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Association between dietary energy density and incident type 2 diabetes in the Women's Health Initiative

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Conflict-of-Interest Disclosure
Lawrence S. Phillips, MD, Atlanta VA Medical Center, Decatur, GA and Division of Endocrinology and Metabolism, Department of Medicine, Emory University School of Medicine, Atlanta, GA.
With regard to potential conflicts of interest, within the past several years, Dr. Phillips has served on Scientific Advisory Boards for Boehringer Ingelheim and Janssen, and has or had research support from Merck, Amylin, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, Abbvie, Glaxo SmithKline, Janssen, Vascular Pharmaceuticals, and the Cystic Fibrosis Foundation. In the past, he was a speaker for Novartis and Merck, but not for the last several years. These activities involve diabetes, but have nothing to do with this manuscript. Dr. Phillips is also cofounder of a company, Diasyst, Inc., which aims to develop and commercialize diabetes management programs.
No other authors declare a conflict of interest.

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Abstract

Background—Dietary energy density (DED), or energy available in relation to gram intake, may inform disease risk.

Objective—The objective of this study was to investigate the association between baseline DED and risk of incident type 2 diabetes in postmenopausal women.

Design—DED, weight status, and type 2 diabetes incidence were prospectively characterized in a large cohort of postmenopausal women participating in one or more clinical trials or an observational study.

Participants/Setting—The study involved 161,808 postmenopausal women recruited to the Women's Health Initiative (WHI) observational study or clinical trials at forty centers across the U.S. between 1993 and 1998.

Main Outcome Measures—The primary outcome was incident type 2 diabetes.

Statistical Analyses Performed—The association between DED quintiles and incident diabetes was tested using Cox proportional hazards regression.

Results—A total of 143,204 participants without self-reported diabetes at enrollment completed baseline dietary assessment and were followed for 12.7 ± 4.6 years. Risk of developing diabetes was 24% greater for women in the highest DED quintile compared with the lowest after adjusting for confounders (95% confidence interval: 1.17, 1.32). BMI and waist circumference mediated the relationship between DED and diabetes. In waist circumference-stratified analysis, women in DED quintiles 2–5 with waist circumferences >88 cm were at 9–12% greater risk of developing diabetes compared to women with waist circumference ≤ 88 cm.

Conclusions—In this prospective study, a higher baseline DED was associated with higher incidence of type 2 diabetes among postmenopausal women, both overall, and in women with elevated waist circumference.

Keywords

dietary energy density; type 2 diabetes; postmenopausal women; dietary behavior; diabetes prevention

INTRODUCTION/BACKGROUND

The prevalence of diabetes mellitus continues to increase, with tens of millions of new cases expected in the United States over the next two decades.[1] Adults 50 years and older comprise 65% of new diabetes cases in the U.S., the majority of which are type 2.[2] Effective prevention strategies are needed to address this major public health challenge. While the management of obesity is considered to be the leading approach to reducing risk of type 2 diabetes,[3] not all overweight or obese adults desire to lose weight or are motivated to attempt weight loss. Many may attempt weight loss, but find long-term adherence to an energy-restricted diet challenging. In the absence of weight loss, following a healthy dietary pattern may reduce diabetes risk,[4–7] and can help manage existing disease.[8]

To support weight control, individuals must have an understanding of dietary quality as well as portion size. Dietary energy density (DED), the ratio of energy (kcal) to food weight (g),[9] is an emerging approach to weight management in that it may provide a comprehensible and feasible approach to reduce energy intake. Specifically, foods can be defined as either low in energy density (e.g., vegetables, whole grains, beans) or high in energy density (e.g., sugar-sweetened beverages, fried foods, processed sweets). Several studies evaluating DED in relation to body weight in adults have shown that regular consumption of high DED foods predicts higher weight and waist circumference[10–13] and contributes to weight gain over time in normal weight and overweight adults.[11, 14] Probable mechanisms include low satiation and greater palatability of high DED foods,[15] which are characterized by their high fat content and glycemic load and low fiber content, thereby contributing to passive overconsumption and higher total energy intake.[16, 17]

