ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Eating Behavior and Qualitative Assessments

Associations of Number of Daily Eating Occasions with Type 2 Diabetes Risk in the Women's Health Initiative Dietary Modification Trial

Marian L Neuhouser,[1] Betsy C Wertheim,[2] Martine M Perrigue,[3] Melanie Hingle,[4] Lesley F Tinker,[5] James M Shikany,[6] Karen C Johnson,[7] Molly E Waring,[8] Rebecca A Seguin-Fowler,[9] Mara Z Vitolins,[10] Eliezer Schnall,[11] Linda Snetselaar,[12] and Cynthia Thomson[13]

[1]Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [2]University of Arizona Cancer Center, Tucson, AZ, USA; [3]Department of Nutrition and Exercise Physiology, Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, USA; [4]Department of Nutritional Sciences, College of Agriculture & Life Sciences, The University of Arizona, Tucson, AZ, USA; [5]Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [6]Division of Preventive Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [7]University of Tennessee Health Science Center, Department of Preventive Medicine, Memphis, TN, USA; [8]Department of Allied Health Sciences, University of Connecticut, Storrs, CT, USA; [9]Department of Nutrition and Life Science, Texas A&M University, College Station, TX, USA; [10]Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA; [11]Psychology Department, Yeshiva University, New York, NY, USA; [12]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA; and [13] Canyon Ranch Center for Prevention & Health Promotion, Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

ABSTRACT

Background: Over 23 million Americans have type 2 diabetes (T2D). Eating habits such as breakfast consumption, time-restricted eating, and limiting daily eating occasions have been explored as behaviors for reducing T2D risk, but prior evidence is inconclusive.

Objectives: Our objectives were to examine associations between number of daily eating occasions and T2D risk in the Women's Health Initiative Dietary Modification Trial (WHI-DM) and whether associations vary by BMI, age, or race/ethnicity.

Methods: Participants were postmenopausal women in the WHI-DM who comprised a 4.6% subsample completing 24-h dietary recalls (24HRs) at years 3 and 6 as part of trial adherence activities ($n = 2159$). Numbers of eating occasions per day were obtained from the year 3 24HRs, and participants were grouped into approximate tertiles as 1–3 ($n = 795$), 4 ($n = 713$), and ≥5 ($n = 651$) daily eating occasions as the exposure. Incident diabetes was self-reported on semiannual questionnaires as the outcome.

Results: Approximately 15% (15.4%, $n = 332$) of the WHI-DM 24HR cohort reported incident diabetes at follow-up. Cox proportional hazards regression tested associations of eating occasions with T2D adjusted for neighborhood socioeconomic status, BMI, waist circumference, race/ethnicity, family history of T2D, recreational physical activity, Healthy Eating Index-2005, 24HR energy intake, and WHI-DM arm. Compared with women reporting 1–3 meals/d, those consuming 4 meals/d had a T2D HR = 1.38 (95% CI: 1.03, 1.84) without further increases in risk for ≥5 meals/d. In stratified analyses, associations for 4 meals/d compared with 1–3 meals/d were stronger in women with BMI <30.0 kg/m^2 (HR = 1.55; 95% CI: 1.00, 2.39) and women aged ≥60 (HR = 1.61; 95% CI: 1.11, 2.33).

Conclusions: Four meals per day compared with 1–3 meals/d was associated with increased risk of T2D in postmenopausal women, but no dose–response effect was observed for additional eating occasions. Further studies are needed to understand eating occasions in relation to T2D risk. *Curr Dev Nutr* 2020;4:nzaa126.

Keywords: eating frequency, 24-hour recall, type 2 diabetes, postmenopausal women, cohort

Manuscript received January 2, 2020. Initial review completed April 15, 2020. Revision accepted July 16, 2020. Published online July 21, 2020.
This work was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, and US Department of Health and Human Services (contract numbers HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C).
WHI data collections tools, data dictionary, the protocol, and instructions for data use requests are available at www.whi.org.
Author disclosures: The authors report no conflicts of interest.

Address correspondence to MLN (e-mail: mneuhous@fredhutch.org).

Abbreviations used: DGA, Dietary Guidelines for Americans; DPP, Diabetes Prevention Program; HEI, Healthy Eating Index; NDS, Nutrition Data Systems; NSES, neighborhood socioeconomic status; T2D, type 2 diabetes; WHI, Women's Health Initiative; WHI-DM, Women's Health Initiative Dietary Modification Trial; 24HR, 24-h recall.

Introduction

The prevalence of type 2 diabetes mellitus (T2D) is very high in the United States (1), and is projected to nearly triple over the coming decades (2). According to the CDC, >23 million Americans have T2D, which is the seventh leading cause of death in the United States (1). T2D is a serious public health problem due to the associated significant comorbidities and medical complications. In 2017, expenditures for T2D and related complications were estimated at $327 billion dollars (3, 4).

