, correlations for %BD and ADBV were both > 0.95. Therefore, results for the two breasts were averaged to provide single measures of %DBV and ADBV for each participant.

Diet was assessed by 3 24-hour dietary recalls collected over two weeks by trained interviewers using the Nutrition Data System for Research (NDS-R: 2007 University of Minnesota, Minneapolis, MN). The first was obtained in person at the clinic visit and two additional non-consecutive recalls were obtained by telephone over the following two weeks. Two recalls were collected on weekdays and one recall was collected on a weekend day. Ninety percent of DISC06 participants provided 3 recalls.

Dietary ED was calculated using three approaches. Average daily energy intakes (kcal) from food only, food and caloric beverages, and food and all beverages were calculated separately for each participant using NDS-R output data. Likewise, the average total respective amounts-consumed daily (g) were estimated. Each of the three measures of ED was then calculated as mean energy (kcal)/mean total amount (g).

STATISTICAL METHODS

Statistical Analyses

Percent DBV and ADBV were transformed to natural logarithms to approximate normality. To evaluate associations with dietary ED, linear mixed-effects models (SAS PROC MIXED) were fit by maximum likelihood with robust standard errors separately for the dependent variables %DBV and ADBV. For each of these breast density models, the three measures of dietary ED were entered as independent continuous variables in separate models. Clinic was included as a random effect and all other variables were included as fixed effects. Associations between each breast density measure and each dietary ED measure were first examined individually in unadjusted models. Subsequent models were adjusted for race (white vs. non-white), education (no college vs. attended college), whole body percent fat, parity, duration of sex hormone use (years), smoking status (current vs. never), and childhood BMI z-score. Energy from beverages alone was also added as a fixed effect in the food-only ED models. DISC treatment group, alcohol use (drinks/wk), and physical activity (met-min/wk) were not retained in final models because they were not significant confounders and did not contribute appreciably to the models. Effect modification by parity, smoking status, DISC treatment group, and baseline BMI z-score was assessed by testing the significance of their cross-product terms with the continuous dietary ED variables in separate multivariable adjusted models. Percentage differences in %DBV and ADBV associated with a 1 kcal/g unit increase of ED were calculated as $\% = (\exp(\beta) - 1) \times 100$. All statistical testing was conducted using two-sided tests, with

significance determined at $p < 0.05$. All data were analyzed using Statistical Analysis Software (version 9.3, 2011, SAS Institute Inc).

RESULTS

The majority of participants were non-Hispanic white (89.5%) with a median age of 27.1 years (interquartile range (IQR) = 26.5–27.8 years). Among all women the median BMI was 23.9 kg/m² (IQR = 21.1 to 28.2 kg/m²) with 25% of the sample categorized as overweight and 16% as obese. The median dietary EDs were 1.67 kcal/g (IQR = 1.46–2.06 kcal/g) for food only, 1.21 kcal/g (IQR = 1.05–1.44 kcal/g) for food and caloric beverages, and 0.66 kcal/g (IQR = 0.48–0.81 kcal/g) for food and all beverages. The median %DBV and ADBV were 24.9% (IQR = 11.1–42.5%) and 92.0 cc (IQR = 47.0–140.0 cc), respectively. Additional characteristics are described in Table 1.

In the adjusted analysis, a unit increase in food-only ED was associated significantly ($p = 0.01$) with a 25.9% increase in %DBV [95% confidence interval (CI) = 6.2 to 56.8%] (Table 2). The large shift in slopes between the unadjusted and adjusted models is due to the adjustment for total body fat; this adjustment accounts for over 50% of the variation in the model. Food-only ED, however, was not associated with ADBV in all women. Food-and-caloric-beverage ED and food-and-all-beverage ED were not associated with either %DBV or ADBV in all women.

Childhood BMI z-score modified the association of food-only ED with %DBV and ADBV (both $p_{\text{interaction}} < 0.01$) (Table 3). In analysis stratified by median childhood BMI z-score (0.2), food-only ED was significantly positively associated with %DBV only among participants who were heavier as children. Food-only ED also was borderline significantly associated positively with the ADBV in this group. None of the other variables evaluated modified associations of dietary ED with breast density measures.

DISCUSSION

In this first analysis of dietary ED and breast density in young premenopausal women, a significant positive association between food-only ED and %DBV was observed. Each 1 kcal/g unit increase of food-only ED corresponded with a 25.9% increase in %DBV.

