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Relationship between frequency of eating and cardiovascular disease mortality in U.S. adults: the NHANES III follow-up study

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Abstract

Purpose—This study examined longitudinal relationship between baseline daily eating frequency and all-cause and cardiovascular disease (CVD) mortality among US adults.

Methods—The Third National Health and Nutrition Examination Survey (1988–1992) participants were followed through 2006. Non-pregnant adults >17 years-old (n=6884) whose dietary recall was of good quality and had fasted at least 8 hours before physical examinations were eligible for this analysis. Frequency of eating was derived from 24-hour dietary recalls. Main outcomes included all-cause and CVD mortality during follow-up, based on National Death Index data.

Results—During follow-up (median time: 176 months), 1,280 subjects died, 503 of them from CVD. Adults reporting eating 6 times/day had a lower hazard ratio for CVD mortality than those reporting eating 4 times/day (HR=0.68, 95% CI: 0.43, 1.08; test for trend, p=0.011). The gradient of CVD mortality risk by eating frequency was significant for the groups with 2500 kcal of total energy intake (test for trend, p=0.037).

Conclusions—Eating frequency was inversely associated with CVD mortality, which was especially marked for people reporting high total energy intake. Nevertheless, public health recommendations should be cautious, as eating frequency was positively associated with total energy intake, which could promote weight gain.

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DISCLOSURES

The authors have no conflict of interests to disclose.

Keywords

Nutrition Surveys; Longitudinal Studies; Mortality; Feeding Behavior

INTRODUCTION

Spreading daily food consumption into more meals is postulated to result in better metabolic health and lower adiposity [1–3], especially for metabolically-normal individuals [4]. People eating fewer times per day and thus consuming more energy per occasion would have worse lipid profiles than those eating more times per day, with lower energy intake per eating occasion [5, 6]. It has also been proposed that a “nibbling” style of eating would favor better glucose regulation than a “gorging” style [7, 8]. Isocaloric experiments suggest that separating total intake into more eating occasions could prolong satiety and decrease appetite at the following meal [9]. Because of these metabolic advantages, dividing daily food intake into more occasions has become an “unofficial consensus” for diabetes management [10].

Many of the existing studies on health benefits of eating frequently are based on controlled laboratory feeding experiments [4, 6–8]. In the real world, total daily energy intake may increase when the number of eating occasions is higher [11–13]. Also of relevance (and possibly a confounding variable) is that physically active adults tend to eat more frequently than those who are more sedentary [1]. These complex interactions of dietary behaviors and lifestyle could complicate the evaluation of the health effects of eating frequently, especially when using cross-sectional observations [14]. Few longitudinal studies have assessed the association between eating frequency and health outcomes [15]. The Health Professionals Follow-up Study showed that eating frequency might be associated with diabetes risk, but not so with risks of colorectal cancer and coronary heart disease [13, 16, 17]. Health professionals, however, differ from the general population: they are of higher socioeconomic status, and possess greater health knowledge, both factors which may improve health risks. Little is known about the association between eating frequency and long-term health outcomes in the general population.

Since the number of eating occasions has been shown protective for metabolic disorders, and major risk factors for cardiovascular diseases (CVD) [18, 19], the current study examined the association between eating frequency and CVD mortality among U.S. adults without CVD at baseline, based on a non-institutionalized national study sample. We hypothesized that cardiovascular mortality was inversely associated with eating frequency.

MATERIAL AND METHODS**Study design and data**

To prospectively examine the relationship between frequency of eating occasions and subsequent mortality, we used Third National Health and Nutritional Examination Survey (NHANES III, 1988–1992) data for baseline observations, and matched it to the NHANES III-Linked Mortality database. The NHANES III is a nationally-representative survey of

non-institutionalized Americans, assessing the health and nutrition status of the population. The subjects were sampled based on a multistage, stratified and clustered, complex sampling scheme. The survey included a home-based interview and a physical examination at a mobile examination center.

Death between the time of the baseline survey through the end of 2006 was ascertained by linking the adult participants to the National Center for Health Statistics' (NCHS) National Death Index [20]. NHANES III was approved by the NCHS Institutional Review Board (IRB) and written informed consent was obtained from all participants.