While growing evidence suggests the effects of high DED diets on type 2 diabetes are largely mediated through body mass and body fat, it is possible that high DED diets also directly influence type 2 diabetes risk independently of weight and visceral adiposity. Limited epidemiological studies have assessed associations between DED of diets, type 2 diabetes, and other metabolic factors.[18, 19] Biological plausibility for these relationships has been derived from experimental studies in which participants consuming high DED meals experienced negative metabolic effects including decreased insulin sensitivity.[20] Two studies have prospectively investigated the relationship between DED and risk of type 2 diabetes within the same study population. A nested case-cohort study within the European Prospective Investigation into Cancer (EPIC) Study of 340,234 older European adults did not find a significant association between DED and risk of type 2 diabetes,[21] while a region-specific study involving participants of the Norfolk EPIC cohort (*n*=21,919) showed 20% higher risk of diabetes per unit increase in DED (HR, 1.2; 95% CI, 1.05–1.37).[22]

The Women's Health Initiative Study (WHI)[23] affords an opportunity to assess the relationship between DED and incident type 2 diabetes in a large, ethnically and racially diverse population of postmenopausal women. Given the limited evidence of the relationship between DED and type 2 diabetes, investigating factors associated with incident diabetes in older women should provide a better understanding of whether DED can be considered as a preventive target. The objective of this study was to investigate the association between baseline DED and risk of incident type 2 diabetes in the WHI. Given previous literature suggesting women with central adiposity may be at particularly high risk for incident diabetes,[24] the association between DED and incident type 2 diabetes among women with and without increased central adiposity as measured by waist circumference was also examined. The central hypothesis was that higher baseline DED would be associated with higher incidence of type 2 diabetes, both overall, and in women with increased central adiposity.

MATERIALS AND METHODS

Study Design, Setting, and Participants

Healthy postmenopausal women age 50 to 79 years old were enrolled in the WHI at one of forty clinical centers across the U.S. between 1993 and 1998. Recruitment methods have been described in detail elsewhere.[25] The study sample included 161,808 participants enrolled in the WHI Observational Study and in the three overlapping clinical trials (hormone therapy, dietary modification, and calcium plus vitamin D) prospectively followed for an average of 12 years or until earliest of treated type 2 diabetes, death, loss to follow-up, or end of study. Written informed consent was obtained from all study participants before study enrollment, and each of the trials was approved by the institutional review boards of the 40 participating institutions. Women excluded from the study included those with a history of diabetes at enrolment (*n*=9,618), incident diabetes within the first year of follow-up (*n*=589), or no follow-up data for the primary outcome of incident diabetes (*n*=823). Additional exclusion criteria were implausible energy intake of <600 or >5000 kcal from the food frequency questionnaire (*n*=4,374), or BMI <18.5 kg/m^2 (*n*=1,298) or >50 kg/m^2 (*n*=634), or missing (*n*=1,267). One individual was excluded for an extreme DED value. After these exclusions, the final study sample comprised 143,204 postmenopausal women.

Height, Weight, and Waist Circumference

Participants came to the study-designated clinical site at baseline to have weight, height, and waist circumferences measured by trained study personnel using standardized protocols and calibrated equipment.[26]

Type 2 Diabetes Outcomes Ascertainment

Type 2 diabetes was documented at baseline by self-report in which each woman was asked whether she had ever been told that she had "sugar diabetes" by her physician, with type 2 diabetes estimated by excluding participants who were diagnosed before 21 years of age. Incident diabetes during follow-up was documented by self-report at each semi-annual contact, when participants were asked, “Since the date given on the front of this form, has a doctor prescribed any of the following pills or treatments?” Choices included “pills for diabetes” and “insulin shots for diabetes.” A WHI diabetes confirmation study has demonstrated consistency between these medical inventories and incident and prevalent diabetes.[27]

Dietary Assessment

Energy, nutrient, and food weight estimations were based on the dietary intake reported by participants, documented using the validated semi-quantitative WHI food frequency questionnaire (FFQ).[28] FFQs were collected during the baseline screening and reviewed by study staff for completeness prior to data processing. Data entry and nutrient analysis was conducted using the Nutrition Data Systems for Research software.[29] Food groups were determined using The MyPyramid Equivalents Database 2.0, which are food group measures based on the USDA’s 2005 Food Guide Pyramid.[30]