Though the changes in the breast density measures observed with a one unit change in ED appear to be substantial, it is important to note that a one unit change in ED is not inconsequential. Because values for food-only ED ranged from 0.92 – 3.42 kcal/g, one kcal/g covers approximately 40 percent of the distance between the lowest and highest values, and a one unit change reflects distinctly different diets. For example, a representative DISC participant with a food-only ED of 1.40 kcal/g consumed 830.4 kcal/day (from food alone) and 594.4 g food as part of an overall diet that included 5.1 servings of fruits and vegetables and 9.0g of dietary fiber. In contrast, another DISC participant with a food-only ED of 2.60 kcal/g consumed a similar gram-amount of food but 1,443.5 kcal/d (from food alone), and only 1 serving of fruits and vegetables and 12.2g fiber.

In analyses stratified by the median BMI z-score at 8–10 years old, higher food-only ED was significantly positively associated with %DBV only in women who were heavier as children. Although only borderline significant, food-only ED was positively associated with ADBV, suggesting that it contributed to the significant positive association with %DBV. We previously reported significant inverse associations of BMI z-scores at 8–10 years old with %DBV and ADBV in this cohort of young women³⁰. Results of the current analysis further suggest that the long-term effects of childhood adiposity may alter effects of more recent exposures, including diet, on breast density.

In general, our results are consistent with those of other investigators who noted that the strongest association with dietary ED are observed with the food-only ED method¹⁸. However, this was not always the case, particularly in stratified analyses. Smaller sample sizes for these analyses may have contributed to discrepancies.

To our knowledge, this is the first study to examine and report the relationships between dietary ED and breast density. While they measure different aspects of the diet, dietary ED takes the entire diet into consideration, as opposed to single foods or nutrients, in a manner similar to dietary patterns and score-based assessments such as the Healthy Eating Index-2005⁴². While much of the research to date surrounding the contributions of dietary factors to breast density remains mixed, diet may be more influential in premenopausal than postmenopausal women^{6, 43, 44}. Breast tissue among premenopausal women is very dynamic because of changes that occur throughout the menstrual cycle and during pregnancy^{45–47}. It is thought to be more susceptible to dietary factors such as vitamin D, calcium, and alcohol at this time compared to the postmenopausal years^{6, 44, 48}.

Many studies have focused on the association between single nutrients and BD with only a small number evaluating the relationship between dietary patterns and BD in samples that included premenopausal women^{12, 14}. BD was inversely associated with consumption of diets higher in fruits, vegetables, and cereals, all of which may lower the overall ED of a diet, in an analysis of pre- and postmenopausal smokers¹⁴. A similar association was also observed in the subset of premenopausal women (including both smokers and non-smokers); however, it was only borderline significant ($p=0.09$)¹⁴. Fat and sugar both contribute to an increased overall dietary ED, and diets higher in fat and sugar were associated with increased %BD in a sample of both pre- and postmenopausal women¹².

Of the macronutrients, fat has the most influence on dietary ED, since it contributes a large amount of energy for a relatively small weight. At least four cross-sectional epidemiologic studies^{7, 10, 22, 23} with samples that included premenopausal women have examined relationships of dietary factors, including fat intake, to breast density. Three of these studies showed positive associations between dietary fat intake and %BD; although, only two reported results that reached statistical significance^{10, 23}.

Our study had several strengths. Participants were 25–29 years old, which is an under-represented age group in studies of diet and breast density. All data were collected by trained and certified individuals. Breast density was measured using MRI, which is more accurate than mammography particularly for dense breasts typical of young women⁴⁹. Diet

was assessed by three 24-hour diet recalls by trained interviewers. Dietary ED was calculated in several ways to capture the influence of all types of food and beverages on breast density measures. Data were available from the original DISC study on childhood BMI z-scores, which was an important predictor that modified the associations of food-only ED with %DBV and ADBV. Our study also had some weaknesses. In particular, because water consumption *per se* was not systematically ascertained as part of dietary recalls, our estimates of food-and-all-beverage ED are approximations. Additionally, participants were mostly non-Hispanic white women who had elevated LDL-C as children, which may limit generalizability of results to a larger population. Even so, data on the association of LDL-C with breast density are inconsistent^{50,51}. Furthermore, only 11 (6.4%) participants included in analyses had high LDL-C levels at follow-up visits based on National Cholesterol Education Program guidelines⁵², and none were using cholesterol lowering medications.

CONCLUSION

In summary, results of our study suggest that food-only ED is positively associated with %DBV in young women who were heavier as children. Additional research is needed to corroborate these findings, identify underlying mechanisms, and look further into the association between breast density and the nutrients that have the strongest influence on dietary ED, such as dietary fat and fiber.