Eligibility and sample size

To avoid including individuals with unusual diets or who might provide low quality 24-hour dietary recalls, we included only subjects: (1) >17 years of age, (2) non-pregnant at the time of the interview, (3) whose 24-hr dietary recall was reported on his/her own and not by a proxy, (4) who reported amount of consumed food in the previous day was typical for them, (5) whose recall was evaluated as good quality by surveyors, (6) who reported total energy intake in the past 24-hours lay in the plausible range of 600–6000 kcal, (7) who did not report a history or current CHD, stroke, and other CVD at baseline, (8) who did not report changing dietary behaviors during the past year due to health concerns (including diabetes, obesity, high blood pressure, high cholesterol, heart disease, or stroke), and (9) who had fasted for 8 hours or more before physical examination. The final sample of eligible subjects was 6,884 U.S. adults.

Outcomes of interest—(1) All-cause death, (2) death from major CVD, (3) death from ischemic heart diseases, and (4) death from cerebrovascular diseases.

Cause of death was identified based on the classification codes for the *List of 113 Underlying Causes of Death* on the public-use NHANES III-Linked Mortality File [20, 21]. The disease codes were validated against ICD-9 and ICD-10 [21]. The category “major CVD” includes causes of death (list numbers: 053–074): diseases of the heart (054–068), essential/primary hypertension or hypertensive renal disease (069), cerebrovascular diseases (070), atherosclerosis (071), and other diseases of the circulatory system (072–074). We further examined two specific groups of cardiovascular causes of death: ischemic heart diseases (058–063, including acute myocardial infarction, and all other acute/chronic ischemic heart diseases) and stroke (cerebrovascular diseases, 070). For subjects who died before the end of 2006, the follow-up time was from the date of NHANES III participation to the date of death. For subjects who survived past 2006, follow-up was censored on December 31, 2006. The unit of follow-up time in the public-use NHANES III-Linked Mortality File was month.

Main exposure

Frequency of eating was extracted from a 24-hour dietary recall at baseline. The time of food consumption was used to differentiate eating occasions. Only eating/drinking occasions with energy intake were counted as an eating occasion. That is, occasions in which the subjects ate zero calories, such as consuming a non-caloric beverage only, were excluded.

Subjects were divided into 5 groups by the number of eating occasions in their 24-hour dietary recall: 1–2, 3, 4, 5, and 6 times.

Baseline covariates

Socioeconomic and demographic: gender, baseline age, race/ethnicity, geography (urban/rural census regions), marital status (married, singled after marriage, never married), years of education (<12, 12, >12 years), and being employed or not. *Diet quality:* total energy intake, and Healthy Eating Index (HEI) total score (range 1–100) [22], derived from 24-hour dietary recall. *Lifestyle:* participants' self-report of their (1) physical activity (weekly frequency of moderate (metabolic equivalent 3–6) and vigorous (metabolic equivalent >6) intensity physical activity), (2) current smoking status. *Health status:* (1) self-rated general health status (5 ordinal categories), (2) weight status (underweight, normal weight, overweight, obese), (3) diabetes status: fasting glucose ≥ 126 mg/dL, ever being diagnosed with diabetes, or taking medications for diabetes, (4) hypertension status: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or ever being diagnosed with hypertension, or taking medications for hypertension, (5) C-creative protein (<0.3 mg/dl, 0.3–0.9 mg/dl, ≥ 1 mg/dl). *Metabolic syndrome* (MetS) based on the Joint Interim definition of 2009 [23]: having 3 of the following conditions: (1) waist circumference ≥ 102 cm for men and ≥ 88 cm for women; (2) fasting glucose ≥ 100 mg/dl or taking anti-diabetes medications, (3) fasting triglycerides ≥ 150 mg/dl, (4) HDL-cholesterol <40 mg/dl for men and <50 mg/dl for women, (5) systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg, or taking anti-hypertensive medications.

Statistical analysis

Cox's proportional hazard model was used for estimating the mortality-hazard ratio (HR) and its 95% confidence interval during the follow up period associated with baseline eating frequency. The categories of frequency of eating were treated as dummy variables. Linear trend in the association was examined by testing the association between subject's exact number of eating occasions and the outcomes. The models were adjusted for demographic, socioeconomic, dietary, lifestyle, and health-status variables as detailed above.

The full model was further applied to examine the association between mortality and number of eating occasions, stratified by subjects' baseline total energy intake (based on tertile groups), as energy intake might modify the association of interest. Further, the combination between total energy intake and number of eating occasions were created to explore the interaction between the two factors. Sampling weight and complex survey design effect were considered (SAS SURVEYPHREG; SAS 9.3, SAS Institute Inc., Cary, NC).