Dietary Energy Density

The DED of a single food is defined as the ratio of its energy (kcal) content to its weight (g), and this ratio remains constant regardless of the amount consumed. There is no consensus on the optimal calculation of DED or what constitutes high or low DED. In general, foods with low or very low energy density - defined as those with energy density values between 0 and 1.5 kcal/g -- are those naturally containing a higher volume of water (e.g., vegetables, fruits, milk), while those of medium or high energy density - defined as those with energy density values >1.5 kcal/g - contain higher amounts of fats and sugar and less water by volume (e.g., meat, cheese, grains, nuts). Proposed methods of DED assessment primarily differ by the inclusion or exclusion of water and other beverages.[9] In this study, energy density for overall diet was calculated from food frequency data, by dividing daily energy intake (kcal) from foods (including solid foods and semi-solid or liquid foods such as soups) by the reported portion sizes and corresponding gram weights of these foods. Ledikwe et al., have shown that inclusion or exclusion of beverages can have a substantial effect on DED values and caution that this variability may influence associations between DED and other variables.[9] DED was calculated with systematic exclusion of all beverages.

Statistical Analysis

The relationships between food groups and macronutrients and DED were assessed by Pearson correlation. The association between quintiles of DED and incident type 2 diabetes was tested using Cox proportional hazards regression, which models incidence rate per unit of time, thereby generating hazard ratios (HR) and 95% confidence intervals (CI). Potential confounding variables selected from the literature or for which there was adequate mechanistic rationale were evaluated for inclusion in the adjusted models, including age, race/ethnicity, neighborhood socioeconomic status (a summary score of education and income by participant Census tract),[31] smoking pack-years (never smoker, <5, 5 to <20, ≥20 pack-years), physical activity (MET-hr/wk) from recreational physical activity, postmenopausal hormone therapy use (never, past, current), family history of diabetes, alcohol intake (<1 drink/week, 1 to <7 drinks/week, ≥ 7 drinks/week), hypertension, and clinical trial arm assignments. Body mass index and waist circumference were mediators of the relationship between DED and risk of diabetes, thus were not included in the adjusted models. Regression models were stratified by waist circumference (≤88 cm and >88 cm), a surrogate measure of visceral adiposity, which is an established risk factor for diabetes.[32] The likelihood ratio test was used to assess the significance of a potential DED-by-waist circumference interaction on diabetes risk.

RESULTS

Baseline demographic, dietary, medical history, and lifestyle characteristics of the 143,204 postmenopausal women in the sample were compared across quintiles of DED, which ranged from 0.46 to 3.94 kcal/g for DED without beverages (Table 1). Significant differences were observed for all characteristics across DED quintiles (p<0.001). Participants with lower DED were more often college graduates; had lower body weight, BMI, and waist circumference; were more physically active; considered themselves "never smokers"; consumed moderate amounts of alcohol; and less often reported being hypertensive compared to participants with higher DED. Lower DED was also associated with higher gram weight of food consumed, lower total energy intake, and lower animal protein, added sugar intake and glycemic load. (Table 1) Among food groups, DED was inversely associated with fruits, vegetables, legumes, soups, and dairy, and DED was positively associated with red meat, poultry, eggs, nuts, grains, pastries, and condiments (Supplementary Table). Among macronutrients, DED was inversely associated with vegetable protein and carbohydrate, and DED was positively associated with total protein, animal protein, alcohol, total fats and fatty acids (saturated, polyunsaturated, monounsaturated), and added sugars. (Supplementary Table)

A total of 143,203 participants completed baseline dietary assessment and were followed for an average of 12.7 years (standard deviation, 4.6 years). During this time period, 16,283 women reported incident diabetes (11.4%). During follow-up, women in the highest DED quintile were at 49% greater risk of developing diabetes compared to women reporting intake in the lowest quintile of DED, after adjusting for age, race/ethnicity, and neighborhood socioeconomic status (HR, 1.49; 95% CI 1.41–1.57) (Table 2, **Adjusted**[b]). While the risk of incident diabetes was somewhat attenuated after further adjusting for smoking, physical activity, postmenopausal hormone therapy use, family history of diabetes, alcohol intake, hypertension, and observational study or clinical trial arm and randomization, it remained significantly elevated (HR, 1.24; 95% CI 1.17–1.32). (Table 2, **Adjusted**[c])

In the stratified analysis based on waist circumference (≤ 88 cm or > 88 cm), women with a waist circumference >88 cm in DED across all quintiles were at greater risk of developing diabetes compared to women with a waist circumference ≤ 88 cm in the fully adjusted model (Table 3). The likelihood ratio test for a DED-by-waist circumference interaction on diabetes was not significant, p<0.57.