T2D is a preventable disease. Genetic susceptibility influences the risk of T2D, but modifiable lifestyle habits such as body weight, diet, and physical activity are equally, if not more important risk factors (5–7). The Diabetes Prevention Program (DPP) clinical trial demonstrated that individuals at increased risk of T2D who were randomly assigned to an energy- and fat-restricted dietary intervention reduced T2D incidence by >50% compared with controls (8, 9). Further, the Look AHEAD study demonstrated that an intensive weight loss/lifestyle intervention was associated with continuous sustained partial or complete remission of T2D for ≤4 y (10). Other diet-modification approaches include consumption of heathy dietary patterns (6) and reducing dietary glycemic load (11, 12).

Eating behaviors such as regular breakfast consumption, time-restricted eating (eating only during specific hours of the day), and the number of daily eating occasions have emerged as potential, but not confirmed, independent factors influencing T2D risk (13–16). There is no consensus as to whether eating frequency increases or decreases risk, independent of associations with weight management. Chronic exposure to hyperglycemia, which could occur with more frequent eating episodes, damages pancreatic β-cell function leading to impaired glucose regulation and increased T2D risk (17). The scientific and clinical dilemma is whether mildly elevated glucose throughout the day that accompanies frequent eating is more (or less) detrimental with regard to T2D risk compared with larger glucose oscillations that occur following sizeable but less frequent meals (14, 18–22). Research examining total eating occasions as an independent and modifiable risk factor for T2D could help address this question. Therefore, our objective was to evaluate the relation between the number of daily eating occasions and T2D risk in the Women's Health Initiative Dietary Modification Clinical Trial (WHI-DM) and whether these associations varied by participant characteristics such as BMI, age, or race/ethnicity. We hypothesized that eating more times throughout the day would be associated with increased risk of T2D.

Methods

The design, recruitment, and data collection methods of the WHI-DM have been previously described (23, 24). Briefly, from 1993 to 1998, 48,835 postmenopausal women from 40 US clinical centers were randomly assigned to a low-fat dietary pattern (n = 19,541; 40%) or to a comparison/usual diet group (n = 29,294; 60%) using a permuted block algorithm with blocks of size 5, 10, or 15 and stratified by clinical center and baseline age group (50–54 y, 55–59 y, 60–69 y, and 70–79 y). The intervention was a behavioral modification program designed to lower fat intake to 20% of total energy and to increase fruit and vegetable and grain servings to ≥5 and ≥6 servings per day, respectively. Neither energy intake restrictions nor weight loss goals were intervention components. The primary trial outcomes were breast and colorectal cancer, and a secondary outcome was coronary heart disease. Although T2D was not a designated primary or secondary outcome, the low-fat/high–fruit-and-vegetable diet intervention did not increase the risk for T2D and might have slowed progression (T2D was not an exclusion for WHI-DM participation) (25, 26). The WHI-DM protocol and all procedures were approved by the institutional review boards at each of the 40 clinical centers and at the WHI Clinical Coordinating Center. All women signed written informed consent. WHI is registered at clinicaltrials.gov as NCT00000611.

WHI-DM participants attended baseline clinic visits where standardized questionnaires on personal and family medical history of major chronic diseases, current and past smoking history, recreational physical activity (usual frequency and duration of recreational physical activity such as walking, biking and computed as metabolic equivalent (MET) h/wk) (27), self-reported race/ethnicity, education (categorical with options ranging from less than high school completion to advanced and professional degrees), income (categorical), and other demographic and lifestyle characteristics were completed as part of the WHI protocol (24). Clinic staff measured waist circumference, height, and weight using standardized study protocols, and BMI was computed as weight/height^2 (kg/m^2).

Dietary assessment

Dietary intake for the WHI-DM was monitored primarily by an FFQ designed for the WHI (28). The FFQ was administered to all participants during screening (baseline), 1 y after randomization, and thereafter annually to one-third of the participants on a rotating basis. Baseline dietary data examined for this analysis included daily intake of energy, added sugars, total sugars, and computed scores on the Healthy Eating Index 2005 (HEI-2005), which measures adherence to the Dietary Guidelines for Americans (DGA) (29). HEI-2005 is on a scale of 1–100, where a higher score reflects greater adherence to DGA. The WHI-DM also included a 4.6% subsample of participants who provided one 24-h dietary recall (24HR) at both years 3 and 6 (but not at WHI-DM enrollment/baseline) as part of trial adherence activities. The year 3 24HRs are used in the analysis in this report to create a measure of eating frequency, because FFQs lack data on meal composition and meal timing. Selection to the WHI 24HR cohort was achieved using sampling stratified on clinic, age, and race/ethnicity. Women from racial/ethnic minority groups were oversampled for the 24HR cohort because the WHI scientific goals included having the statistical power for racial/ethnic-specific analyses of trial response (23, 24). The 24HRs were collected by trained interviewers who used the USDA multiple pass method (30) and the Nutrition Data Systems (NDS) software (Nutrition Coordinating Center, University of Minnesota). Quality assurance was performed, and 10% of all 24HR records were reviewed by a registered dietitian supervisor.