RESULTS

Differences between groups by meal frequency (Table 1)

Among the 6,884 adults who reported that their diet in the past 24 hours was their usual diet, 403 (3.6%) reported eating 1–2 times, and 1528 (29.2%) ≥ 6 times. Those who ate more frequently reported greater total energy intake, but the average energy intake per eating occasion was lower. Moreover, the dietary quality, as indicated by the Healthy Eating Index,

was better for people eating more frequently, except for sodium intake. In general, people eating more frequently were more likely to be married, to have a higher education level, and to be employed. The group with 1–2 eating occasions was about 6 years younger than the other groups. People eating more frequently had better metabolic health: they were less likely to have metabolic syndrome, a large waist circumference, or to be obese. Number of eating occasions was positively associated with more frequent moderate physical activity.

Number of eating occasions and cardiovascular mortality

During the follow-up period, a total of 1,280 subjects died, 503 of them from CVD, including 89 deaths from cerebrovascular events, and 284 from ischemic heart disease. The median follow-up time was 176 months (i.e. 14 years and 8 months), and the maximum follow-up time was 218 months (i.e. 18 years and 2 months). All-cause and cardiovascular deaths, especially ischemic heart disease, significantly decreased with greater eating frequency (p for trend <0.01).

Cox's proportional hazard models revealed a decreasing trend in mortality associated with increasing baseline eating frequency, which was no longer significant when HEI score and energy intake were controlled for (Table 2). Nevertheless, the gradient in association between CVD mortality and eating frequency remained significant in the full model. Ischemic heart disease and cerebrovascular event mortality decreased with increasing number of eating occasions as well, but the trends were no longer significant after adjusting for socioeconomic variables. Table 3 demonstrates that the patterns of association between eating frequency and CVD mortality were similar for women and men. However, a significant trend for CVD mortality was found only in women. There was no significant interaction between sex and eating frequency.

Stratified by baseline total energy intake, the inverse association between cardiovascular mortality and eating frequency was present for those who consumed < 1600 kcal or ≥ 2500 kcal (Table 4, p values of test for trend <0.05). Crude mortality rates were in general higher in the <1600 kcal group, compared to the other two strata.

The Figure demonstrates the HR of cardiovascular mortality for combinations of total energy intake and eating frequency. The trend in HR for the <1600 kcal group appeared much less marked than the trend for the ≥ 2500 kcal group. The group having ≥ 2500 kcal total energy intake consumed over only 1–2 eating occasions had a very high HR (6.7, 95% CI: 2.1, 21.1). These findings suggest that the cardiovascular mortality increased the most when large amounts of energy were consumed over only 1–2 meals per day.

DISCUSSION

This is the first population-based prospective study that examined the relationship between eating frequency and mortality. We found that cardiovascular mortality was significantly and inversely associated with eating frequency. The benefit of greater meal frequency on cardiovascular mortality risk seemed to be more pronounced among those who had higher reported total daily energy intake (≥ 2500 kcal) than among those reporting lower energy intake. A previous study found that healthy adults' carotid artery intima media thickness

differed by eating frequency by a greater degree for those who had higher total caloric intake [24]. Thus, it may be of particular value to separate large quantities of food consumed into more eating occasions.

Our observation of the correlation between frequency of eating occasions and improved baseline metabolic profiles is supported by findings in other studies [1]. For example, more frequent meals with smaller energy loads could ease regulation of glucose metabolism [8, 9, 16]. Derangement of insulin and glucose metabolism is a hallmark of type-2 diabetes and metabolic syndrome, which leads to a cascade of metabolic disorders and atherosclerotic risks [25]. Even though our model adjusted for metabolic variables, the significant inverse relationship between eating frequency and cardiovascular mortality suggests that less frequent meals may lead to subsequent metabolic deterioration. Since NHANES did not follow up for changes in metabolic variables, the impact of eating frequency on metabolic variables and subsequent mortality must be determined by longitudinal studies that repeatedly measure metabolic parameters over time.