DISCUSSION

A positive association between DED and incident diabetes was found in this prospective study in a cohort of postmenopausal women. Diabetes risk was 24% higher in the highest DED quintile compared to the lowest in adjusted models. Previous epidemiological studies evaluating the relationship between DED and incident diabetes in adults have been limited in number[21, 22, 33] and conducted with participants at higher risk of type 2 diabetes[33] or participants of solely European-Caucasian origin[22]; however, these generally corroborate with the present study's results. Findings from the EPIC-Norfolk case-cohort study (n=21,919 adults age 40 to 79 years old in Norfolk, U.K.) suggested that higher DED (calculated using food plus beverages, excluding water) was associated with 60% higher risk of incident diabetes for participants in the highest quintile compared to the lowest (OR 1.60, 95% CI 1.19–2.16).[22] These findings were not directly comparable to the present study due to different methods of calculating DED. In another larger study which also involved EPIC study participants (n=340,234 men and women across 8 European countries),[21] DED was calculated to systematically exclude all beverages. This study found no association between the DED of foods and risk of incident type 2 diabetes; however, these disparate findings may be explained by participant differences. Compared to WHI participants, EPIC participants were 38% male, on average 10 years younger, had lower average BMIs, and exhibited different lifestyle behavioral patterns (more likely to smoke, be active, and eat vegetables and fruits).[34, 21]

The present study's findings with regard to stratification by waist circumference were not surprising, as the combined exposure to central adiposity and higher DED would be expected to increase diabetes risk more than either alone. While both adiposity and patterns of dietary intake have been associated with diabetes risk in older women,[24, 35–37] the present study was the first to characterize the relationship between high DED and diabetes risk in a large prospective cohort of postmenopausal women. While not explored in the context of this study, several mechanisms explaining the association of DED with type 2 diabetes risk have been posited. Data from experimental studies have suggested that individuals use food volume as an indicator of satiation and consume a roughly constant food volume each day; thus, consuming more energy-dense foods with the same volume may lead to overconsumption of energy.[16, 17] This hypothesis has been explored with epidemiological data, where several observational studies have demonstrated positive associations between DED and weight gain in adults.[10, 13, 14] Another potential mechanism by which high DED could impact diabetes risk is through the composition of the diet. In the present study, higher DED scores were associated with lower intake of plant protein, fruits and dairy, and higher consumption of total protein, animal protein, alcohol, total fats and fatty acids (particularly saturated and monounsaturated fatty acids), added sugars, and a higher dietary glycemic load. High saturated fat intake has been associated with impaired insulin sensitivity,[20] while high glycemic load diets rapidly increase blood glucose and postprandial free fatty acids,[38] thereby increasing inflammation and oxidative stress, which could further challenge the integrity of the beta cells and contribute to insulin resistance.[38, 39]

Strengths and Limitations

Study strengths included a large sample of ethnically and racially diverse postmenopausal women recruited across three clinical trials and an observational study. Further, the WHI cohort was followed for more than 12 years on average, providing a unique opportunity to prospectively evaluate the relationship between DED and incident type 2 diabetes in this population. Several limitations of the current study are related to calculation of DED, a relatively new metric. DED is the weighed energy density of individual food components that comprise the entire diet. In the present study, we chose to calculate DED excluding beverages. Beverages represent a unique challenge to DED calculations because they have substantially higher water content and lower energy density than most foods, which may disproportionately influence energy density values. However, calculating DED only as food ignores the contributions of energy-containing beverages – e.g., sugar-sweetened beverages - which affect energy density and total calories consumed, as well as potentially increasing risk of metabolic disease.[40] More research is needed to understand the impact of beverages (both caloric and non-caloric) in the calculation of DED. Another potential limitation related to DED is the gram weights underlying the calculations of energy density of each reported food. Weights for each of the foods listed in the WHI FFQ were constructed using the portion sizes on the WHI FFQ and the weight of these food line items in the Nutrition Data Systems for Research (NDS-R, version 2005) food and nutrient database. Notably, the cup weights may not fully account for water lost during cooking, thus, having the potential to influence food energy density, and overall DED.