The 24HR data are well suited for studying meal timing and the number of daily meals because discrete eating occasions and time of consumption are collected as part of the recall record. The 24HR protocol included collection of all meals and snacks for foods and beverages consumed the previous day. The number of daily eating occasions was calculated by summing the number of distinct occasions recorded in the recall record as the variable MEALNAME in NDS: Breakfast, Lunch, Dinner, Snack(s). For this analysis, eating occasions were defined in 30-min increments such that 30 min between recorded eating episodes was recorded as a new eating event. Participants were grouped into approximate tertiles according to their eating occasion totals: 1–3/d, 4/d, and ≥5/d.

Outcomes

Prevalent diabetes was documented by self-report at the WHI baseline visit by asking each participant if she had ever been told by a

TABLE 1 Baseline characteristics of participants in the Women's Health Initiative Dietary Modification Trial with available 24-h dietary recall data at year 3, by number of eating occasions per day ($n = 2159$)[1]

Characteristic	Number of eating occasions per day		
	1–3 ($n = 795$)	4 ($n = 713$)	5+ ($n = 651$)
Demographics			
Age, y	62.6 ± 6.7	62.0 ± 6.8	60.4 ± 6.5
NSES	73.1 ± 10.5	74.6 ± 9.3	75.2 ± 8.8
Race/ethnicity			
Non-Hispanic white	420 (52.8)	434 (60.9)	428 (65.8)
Black	220 (27.7)	145 (20.3)	91 (14.0)
Hispanic	72 (9.06)	53 (7.43)	50 (7.68)
Asian/Pacific Islander	48 (6.04)	47 (6.59)	60 (9.22)
Other/unknown	35 (4.40)	34 (4.77)	22 (3.38)
Anthropometry			
Weight, kg	78.0 ± 17.5	75.0 ± 15.1	74.3 ± 16.0
BMI, kg/m^2	29.8 ± 6.3	28.6 ± 5.2	28.3 ± 5.4
Waist circumference, cm	89.7 ± 13.8	87.7 ± 12.6	86.4 ± 12.9
Physical activity, MET-h/wk	10.2 ± 13.1	9.7 ± 10.8	10.6 ± 12.7
Current smoking (yes)	47 (6.0)	44 (6.3)	42 (6.5)
Family history of type 2 diabetes	277 (37.4)	247 (36.5)	242 (38.9)
Dietary intake[2]			
Energy, kcal/d	1753 ± 731	1772 ± 693	1831 ± 723
Total sugar, g/d	94.0 ± 45.7	96.2 ± 44.5	98.1 ± 45.3
Added sugar, g/d	51.8 ± 35.3	51.2 ± 31.1	53.6 ± 33.5
Diet quality (HEI-2005)	63.2 ± 10.3	64.1 ± 10.3	64.0 ± 9.5
Energy from 24-h recall, kcal	1431 ± 495	1568 ± 523	1648 ± 510

[1]Values are given as mean ± SD or *n* (%). HEI-2005, Healthy Eating Index 2005; MET-h/wk, metabolic equivalent hours per week; NSES, neighborhood socioeconomic status.
[2]Baseline intake assessed by FFQ.

physician that she had "sugar diabetes" when not pregnant. Incident T2D 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?" Response options included "pills for diabetes" and "insulin shots for diabetes." The self-report for these medications was previously shown to be very consistent with medication inventories (31, 32). During the trial period follow-up through 2005, 18.6% of all WHI-DM participants were diagnosed with T2D. For this analysis we excluded those with either any reported T2D prior to the cohort entry time at WHI-DM year 3 as well as those diagnosed within the first 3 y of follow-up.

Statistical analysis

The 24HR cohort began recalls in year 3 (WHI-DM baseline and year 1 used four-day food records for adherence and retention activities), so the 24HR cohort ($n = 2460$) entry date was designated as WHI-DM year 3. Exclusions for analysis included 24HR energy intake <600 kcal or >5000 kcal ($n = 49$)—because these were considered unreliable intakes—baseline history of self-reported diabetes ($n = 142$), incident diabetes between recall cohort start date and 12 mo later ($n = 91$), and loss to follow-up ($n = 19$), leaving $n = 2159$ for analysis. Missing data for covariates were all <1% with the exception of neighborhood socioeconomic status (NSES; $n = 201$; 9.3%) and recreational physical activity ($n = 255$; 11.8%). Participants with missing data drop out of multivariate adjusted models.

Cox proportional hazards regression was used to examine the relation across the tertiles of eating occasions and risk of T2D. A priori subgroup analyses examined these associations stratified by baseline BMI (<30.0/≥30.0), race/ethnicity, and age. The WHI-DM was one of the first dietary intervention trials to have specific minority recruitment goals as well as goals to achieve a broad distribution across the range of the postmenopausal years (33). This heterogeneity has enabled many subgroup analyses not possible without this heterogeneity (see, e.g., references 34–36) and supports the a priori subgroups for this analysis. All models were adjusted for NSES (37), race/ethnicity, BMI, waist circumference, recreational physical activity, family history of diabetes, self-reported energy intake from the 24HR, time between study enrollment and recall administration, HEI-2005, and WHI trial arm assignment. Models are intended to be parsimonious to avoid overfitting; therefore, variables without evidence of confounding in this study sample, such as smoking, were not included. All tests were 2-sided and $P < 0.05$ was considered statistically significant. Statistical analyses were conducted in Stata (StataCorp LLC).