Diet quality could also account for the association between eating frequency and cardiovascular death. We found that individuals who ate more frequently reported higher HEI scores than those eating less frequently. Higher HEI scores have been associated with a generally more healthful metabolic profile, and lower levels of chronic inflammation and oxidative stress [26, 27]. Serum levels of antioxidants were associated with reduced levels of inflammatory markers, such as high-sensitivity C-reactive protein, as well as other metabolic aberrations [30]. Eating frequency would likely also be associated with more frequently consuming bioactive compounds found in certain noncaloric beverages, such as non-sugared tea and coffee, leading to a lower morbidity and mortality [28, 29]. This may account for why the association between eating frequency and cardiovascular mortality was attenuated after controlling for diet quality.

The way fewer eating occasions are operationalized might also influence the metabolic consequences. Meal skipping, in particular skipping breakfast, has been associated with such health risks as obesity, metabolic disorders, and CVD [16, 31–35]. Breakfast skippers have been found to have a poorer diet quality than breakfast eaters, e.g. higher fat and sugar intakes, lower micronutrient adequacy, and worse HEI scores [31, 36]. Hunger after a skipped meal could increase food consumption on subsequent eating occasions [34, 37], though breakfast skippers may have lower overall daily energy intake than breakfast eaters. Thus, cutting energy intake by skipping meals like breakfast may lead to adverse health effects, due to compensatory overeating on subsequent meals, as well as a potentially unbalanced diet.

Although the present study supports prior trials that found more frequent meals may be beneficial, dietary behaviors in the real world are much more complex than controlled laboratory feeding experiments [10]. It can be challenging for individuals to monitor the quantity and quality of their every meal in daily practice. From the 1970s to 2000s, the mean frequency of eating occasions among U.S. adults increased from 3.8 to 4.9 per day, while total energy intake and food portion size increased as well [11]. A higher eating frequency in societies with a superabundance of energy-dense foods may in fact reflect the greater

consumption of energy-dense foods. Given these factors, simply recommending that the general public increase eating frequency could lead to excess energy intake, and affect health via energy imbalance and increased empty calories.

Some unmeasured pathways may contribute to the observed independent relationship between eating frequency and mortality. Health-conscious individuals may tend to report more details about the timing and content of food consumption in their 24-hour dietary recalls. Meanwhile, their healthier lifestyles could decrease cardiovascular risks independently of the risk associated with meal frequency. In this study, we tried to adjust for lifestyle variables as much as possible to reduce the potential confounding effect of health consciousness.

Another unmeasured factor is subjects' mood and stress level. Of note, people afflicted with anorexia nervosa, which by definition entails lesser meal frequency, have been found to have a greater than two-fold higher risk of CVD mortality than the general population [40, 41]. Thus, a low frequency of eating occasions may sometimes reflect psychosocial conditions associated with elevated cardiovascular risks. Unmeasured behavioral pathways may in part account for the independent association between eating frequency and mortality, and need further study.

Some limitations of our study need be noted. First, the endpoint we measured was mortality. Death is a result of the complex interaction between incidence of potentially fatal conditions and diseases, and the imperfectly practiced and disparity-prone provision of healthcare that works to prevent morbidity and mortality. Results based on mortality analysis are an underestimate of disease incidence, as death from CVD is only a subset of CVD cases in the population. Second, dietary variables were derived from 24-hour dietary recall, which does not capture daily variation of eating behaviors, nor measure usual intakes [42]. Nevertheless, the 24-hour dietary recall can more precisely measure the time of food intake than does a food frequency questionnaire that captures only a general dietary pattern, compared to other frequency-based and single-question instruments [16, 35]. Based on the second day recall of 560 subjects in this study, the agreement between the eating frequencies of the two recalls was fair (weight kappa=0.31). We tried to limit the impact of dietary variation by including only those recalls described as being similar to the subject's usual diet, and to those described by interviewers as of better recall quality. Weight status and its associated factors were controlled for in the models, though there may be a residual influence based on differential reporting errors between obese and normal-weight subjects. Third, NHANES III was conducted in 1988–94, and the food industry and environment in the US have changed significantly since then. The health impact of eating frequency may have evolved with the population's changing diet.

The major strengths of this study are the large, representative sample, and the prospective, longitudinal study design. NHANES III recruited non-institutionalized US residents, and thus findings would have good generalizability for the overall US population, better than previous studies in this area of investigation. Furthermore, the ascertainment of death based on nationwide death certificates covers mortality in the specific study population, and the long follow-up (up to 18+ years) provides a sufficient incubation time for capturing CVD

mortality. This follow-up period is sufficiently long to span the entire course from preclinical disease through the occurrence of CVD and deaths.