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Table 1

Demographics of a Cohort of 172 Premenopausal Women Participating in the DISC06 Follow-Up Study

Characteristics	Median (IQR) *
Age at visit (y)	27.1 (26.5 – 27.8)
BMI (kg/m ²)	23.9 (21.1–28.2)
Whole body percent fat	34.8 (28.8 to 42.5)
Waist circumference (cm)	79.0 (73.6 – 90.8)
BMI z-score at baseline (8–10y)	0.19 (–0.47 – 0.97)
Duration of hormone use (y)	5.1 (1.9 – 8.0)
%DBV (%) ¹	24.9 (11.1 – 42.5)
ADBV (cc) ¹	92.0 (47.0 to 140.0)
Characteristics	%
Non-Hispanic white	89.5
Current smokers	23.8
Attended college	90.1
% Parous	26.2
Dietary Energy Density Method	Median (IQR) *
Food–Only (kcal/g)	1.67 (1.46 – 2.06)
Food + Caloric Beverages Only (kcal/g)	1.21 (1.05 – 1.44)
Food + All Beverages (kcal/g)	0.66 (0.48 – 0.81)

* IQR: Interquartile Range; %DBV: Percent Dense Breast Volume; ADBV: Absolute Dense Breast Volume

Table 2

Percent Difference (% Difference, (95% CI) in Breast Density Measures with Increasing Dietary Energy Density in a Cohort of 172 Premenopausal Women Participating in the DISC06 Follow-Up Study

Variable	% Difference (95% CI) [*] (n=172)	P-value	% Difference (95% CI) ^{**} (n=172)	P-value
% Dense Breast Volume (%DBV)				
Food-Only ED ^{***}	9.4% (−7.6 – 30.0%)	0.29	25.9% (6.2 – 56.8%)	0.01
Food + Caloric Beverages ED	23.4% (−18.3 – 86.7%)	0.31	21.3 % (−11.9 – 67.0%)	0.23
Food + All Beverages ED	−23.7% (−54.3 – 27.3%)	0.30	9.2% (−29.0 – 67.8%)	0.69
Absolute Dense Breast Volume (ADBV)				
Food-Only ED ^{***}	13.9% (−9.0 – 41.6%)	0.26	8.5% (−18.1 – 44.8%)	0.57
Food + Caloric Beverages ED	22.1% (−18.5 – 82.9%)	0.33	8.1% (−26.5 – 59.0%)	0.69
Food + All Beverages ED	4.1% (−36.1 – 70.8%)	0.86	−0.1% (−36.2 – 57.1%)	0.99

* Estimates from linear mixed-effects models including clinic as a random effect and dietary energy density as fixed effects.

** Estimates from linear mixed-effects models including clinic as a random effect and dietary energy density, race, smoking status, education, duration of hormone use, whole body percent fat, parity, and childhood BMI z-score as fixed effects.

*** Energy from beverages (kcal) was included as an additional fixed effect in the food-only ED models only.

Percent Difference (% Difference, (95% CI) in Breast Density Measures with Increasing Dietary Energy Density by Strata of Childhood BMI z-score in a Cohort of 172 Premenopausal Women Participating in the DISC06 Follow-Up Study

Table 3

	BMI z-score (n=86)	0.2 (low) % Difference (95% CI)	P- Value	BMI z-Score > 0.2 (high) (n=86) % Difference (95% CI)	P- Value	P-for interaction
% Dense Breast Volume (%DBV)						
Food-Only ED **	3.0%	(-21.3 to 33.6%)	0.84	82.2%	(27.1 to 158.6%)	0.0001
Food + Caloric Beverages	4.4%	(-26.2 to 47.9%)	0.81	42.4%	(-14.4 to 137.1%)	0.47
Food + All Beverages	-19.6%	(-36.1 to 1.2%)	0.06	65.8%	(14.8 to 222.7%)	0.01
Absolute Dense Breast Volume (ADBV)						
Food-Only ED **	2.0%	(-25.2 to 27.1%)	0.87	47.7%	(-6.8 to 136.3%)	0.008
Food + Caloric Beverages	-13.5%	(-40.8 to 26.3 %)	0.45	59.2%	(2.1 % to 148.3%)	0.21
Food + All Beverages	-20.0%	(-53.5 to 27.3%)	0.41	50.0%	(-28.3 to 214.1%)	0.13

* Estimates from linear mixed effects models including clinic as a random effect and dietary energy density, whole body percent fat, race, smoking status, duration of hormone use, and parity as fixed effects.

** Energy from beverages (kcal) was included as an additional fixed effect in the food-only ED models only.