Additionally, in general, use of FFQs results in underestimation of energy intake compared with 24-hour recalls or diet records,[41] particularly with regard to energy dense foods.[42] This phenomenon could bias DED estimates. In previous WHI studies that established biomarker-calibrated energy and protein intake adjustments, underestimation of energy intake was more likely to occur in overweight and obese women.[43] The calibration equations developed through previous work could not be applied to DED in the WHI, since these calibration data are not available for individual foods and only a limited number of nutrients (energy, protein, protein density, sodium, potassium, and sugars). Finally, the WHI is comprised of mostly healthy women with high educational attainment and low rates of smoking, making it more difficult to sort out independent associations of DED with type 2 diabetes risk.[34]

Conclusions

In summary, a higher baseline DED was prospectively associated with incident diabetes risk in postmenopausal women. Higher baseline DED was also associated with higher incidence of type 2 diabetes among women with elevated central adiposity. These findings provide support for consumption of lower DED diets for diabetes prevention in postmenopausal women, and warrant further research to examine the effect of DED on diabetes risk factors in other demographic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline dietary, medical history, and lifestyle characteristics of postmenopausal women participating in the Women's Health Initiative across quintiles of dietary energy density (mean ± standard deviation or percentage)

Dietary Energy Density (kcal/gram weight of food)[a]	**Overall (0.46–3.94)**	**Quintile 1 (0.46–1.16)**	**Quintile 2 (1.16–1.35)**	**Quintile 3 (1.35–1.52)**	**Quintile 4 (1.52–1.75)**	**Quintile 5 (1.75–3.94)**
Characteristics[***]	***n* = 143,204**	***n* = 28,641**	***n* = 28,641**	***n* = 28,641**	***n* = 28,641**	***n* = 28,640**
Age (years)	63.2 ± 7.2	64.4 ± 7.3	63.7 ± 7.2	63.2 ± 7.1	62.7 ± 7.1	61.7 ± 7.0
Race/ethnicity						
Non-Hispanic white	84.5	86.5	87.4	85.8	84.1	78.6
Black	7.76	5.27	5.15	6.65	8.26	13.5
Hispanic	3.63	3.12	2.95	3.37	3.83	4.88
Asian or Pacific Islander	2.41	3.33	2.78	2.46	2.14	1.34
American Indian or Alaskan Native	0.36	0.32	0.30	0.37	0.37	0.46
Other or unknown	1.36	1.49	1.40	1.33	1.30	1.26
Neighborhood socioeconomic status[b]	76.0 ± 8.4	77.1 ± 7.8	76.9 ± 7.8	76.3 ± 8.2	75.7 ± 8.4	74.1 ± 9.2
Weight (kg)	72.5 ± 14.8	68.3 ± 13.0	70.5 ± 13.7	72.6 ± 14.4	74.2 ± 15.0	77.1 ± 16.3
BMI (kg/m^2)	27.7 ± 5.4	26.2 ± 4.7	26.9 ± 5.0	27.6 ± 5.2	28.2 ± 5.4	29.3 ± 5.9
Waist circumference (cm)	85.8 ± 13.1	82.1 ± 11.9	84.0 ± 12.3	85.7 ± 12.7	87.2 ± 13.1	89.8 ± 13.9
Physical activity (MET-hr/wk)[c]	12.7 ± 13.8	18.2 ± 16.2	14.5 ± 13.8	12.3 ± 13.0	10.3 ± 12.0	7.76 ± 10.7
Smoking						
Never smoker	52.1	53.8	53.1	52.7	51.8	48.8
< 5 pack-years[d]	14.6	15.8	15.4	14.6	14.3	12.8
5 to < 20 pack-years	14.5	14.4	14.6	14.9	14.4	14.1
≥ 20 pack-years	18.9	16.0	16.9	17.8	19.5	24.3
Alcohol						
< 1 drink/wk	60.4	60.9	56.9	58.3	59.6	66.4
1 to < 7 drinks/wk	27.1	27.4	29.9	28.5	27.4	22.3
≥ 7 drinks/wk	12.5	11.7	13.2	13.2	13.0	11.4
Hypertension						
Never hypertensive	68.1	69.8	69.4	68.3	67.3	65.7
Untreated hypertensive	7.92	7.75	7.60	7.71	7.93	8.64