CONCLUSION

This large population-based study revealed an inverse association between frequency of eating occasions and CVD mortality. The protective health benefit of more frequent meals was especially marked for those who had higher total energy intake. However, it is noteworthy that making a blanket recommendation for adding eating frequency could increase energy total caloric intake. More research is needed for future development of more definitive recommendations regarding eating frequency.

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Figure. Hazard ratios of cardiovascular mortality by total energy intake (TEI) and frequency of eating occasions: NHANES III mortality data

Reference group: 2500 > TEI 1600 kcal and 4 eating occasions in the 24-hour dietary recall.

Hazard ratios were estimated from 14 dummy categories of the combinations of total energy intake and eating frequency, with adjustment of the same covariates in the full models

(Model 4) in Table 2. The global test of the interaction terms between eating frequency and TEI was significant ($p=0.0035$ for chi-square test).

Table 1

Basic characteristics, dietary, metabolic profiles, and outcome distribution of US adults with different eating frequency at baseline: NHANES III

	1–2 occasions n=403 (3.6%)		3 occasions n=1520 (16.4%)		4 occasions n= 1901 (25.2%)		5 occasions n=1532 (25.6%)		6+ occasions n=1528 (29.2%) [†]		p	
	Mean or %	SE	Mean or %	SE	Mean or %	SE	Mean or %	SE	Mean or %	SE		
Dietary quality												
Average EI per occasion	(kcal/occasion)	926.50	37.42	659.22	14.79	542.50	7.67	466.28	6.84	375.23	5.86	<.0001
Total energy intake (EI)	(kcal)	1813.73	76.89	1977.67	44.38	2170.00	30.66	2331.42	34.22	2571.40	41.91	<.0001
Total HEI score	1–100	52.40	0.75	60.73	0.62	62.74	0.48	64.39	0.59	65.33	0.61	<.0001
Demographics and socioeconomic												
Age	(year)	34.26	1.14	40.14	0.81	40.43	0.81	40.81	0.74	41.24	0.50	<.0001
Gender (women)	%	37.72	3.68	50.15	2.40	50.58	1.72	52.21	1.77	50.38	1.66	0.0334
Race/ethnicity	White, %	56.75	4.00	65.02	3.25	73.37	1.74	78.53	1.96	86.14	1.03	<.0001
	Black, %	28.23	2.78	14.96	1.28	11.50	0.99	8.52	0.95	6.52	0.57	
	Mexican, %	11.49	1.88	9.62	1.13	6.75	0.70	4.83	0.54	3.38	0.31	
	Other, %	3.53	2.23	10.40	2.38	8.39	1.41	8.12	1.78	3.96	0.65	
Education years	<12, %	38.92	5.08	33.05	2.04	27.59	1.34	21.50	1.61	16.89	1.62	<.0001
	=12, %	35.48	3.79	35.22	2.25	33.24	1.47	32.30	1.74	33.15	1.95	
	>12, %	25.60	3.98	31.74	2.42	39.17	1.89	46.20	1.90	49.96	2.11	
Currently employed	%	61.87	3.78	66.43	2.09	64.63	1.72	73.36	1.63	76.39	1.52	<.0001
Lifestyles and health conditions												
Current smoker	%	32.41	4.95	27.21	2.18	25.38	1.60	27.42	1.83	32.18	2.18	0.0692
Moderate physical activity	times/week	4.58	0.41	4.53	0.27	4.39	0.18	4.78	0.22	5.04	0.28	0.0408
Vigorous physical activity	times/week	0.63	0.12	0.56	0.07	0.61	0.09	0.61	0.08	0.52	0.07	0.2994
Weight status												
Underweight, %		1.90	0.93	1.74	0.46	3.56	0.71	3.80	0.80	2.98	0.59	0.0011
Normal weight, %		45.32	4.30	41.92	2.01	43.01	1.78	50.04	1.91	49.14	1.75	
Overweight, %		27.81	4.09	31.64	1.70	33.40	1.56	30.66	1.70	31.78	1.68	
Obese, %		24.97	4.39	24.70	2.21	20.03	1.55	15.51	1.69	16.10	1.36	
Elevated blood pressure	%	27.23	2.97	33.42	1.96	27.93	1.99	25.55	1.94	24.81	1.48	0.0108
Declined HDL -C	%	34.08	4.19	40.13	2.69	37.93	2.33	32.13	2.32	34.73	1.80	0.1991