Results

The characteristics of the study sample by tertiles of eating occasions are presented in **Table 1**. Approximately 15% (15.4%, $n = 332$) of the sample reported incident diabetes after the start of the recall cohort. Compared with the referent (1–3 eating occasions per day), women reporting 4 daily eating occasions had a multivariate-adjusted diabetes HR = 1.38 (95% CI: 1.03, 1.84) (**Table 2**). In women reporting ≥5 eating occasions per day the multivariate-adjusted HR was attenuated and not statistically significant (HR = 0.95; 95% CI: 0.70, 1.29).

TABLE 2 Associations of daily eating occasions with incident diabetes in the Women's Health Initiative Dietary Modification Trial

Eating frequency	*n* events/total (%)	Model 1 HR (95% CI)[1]	Model 2 HR (95% CI)[2]
1–3 times/d	117/795 (14.7)	1.0 (ref)	1.0 (ref)
4 times/d	129/713 (18.1)	1.18 (0.92, 1.51)	1.38 (1.03, 1.84)
5+ times/d[3]	86/651 (13.2)	0.80 (0.61, 1.06)	0.95 (0.70, 1.29)

[1]Model 1 adjusted for age.
[2]Model 2 adjusted for age, neighborhood socioeconomic status, race/ethnicity, BMI, waist circumference, energy intake from 24-h recall, family history of type 2 diabetes, physical activity, Healthy Eating Index 2005, time between baseline and 24-h recall, and Women's Health Initiative clinical trial arm(s).
[3]Range 5–10 times/d.

We next examined whether BMI, race/ethnicity, or age influenced the eating occasions–diabetes risk associations in stratified analyses (**Table 3**). Women with BMI <30 who reported 4 eating occasions per day had a significantly increased risk of diabetes (HR = 1.55; 95% CI: 1.00, 2.39) compared with those reporting 1–3 meals/d. However, in women with BMI ≥30 the number of daily eating occasions had no apparent relation to diabetes risk. Older (≥60 y), but not younger, women who reported 4 eating occasions per day had nearly a 60% greater risk of diabetes (HR = 1. 61; 95% CI: 1.11, 2.33) compared with those reporting 1–3 eating occasions per day. Associations of eating occasions with T2D risk did not differ by race/ethnicity.

Discussion

In the WHI-DM, participants who reported 4 daily eating occasions had a 36% increased risk of incident diabetes compared with those reporting 1–3 daily eating occasions. These associations were stronger in women with BMI <30 or in women aged ≥60 y. No additional increase in risk was found for higher daily eating occasions (≥5/d) and no dose–response association was detected. We are not certain why the results became attenuated and null for >5 eating occasions per day and we cannot rule out chance as a reason for any of the findings. It is possible that the participants with >5 eating occasions per day represent a heterogeneous phenotype because the range of eating occasions in this tertile was 5–10. Combining into a single group could have masked other characteristics that we are unable to discern at this time.

The hypothesis for this study was based on the following biological rationale. Eating multiple times throughout the day keeps blood glucose and insulin at mildly elevated concentrations but with lower peaks and troughs, effectively demonstrated by Munsters and Saris (38). Importantly, insulin resistance, which is known to escalate with age (39, 40), can increase the irregularity in circulating glucose, supporting our finding in women aged >60 y. Further, a constant postprandial state that accompanies multiple eating occasions places excess stress on the pancreas while continued insulin secretion prevents the secretion of counterregulatory hormones. Animal models consistently demonstrate metabolic advantage and reduced metabolic stress in mice consuming kilocalorie-controlled and time-controlled eating (41). Recent studies of intermittent fasting in humans suggest that meal restriction can benefit metabolic health and diabetes risk (22, 42–44). In contrast, other research findings have reported metabolic advantages with more, not less, frequent eating. Jenkins et al. (45) conducted a randomized crossover trial in 17 overweight men. Participants in one arm consumed provided foods on an outpatient basis 3 times daily (termed the "meals" phase). On the other arm, the same foods were divided into 17 energy- and macronutrient-equivalent portions and participants were instructed to consume 1 food packet per hour (termed the "nibbling" phase). Serum insulin and C-peptide were substantially and significantly lower following the nibbling phase compared with the meals phase. Heden et al. (21)

TABLE 3 Associations of daily eating occasions with incident diabetes in the Women's Health Initiative Dietary Modification Trial, stratified by BMI, race/ethnicity, and age[1]