Dietary Energy Density (kcal/gram weight of food)[a]	Overall (0.46–3.94)	Quintile 1 (0.46–1.16)	Quintile 2 (1.16–1.35)	Quintile 3 (1.35–1.52)	Quintile 4 (1.52–1.75)	Quintile 5 (1.75–3.94)
Characteristics* **	***n* = 143,204**	***n* = 28,641**	***n* = 28,641**	***n* = 28,641**	***n* = 28,641**	***n* = 28,640**
Treated hypertensive	24.0	22.5	23.1	24.0	24.8	25.6
Family history of diabetes						
No	65.1	67.0	66.7	65.7	64.2	61.9
Yes	30.5	29.0	29.4	30.2	31.4	32.4
Don't know	4.44	3.96	3.85	4.14	4.49	5.74
Hormone therapy use						
Never	32.5	31.8	30.9	31.2	32.6	35.8
Past	22.9	22.8	22.6	22.9	22.8	23.6
Current	44.6	45.4	46.5	46.0	44.6	40.6
Dietary intake						
Total energy (kcal/d)	1449 ± 591	1178 ± 402	1350 ± 482	1445 ± 541	1550 ± 609	1723 ± 723
Total weight dietary intake (g/d)	1014 ± 390	1164 ± 384	1075 ± 382	1009 ± 377	953 ± 374	868 ± 364
Total protein (g/d)	62.2 ± 26.4	53.8 ± 20.9	60.5 ± 23.8	63.3 ± 25.8	65.7 ± 27.9	67.5 ± 30.5
Animal protein (g/d)	43.0 ± 21.2	34.6 ± 16.7	41.2 ±18.7	44.2 ± 20.4	46.7 ± 22.1	48.3 ± 24.6
Plant protein (g/d)	19.2 ± 8.5	19.2 ± 8.2	19.3 ± 8.2	19.1 ± 8.3	19.0 ± 8.6	19.2 ± 9.2
Carbohydrates (g/d)	174.4 ± 70.8	174.1 ± 63.2	176.1 ± 67.4	173.5 ± 69.7	173.0 ± 73.1	175.5 ± 79.3
Total fat (g/d)	59.0 ± 31.7	33.8 ± 14.5	48.4 ± 19.5	58.4 ± 23.7	68.7 ± 28.6	85.6 ± 38.6
Saturated fat (g/d)	19.4 ± 11.2	10.6 ± 5.0	15.7 ± 6.9	19.2 ± 8.5	22.8 ± 10.3	28.7 ± 13.9
Polyunsaturated fat (g/d)	12.4 ± 6.9	7.7 ± 3.5	10.4 ± 4.6	12.2 ± 5.4	14.2 ± 6.5	17.6 ± 8.8
Monounsaturated fat (g/d)	22.4 ± 12.3	12.5 ± 5.7	18.3 ± 7.6	22.2 ± 9.2	26.3 ± 11.1	32.9 ± 14.9
Added sugar (g/d)	40.8 ± 23.9	33.0 ± 18.1	38.2 ± 20.6	40.4 ± 22.1	43.5 ± 24.4	49.2 ± 29.6
Glycemic load (based on total carb.)	92.7 ± 38.8	87.7 ± 33.1	91.8 ± 35.9	92.3 ± 37.9	94.0 ± 40.3	97.9 ± 45.0
Energy density (kcal/g)	1.46 ± 0.36	1.02 ± 0.11	1.26 ± 0.05	1.43 ± 0.05	1.63 ± 0.06	2.00 ± 0.23
Hormone therapy trial arm						
Estrogen-alone intervention	3.13	2.63	2.65	2.89	3.30	4.20
Estrogen-alone control	3.18	2.59	2.66	2.87	3.44	4.37
Estrogen + progesterone intervention	5.29	4.65	5.27	5.14	5.27	6.13
Estrogen + progesterone control	5.03	4.60	4.79	4.75	5.28	5.72
Not randomized	83.4	85.5	84.6	84.3	82.7	79.6