		1–2 occasions n=403 (3.6%)		3 occasions n=1520 (16.4%)		4 occasions n=1901 (25.2%)		5 occasions n=1532 (25.6%)		6+ occasions n=1528 (29.2%) [†]		p
		Mean or %	SE	Mean or %	SE	Mean or %	SE	Mean or %	SE	Mean or %	SE	
Elevated fasting glucose	%	22.61	4.52	27.31	2.52	23.93	2.39	22.03	2.46	22.36	1.96	0.4763
Elevated triglycerides	%	20.21	3.32	29.13	2.35	24.83	2.27	25.02	1.51	22.96	1.90	0.0622
Large waist circumference	%	35.45	3.95	37.43	2.49	30.96	1.55	28.20	2.25	28.44	1.68	0.0268
Metabolic syndrome	%	21.57	4.45	28.00	2.41	21.75	1.86	18.81	1.37	19.45	1.69	0.0113
C-reactive protein	mg/dL	0.42	0.05	0.37	0.01	0.35	0.01	0.34	0.02	0.34	0.01	0.0556
Diabetic	%	9.00	2.05	7.39	1.07	7.56	0.96	7.66	1.13	5.37	0.58	0.182
Hypertensive	%	17.79	2.34	24.70	1.60	25.64	1.89	25.24	1.97	22.66	1.67	0.0713
Outcomes during follow-up												
Death (all-cause)	%	15.29	3.08	13.92	1.32	13.44	1.37	11.71	0.90	9.32	0.98	0.0341
Death from CVD	%	4.42	1.31	6.48	0.95	4.87	0.85	4.04	0.56	2.47	0.48	0.0032
Death from IHD	%	3.05	1.09	3.63	0.70	2.83	0.49	2.18	0.43	1.76	0.46	0.1163
Death from cerebrovascular diseases	%	0.69	0.51	1.10	0.31	0.78	0.24	0.56	0.17	0.43	0.19	0.3316

P value: ANOVA test or Wald's chi-square test for testing the equal distribution across four eating frequency group.,

[†] Sample size and projected percentage in the population.

Table 2
Eating frequency and the relative risk of all-cause and cardiovascular mortality: NHANES III mortality data

	1–2 occasions		3 occasions		4 occasions		5 occasions		6+ occasions		Test for trend [†]
	HR	95% CI	HR	95% CI	(ref)	HR	95% CI	HR	95% CI		
All-cause mortality											
Weighted mortality	1054.7		981.9		948.4		805.3		642.4		
Model 1	1.28	(0.83, 1.97)	1.02	(0.81, 1.28)			0.97	(0.77, 1.23)	0.85	(0.62, 1.18)	0.013
Model 2	1.25	(0.80, 1.96)	1.04	(0.82, 1.33)			1.01	(0.79, 1.28)	0.83	(0.62, 1.13)	0.044
Model 3	1.23	(0.78, 1.95)	1.03	(0.81, 1.32)			1.02	(0.80, 1.28)	0.84	(0.62, 1.14)	0.097
Model 4	1.17	(0.74, 1.86)	1.01	(0.80, 1.27)			1.02	(0.81, 1.29)	0.86	(0.63, 1.16)	0.151
Death from all CVDs											
Weighted mortality	304.9		456.8		343.4		278.1		170.6		
Model 1	1.13	(0.63, 2.03)	1.31	(0.91, 1.87)			0.97	(0.66, 1.44)	0.66	(0.41, 1.06)	<.001
Model 2	1.13	(0.61, 2.11)	1.34	(0.89, 2.01)			1.03	(0.69, 1.54)	0.66	(0.42, 1.05)	0.001
Model 3	1.03	(0.54, 1.97)	1.28	(0.85, 1.92)			1.08	(0.73, 1.58)	0.69	(0.43, 1.10)	0.022
Model 4	1.09	(0.55, 2.14)	1.32	(0.87, 2.02)			1.05	(0.70, 1.59)	0.68	(0.43, 1.08)	0.011

Weighted mortality (per 100,000 person-years) was calculated by dividing the weighted number of deaths and weighted total person-years.

Model 1: Adjusted for sex, age, race/ethnicity, marital status, education level, employment status, urban area and census region.

Model 2: In addition to the variables in Model 1, adjusted for current smoking status, frequency of moderate and vigorous physical activity, weight status, diabetes and hypertension statuses, self-rated health status, and metabolic syndrome status.