Eating frequency	*n* events/total (%)	HR (95% CI)	*n* events/total (%)	HR (95% CI)
	BMI <30		BMI ≥30	
1–3 times/d	43/461 (9.33)	1.0 (ref)	74/331 (22.4)	1.0 (ref)
4 times/d	71/460 (15.4)	1.55 (1.00, 2.39)	58/251 (23.1)	1.14 (0.76, 1.69)
5+ times/d[2]	42/428 (9.81)	0.80 (0.47, 1.34)	44/222 (19.8)	0.72 (0.45, 1.14)
	Non-Hispanic white		All other races/ethnicities	
1–3 times/d	50/420 (11.9)	1.0 (ref)	67/375 (17.9)	1.0 (ref)
4 times/d	66/434 (15.2)	1.45 (0.95, 2.21)	63/279 (22.6)	1.26 (0.85, 1.89)
5+ times/d[2]	47/428 (11.0)	0.71 (0.43, 1.15)	39/223 (17.5)	0.86 (0.52, 1.41)
	Age <60 y		Age ≥60 y	
1–3 times/d	49/268 (18.3)	1.0 (ref)	68/527 (12.9)	1.0 (ref)
4 times/d	46/268 (17.2)	1.13 (0.71, 1.82)	83/445 (18.7)	1.61 (1.11, 2.33)
5+ times/d[2]	45/319 (14.1)	1.06 (0.48, 1.32)	41/332 (12.4)	0.77 (0.47, 1.24)

[1]Models are adjusted for age, neighborhood socioeconomic status, race/ethnicity, waist circumference, physical activity, family history of type 2 diabetes, Healthy Eating Index 2005, energy intake from 24-h recall, time between baseline and 24-h recall, and clinical trial arm(s). BMI (kg/m^2) <30 combines normal and overweight; BMI ≥30.0 is obese.
[2]Range 5–10 times/d.

reported that the incremental AUC for insulin was significantly larger following a 3 meal per day experimental condition in 8 obese women compared to a 6 meal per day condition. We previously reported a randomized crossover trial comparing meals (eating 3 times per day) with grazing (eating 8 times per day) (46). A registered dietitian gave detailed guidance to study participants as they prepared and consumed their own meals throughout the 2 study periods. The protocol specified that total energy and macronutrient distribution were to be kept constant on both study arms. We found that compared with the grazing pattern, the meals pattern led to significantly higher serum insulin-like growth factor 1, which is secreted in response to an insulin stimulus (46). Taken together, the data to date are not consistent.

Behavioral factors might account for our findings in this WHI report. It is possible that those who limit eating occasions to 1–3 times/d (referent group) have less emotional and binge eating levels. In the DPP, higher scores on food cravings, binge eating, and episodic overeating were linked with higher baseline BMI, which is a strong risk factor for T2D (47). We were not able to specifically evaluate these eating behavioral measures because they were not part of the WHI-DM trial data collection protocol.

Few prospective studies on total eating occasions in healthy volunteers at average risk of T2D have been conducted. The Nurses' Health Study examined breakfast consumption and skipping breakfast, but not eating occasions per se as a goal (14). However, 1 of their subgroup analyses found no association of number of daily eating occasions with T2D risk (14). In the Health Professionals Follow-Up Study, a similar analysis focused primarily on breakfast consumption also included a subgroup analysis incorporating both breakfast consumption and number of meals per day (15). The association of 4–7 meals/d with increased risk of T2D was strongest in those who reported no breakfast (15). Both the Health Professionals study and Nurses' Health Study inquired about breakfast on separate questionnaires. WHI did not explicitly inquire about breakfast consumption so we were not able to perform a similar analysis. Other published studies have primarily examined inclusion or omission of a specific meal on T2D risk (48), and there remains a paucity of data on whether fewer or greater overall eating occasions per day is associated with higher or lower T2D risk. Numerous studies, including randomized controlled trials (20), have examined the optimal number of daily eating occasions for management of existing T2D, but we are unaware of additional prospective studies aimed at understanding dietary behavioral risk factors for subsequent diagnosis of T2D.

This report focused on examining whether a modifiable risk factor, the number of eating occasions per day, was associated with T2D risk. We recognize that analysis of daily eating occasions is notoriously difficult due to problems with methodology and meal definitions (49). In this study we used the eating occasions as reported on the 24HR recall record. Some studies have used a single question with unknown validity on how many meals are consumed daily (49). Other complexities in studying eating occasions relate to diet quality; foods and beverages commonly consumed as "snacks" tend to have a less favorable nutrient profile and higher energy density (e.g., fats and sweets, baked goods, dairy-based desserts, chips, cookies, and crackers) (50, 51). Increased frequency of intake is also highly correlated with overall energy intake and weight gain—both risk factors for T2D (51–54). Randomized controlled trials testing low compared with high eating frequency while maintaining eucaloric energy as well as comparable macronutrient distribution and diet quality are well suited to testing whether the number of eating occasions affects metabolic health (21, 55). However, such studies are usually short term and typically employ surrogate end points (e.g., biomarkers, weight) as outcomes instead of disease end points; cohort studies such as WHI afford the opportunity to test these important associations with confirmed disease end points.

