



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

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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/m² (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

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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.

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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 healthy 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/height² (kg/m²).

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

¹Values 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.

²Baseline 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)

¹Model 1 adjusted for age.

²Model 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).

³Range 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 age¹

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)

¹Models 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/m²) <30 combines normal and overweight; BMI ≥30.0 is obese.

²Range 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.

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