Dietary Energy Density (kcal/gram weight of food)[a]	Overall (0.46–3.94)	Quintile 1 (0.46–1.16)	Quintile 2 (1.16–1.35)	Quintile 3 (1.35–1.52)	Quintile 4 (1.52–1.75)	Quintile 5 (1.75–3.94)
Characteristics[***]	***n* = 143,204**	***n* = 28,641**	***n* = 28,641**	***n* = 28,641**	***n* = 28,641**	***n* = 28,640**
Dietary modification trial arm						
Intervention	12.5	2.46	8.68	14.4	18.2	18.8
Control	18.7	3.65	13.2	21.7	26.8	28.3
Not randomized	68.8	93.9	78.1	63.9	54.9	53.0
Calcium-vitamin D trial arm						
Intervention	11.5	5.56	9.25	12.6	14.4	15.8
Control	11.5	5.56	9.38	12.4	14.8	15.3
Not randomized	77.0	88.9	81.4	75.0	80.8	69.0
Observational study only	57.2	80.3	65.9	53.5	44.9	41.3

[a] Apparent overlap in DED quintiles is due to rounding at the 4th decimal place

[b] **neighborhood socioeconomic status** is a summary score used to indicate both education and income of a participant's Census tract, where a higher score indicates greater educational attainment and/or income

[c] **MET-hr/week** = metabolic equivalent/week

[d] A **pack-year** is the amount of packs smoked daily for a period of one year; e.g., 1 pack-year = 1 pack per day, for one year

[***] All characteristics were significantly different across DED quintiles (chi-square tests for categorical variables and ANVOA for continuous variables, $p<0.001$)

Table 2

Association between dietary energy density (DED) and incident type 2 diabetes in postmenopausal women participating in the Women's Health Initiative

DED quintile	*n* cases of diabetes (%)	Rate[a]	Crude Hazard Ratio (95% CI)	Adjusted[b] Hazard Ratio (95% CI)	Adjusted[c] Hazard Ratio (95% CI)
1	2571 (8.98)	7.0	1.00	1.00	1.00
2	3004 (10.5)	8.1	1.15 (1.09–1.21)	1.14 (1.07–1.20)	1.08 (1.02–1.15)
3	3203 (11.2)	8.7	1.23 (1.16–1.29)	1.22 (1.16–1.29)	1.13 (1.07–1.20)
4	3461 (12.1)	9.5	1.35 (1.28–1.42)	1.30 (1.23–1.37)	1.15 (1.08–1.22)
5	4044 (14.1)	11.5	1.64 (1.56–1.73)	1.49 (1.41–1.57)	1.24 (1.17–1.32)
P_{trend}			< 0.001	< 0.001	< 0.001

[a] Crude rate per 1000 woman-years

[b] Adjusted for age, race/ethnicity (non-Hispanic white, black, Hispanic, Asian, Native American, other/unknown), and neighborhood socioeconomic status

[c] Further adjusted for smoking pack-years (never smoker, < 5 pack-years, 5 to < 20 pack-years, ≥ 20 pack-years), where 1 pack-year = 1 pack per day for one year, physical activity, hormone therapy use, family history of diabetes, alcohol use, hypertension, and observational study or clinical trial arm(s)

Table 3

Association between dietary energy density (DED) and incident type 2 diabetes in postmenopausal women participating in the Women's Health Initiative, stratified by waist circumference

DED quintile	≤ 88 cm waist circumference			> 88 cm waist circumference		
	n **cases of diabetes (%)**	**Hazard Ratio (95% CI)[a]**	***P***	***n*** **cases (%)**	**Hazard Ratio (95% CI)[a]**	***P***
1	1131 (6.56)	1.00		948 (15.8)	1.00	
2	1090 (6.85)	1.02 (0.94–1.11)	0.676	1307 (17.8)	1.09 (1.01–1.19)	0.037
3	1053 (7.21)	1.05 (0.96–1.15)	0.257	1567 (18.4)	1.09 (1.01–1.19)	0.034
4	954 (7.17)	1.03 (0.94–1.12)	0.593	1794 (18.7)	1.09 (1.00–1.18)	0.045
5	878 (7.76)	1.08 (0.98–1.19)	0.113	2318 (20.1)	1.12 (1.03–1.22)	0.006
P_{trend}			0.148			0.029

[a]Adjusted for age, race/ethnicity (non-Hispanic white, black, Hispanic, Asian, Native American, other/unknown), neighborhood socioeconomic status, smoking pack-years (never smoker, < 5 pack-years, 5 to < 20 pack-years, ≥ 20 pack-years), where 1 pack-year = 1 pack per day, for one year, physical activity, hormone therapy use, family history of diabetes, alcohol use, hypertension, and observational study or clinical trial arm(s)