The strengths of this study include embedding the analysis in a randomized controlled trial, trained interviewers who followed a standardized protocol to collect the 24HR data, a diverse study sample, and carefully collected disease end points. Additionally, the WHI-DM 24HR cohort was designed to have higher race/ethnicity diversity than the overall WHI-DM. Limitations include the use of one 24HR, which we recognize might not reflect usual dietary patterns or eating frequency habits. No consensus exists on whether eating frequency occasions should be any reported eating occasion, minimal kilocalorie thresholds, time intervals, or other criteria (49). We used a 30-min interval between reported eating occasions to allow enough time for completion of an eating occasion in this postmenopausal age group. An alternative approach could have used 15-min intervals, as used in some other studies (49, 56, 57). Another limitation is that we were not able to assess the nutritional quality of specific foods because these 24HRs were collected prior to the routine inclusion of food group data in the 24HR output. The lack of technical ability to map eating occasions with specific foods could have affected the interpretation of the findings across the tertiles of eating occasions. Furthermore, because the 24HR cohort was a 4.6% subsample of the WHI-DM, results might not pertain to all WHI participants. Another limitation is that all studies of dietary self-report are subject to misreporting and measurement error, including the WHI (58, 59). Although we have not specifically examined measurement error in this study, others have reported measurement error in reporting of eating frequency and that such measurement error can influence eating frequency–disease association outcomes (60, 61). Finally, as with all studies, uncontrolled confounding can occur when potential confounding variables are either not measured or not measured with precision.

In conclusion, data from the WHI-DM suggest that eating 4 times/d compared with 1–3 times/d is associated with a 38% higher risk of T2D, but no association was observed when daily eating occasions equaled or exceeded 5 times/d, possibly due to too much variation in the top tertile (5–10 eating occasions per day). The risk was shown to be slightly stronger in women with a BMI <30.0 (55% higher risk) or in women aged ≥ 60 y (61% higher risk). Because our results are not entirely consistent with our hypothesized dose–response association, future cohort studies would be informed by including biomarkers of insulin resistance that would provide more definitive evidence on whether the total number of daily eating occasions is or is not associated with risk of T2D.

Acknowledgments

We acknowledge the WHI Program Office (National Heart, Lung, and Blood Institute, Bethesda, MD): Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller; the WHI Clinical Coordinating Center (Fred Hutchinson Cancer Research Center, Seattle, WA): Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg; the WHI Investigators and Academic Centers:

(Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kullar; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner; and the WHI Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland. For a list of all the investigators who have contributed to WHI science, please visit: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

The authors' responsibilities were as follows—MLN, MMP, and CT: designed research; MLN, MMP, BCW, and CT: conducted research; BCW: analyzed data; MLN and CT: wrote the paper; BCW, MMP, MH, LFT, JMS, KCJ, MEW, RAS-F, MZV, ES, LA, and CT: gave critical feedback on the data analysis and manuscript writing; MLN: had primary responsibility for final content; and all authors: read and approved the final manuscript.