Model 3: In addition to the variables in Model 2, adjusted for total energy intake

Model 4: In addition to the variables in Model 3, adjusted for the scores of 10 subcategories of healthy eating index (continuous score: 1–10 for each subcategory)

[†]Testing for linear trend that the five categories were treated as ordinal variables (i.e. 1, 2, 3, 4, 5, 6 times/day)

Table 3

Eating frequency and the relative risk of all-cause and cardiovascular (CVD) mortality by sex: NHANES III mortality data

	1–2 occasions		3 occasions		4 occasions (ref)		5 occasions		6+ occasions		Test for trend [†]
	Mortality rate	HR 95% CI	Mortality rate	HR 95% CI	Mortality rate	HR 95% CI	Mortality rate	HR 95% CI	Mortality rate	HR 95% CI	
Women											
All-cause mortality	590.9	0.70 (0.38,1.29)	964.1	0.86 (0.59,1.25)	1043.6		712.1	0.87 (0.64,1.19)	607.5	0.66 (0.44,0.998)*	0.193
CVD	203.8	1.11 (0.24,5.06)	562.1	1.55 (0.88,2.75)	348.3		246.6	0.97 (0.51,1.88)	187.2	0.63 (0.33,1.22)	0.032
Men											
All-cause mortality	1345.6	1.46 (0.71,2.99)	1000.0	1.16 (0.82,1.63)	851.3		908.2	1.16 (0.86,1.57)	678.4	1.07 (0.66,1.74)	0.637
CVD	368.4	1.04 (0.42,2.61)	349.9	1.02 (0.57,1.82)	338.5		313.0	1.22 (0.69,2.18)	153.4	0.70 (0.39,1.25)	0.383

[†] Testing for linear trend that the five categories were treated as ordinal variables (i.e. 1, 5, 3, 4, 5, 6 times/day)

Testing for the hazard ratio different from 1:

* p < 0.05;

** p < 0.01

Mortality rate (per 100,000 person-years): dividing the weighted number of deaths by the weighted total person-years

HR: Hazard ratio after adjusted for the same covariates as ones in the Model 4 in Table 2.

Table 4

Eating frequency and the relative risk of all-cause and cardiovascular (CVD) mortality by total energy intake level: NHANES III mortality data

	1-2 occasions		3 occasions		4 occasions (ref)		5 occasions		6+ occasions		Test for trend [†]
	Mortality rate	HR 95% CI	Mortality rate	HR 95% CI	Mortality rate	HR 95% CI	Mortality rate	HR 95% CI	Mortality rate	HR 95% CI	
TEI<1600											
All-cause mortality	1236.4	1.01 (0.61,1.66)	1626.5	0.80 (0.56,1.15)	1931.2		1146.8	0.70 (0.49,1.00)	855.5	0.53 (0.32,0.88)*	0.026
CVD	341.5	0.76 (0.31,2.07)	832.6	1.04 (0.64,1.67)	787.7		425.5	0.65 (0.35,1.19)	294.9	0.41 (0.18,0.93)*	0.017
2500>TEI 1600											
All-cause mortality	802.5	1.42 (0.53,3.77)	641.2	1.25 (0.84,1.88)	739.1		758.5	1.27 (0.86,1.87)	844.5	1.39 (0.96,1.99)	0.445
CVD	173.1	2.75 (0.31,7.85)	289.9	2.72 (1.40,5.27)**	199.8		361.3	2.50 (1.33,4.71)**	203.0	1.12 (0.62,2.03)	0.268
TEI 2500											
All-cause mortality	1149.9	4.37 (1.40,13.65)*	594.4	1.63 (0.85,3.12)	343.2		657.7	1.36 (0.79,2.33)	402.8	1.09 (0.65,1.81)	0.118
CVD	483.7	1.68 (0.76,7.34)	179.1	1.19 (0.20,6.90)	137.4		104.8	0.56 (0.19,1.63)	97.6	0.61 (0.20,1.81)	0.037

[†] Testing for linear trend that the five categories were treated as ordinal variables (i.e. 1, 5, 3, 4, 5, 6 times/day)

Testing for the hazard ratio different from 1:

* p < 0.05;

** p < 0.01

Mortality rate (per 100,000 person-years): dividing the weighted number of deaths by the weighted total person-years

HR: Hazard ratio after adjusted for the same covariates in the Model 4 in Table 2.