References

1. Bullard KM, Cowie CC, Lessem SE, Saydah SH, Menke A, Geiss LS, Orchard TJ, Rolka DB, Imperatore G. Prevalence of diagnosed diabetes in adults by diabetes type – United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:359–61.
2. Lin J, Thompson TJ, Cheng YJ, Zhuo X, Zhang P, Gregg E, Rolka DB. Projection of the future diabetes burden in the United States through 2060. Popul Health Metr 2018;16:9.
3. American Diabetes Association . Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917–28.
4. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Barnighausen T, Davies J, Vollmer S. Global economic burden of diabetes in adults: projections from 2015 to 2030. Diabetes Care 2018;41:963–70.
5. Siegel KR, Bullard KM, Imperatore G, Ali MK, Albright A, Mercado CI, Li R, Gregg EW. Prevalence of major behavioral risk factors for type 2 diabetes. Diabetes Care 2018;41:1032–9.
6. Cespedes EM, Hu FB, Tinker L, Rosner B, Redline S, Garcia L, Hingle M, Van Horn L, Howard BV, Levtitan EB, et al. Multiple healthful dietary patterns and type 2 diabetes in the Women's Health Initiative. Am J Epidemiol 2016;183:622–33.
7. Dunkley AJ, Bodicoat DH, Greaves CJ, Russell C, Yates T, Davies MJ, Khunti K. Diabetes prevention in the real world: effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations: a systematic review and meta-analysis. Diabetes Care 2014;37:922–33.
8. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
9. Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677–86.
10. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, Pownall HJ, Johnson KC, Safford MM, Kitabchi AT,, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489–96.
11. Runchey SS, Pollak MN, Valsta LM, Coronado GD, Schwarz Y, Breymeyer KL, Wang C, Wang CY, Lampe JW, Neuhouser ML. Glycemic load effect on fasting and post-prandial serum glucose, insulin, IGF-1 and IGFBP-3 in a randomized, controlled feeding study. Eur J Clin Nutr 2012;66:1146–52.
12. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. Diabetes Care 2004;27:538–46.
13. Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. Cell Metab 2014;20:991–1005.
14. Mekary RA, Giovannucci E, Cahill L, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in older women: breakfast consumption and eating frequency. Am J Clin Nutr 2013;98:436–43.
15. Mekary RA, Giovannucci E, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. Am J Clin Nutr 2013;98:436–43.
16. Hutchison AT, Wittert GA, Heilbronn LK. Matching meals to body clocks—impact on weight and glucose metabolism. Nutrients 2017;9(3):222.
17. Faerch K, Vaag A, Holst JJ, Hansen T, Jorgensen T, Borch-Johnsen K. Natural history of insulin sensitivity and insulin secretion in the progression from normal glucose tolerance to impaired fasting glycemia and impaired glucose tolerance: the Inter99 study. Diabetes Care 2009;32:439–44.
18. Zarrinpar A, Chaix A, Panda S. Daily eating patterns and their impact on health and disease. Trends Endocrinol Metab 2016;27:69–83.
19. Kliewer KL, Ke JY, Lee HY, Stout MB, Cole RM, Samuel VT, Shulman GI, Belury MA. Short-term food restriction followed by controlled refeeding promotes gorging behavior, enhances fat deposition, and diminishes insulin sensitivity in mice. J Nutr Biochem 2015;26:721–8.
20. Kahleova H, Belinova L, Malinska H, Oliyarnyk O, Trnovska J, Skop V, Kazdova L, Dezortova M, Hajek M, Tura A, et al. Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study. Diabetologia 2014;57:1552–60.
21. Heden TD, Liu Y, Sims LJ, Whaley-Connell AT, Chockalingam A, Dellsperger KC, Kanaley JA. Meal frequency differentially alters postprandial triacylglycerol and insulin concentrations in obese women. Obesity 2013;21:123–9.
22. Mattson MP. The need for controlled studies of the effects of meal frequency on health. Lancet 2005;365:1978–80.
23. Anderson GL, Manson J, Wallace R, Lund B, Hall D, Davis S, Shumaker S, Wang CY, Stein E, Prentice RL. Implementation of the Women's Health Initiative study design. Ann Epidemiol 2003;13:S5–17.
24. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials 1998;19:61–109.
25. Howard BV, Aragaki AK, Tinker LF, Allison M, Hingle MD, Johnson KC, Manson JE, Shadyab AH, Shikany JM, Snetselaar LG, et al. A low-fat dietary pattern and diabetes: a secondary analysis from the Women's Health Initiative dietary modification trial. Diabetes Care 2018;41:680–7.
26. Tinker LF, Bonds DE, Margolis KL, Manson JE, Howard BV, Larson J, Perri MG, Beresford SA, Robinson JG, Rodriguez B, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. Arch Intern Med 2008;168:1500–11.
27. Neuhouser ML, Di C, Tinker LF, Thomson C, Sternfeld B, Mossavar-Rahmani Y, Stefanick ML, Sims S, Curb JD, LaMonte M, et al. Physical activity assessment: biomarkers and self-report of activity-related energy expenditure in the WHI. Am J Epidemiol 2013;177:576–85.
28. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 1999;9:178–87.
29. Guenther PM, Reedy J, Krebs-Smith SM. Development of the Healthy Eating Index-2005. J Am Diet Assoc 2008;108:1896–901.

30. Conway JM, Ingwersen LA, Vinyard BT, Moshfegh AJ. Effectiveness of the US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women. Am J Clin Nutr 2003;77:1171–8.
31. Margolis KL, Lihong Q, Brzyski R, Bonds DE, Howard BV, Kempainen S, Simin L, Robinson JG, Safford MM, Tinker L, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clinical Trials 2008;5: 240–7.
32. Jackson JM, DeFor TA, Crain AL, Kerby TJ, Strayer LS, Lewis CE, Whitlock EP, Williams SB, Vitolins MZ, Rodabough RJ, et al. Validity of diabetes self-reports in the Women's Health Initiative. Menopause 2014;21:861–8.
33. Ritenbaugh C, Patterson RE, Chlebowski RT, Caan B, Fels-Tinker L, Howard B, Ockene J. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. Ann Epidemiol 2003;13:S87–97.
34. Ma Y, Hebert JR, Manson JE, Balasubramanian R, Liu S, Lamonte MJ, Bird CE, Ockene JK, Qiao Y, Olendzki B, et al. Determinants of racial/ethnic disparities in incidence of diabetes in postmenopausal women in the U.S.: the Women's Health Initiative 1993–2009. Diabetes Care 2012;35:2226–34.
35. Manini TM, Lamonte MJ, Seguin RA, Manson JE, Hingle M, Garcia L, Stefanick ML, Rodriguez B, Sims S, Limacher M. Modifying effect of obesity on the association between sitting and incident diabetes in post-menopausal women. Obesity 2014;22:1133–41.
36. Prentice RL, Aragaki AK, Howard BV, Chlebowski RT, Thomson CA, Van Horn L, Tinker LF, Manson JE, Anderson GL, Kuller LE, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer, cardiovascular disease, and diabetes outcomes. J Nutr 2019;149:1565–74.
37. Dubowitz T, Ghosh-Dastidar M, Eibner C, Slaughter ME, Fernandes M, Whitsel EA, Bird CE, Jewell A, Margolis KL, Li W, et al. The Women's Health Initiative: the food environment, neighborhood socioeconomic status, BMI, and blood pressure. Obesity 2012;20:862–71.
38. Munsters MJ, Saris WH. Effects of meal frequency on metabolic profiles and substrate partitioning in lean healthy males. PLoS One 2012;7:e38632.
39. Navin Cristina TJ, Stewart Williams JA, Parkinson L, Sibbritt DW, Byles JE. Identification of diabetes, heart disease, hypertension and stroke in mid- and older-aged women: comparing self-report and administrative hospital data records. Geriatr Gerontol Int 2016;16:95–102.
40. Geiss LS, Wang J, Cheng YJ, Thompson TJ, Barker L, Li Y, Albright AL, Gregg EW. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980–2012. JAMA 2014;312: 1218–26.
41. Hatori M, Vollmers C, Zarrinpar A, DiTacchio L, Bushong EA, Gill S, Leblanc M, Chaix A, Joens M, Fitzpatrick JA, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metab 2012;15:848–60.
42. Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, Malaisse WJ, Mosley M, Notterpek L, Ravussin E, Scheer FA, et al. Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A 2014;111:16647–53.
43. McCrory MA, Campbell WW. Effects of eating frequency, snacking, and breakfast skipping on energy regulation: symposium overview. J Nutr 2011;141:144–7.
44. Horne BD, Muhlestein JB, Anderson JL. Health effects of intermittent fasting: hormesis or harm? A systematic review. Am J Clin Nutr 2015;102:464–70.
45. Jenkins DJ, Wolever TM, Vuksan V, Brighenti F, Cunnane SC, Rao AV, Jenkins AL, Buckley G, Patten R, Singer W, et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. N Engl J Med 1989;321:929–34.
46. Perrigue MM, Drewnowski A, Wang CY, Song X, Kratz M, Neuhouser ML. Randomized trial testing the effects of eating frequency on two hormonal biomarkers of metabolism and energy balance. Nutr Cancer 2017;69: 56–63.
47. Delahanty LM, Meigs JB, Hayden D, Williamson DA, Nathan DM. Psychological and behavioral correlates of baseline BMI in the diabetes prevention program (DPP). Diabetes Care 2002;25:1992–8.
48. Ballon A, Neuenschwander M, Schlesinger S. Breakfast skipping is associated with increased risk of type 2 diabetes among adults: a systematic review and meta-analysis of prospective cohort studies. J Nutr 2019;149: 106–13.
49. St-Onge MP, Ard J, Baskin ML, Chiuve SE, Johnson HM, Kris-Etherton P, Varady K. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American Heart Association. Circulation 2017;135:e96–e121.
50. Kant AK. Eating patterns of US adults: meals, snacks, and time of eating. Physiol Behav 2018;193:270–8.
51. Leech RM, Timperio A, Livingstone KM, Worsley A, McNaughton SA. Temporal eating patterns: associations with nutrient intakes, diet quality, and measures of adiposity. Am J Clin Nutr 2017;106:1121–30.
52. Kahleova H, Lloren JI, Mashchak A, Hill M, Fraser GE. Meal frequency and timing are associated with changes in body mass index in Adventist Health Study 2. J Nutr 2017;147:1722–8.
53. Zhu Y, Hollis JH. Associations between eating frequency and energy intake, energy density, diet quality and body weight status in adults from the USA. Br J Nutr 2016;115:2138–44.
54. Wang YQ, Zhang YQ, Zhang F, Zhang YW, Li R, Chen GX. Increased eating frequency is associated with lower obesity risk, but higher energy intake in adults: a meta-analysis. Int J Environ Res Public Health 2016;13:603.
55. Neuhouser ML, Clowry C, Beatty SJ, Wang CY, Drewnowski A, Perrigue MM. Rationale and design of the Frequency of Eating and Satiety Hormones (FRESH) study: a randomized cross-over clinical trial. Contemp Clin Trials Commun 2019;14:100334.
56. Duval K, Strychar I, Cyr MJ, Prud'homme D, Rabasa-Lhoret R, Doucet E. Physical activity is a confounding factor of the relation between eating frequency and body composition. Am J Clin Nutr 2008;88:1200–5.
57. Leech RM, Timperio A, Worsley A, McNaughton SA. Eating patterns of Australian adults: associations with blood pressure and hypertension prevalence. Eur J Nutr 2019;58:1899–909.
58. Neuhouser ML, Tinker L, Shaw PA, Schoeller D, Bingham SA, Horn LV, Beresford SA, Caan B, Thomson C, Satterfield S, et al. Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. Am J Epidemiol 2008;167:1247–59.
59. Prentice RL, Mossavar-Rahmani Y, Huang Y, Van Horn L, Beresford SA, Caan B, Tinker L, Schoeller D, Bingham S, Eaton CB, et al. Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers. Am J Epidemiol 2011;174: 591–603.
60. Leech RM, Worsley A, Timperio A, McNaughton SA. The role of energy intake and energy misreporting in the associations between eating patterns and adiposity. Eur J Clin Nutr 2018;72:142–7.
61. Murakami K, Livingstone MBE. Eating frequency in relation to body mass index and waist circumference in British adults. Int J Obes 2014;38:1200–6.