RESEARCH
Research Paper

Meal Skipping and Shorter Meal Intervals Are Associated with Increased Risk of All-Cause and Cardiovascular Disease Mortality among US Adults

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ABSTRACT

Background Previous dietary studies and current dietary guidelines have mainly focused on dietary intake and food patterns. Little is known about the association between eating behaviors such as meal frequency, skipping and intervals, and mortality.

Objective The objective was to examine the associations of meal frequency, skipping, and intervals with all-cause and cardiovascular disease (CVD) mortality.

Design This was a prospective study.

Participants/setting A total of 24,011 adults (aged ≥40 years) who participated in the National Health and Nutrition Examination Survey 1999-2014 were included in this study. Eating behaviors were assessed using 24-hour recall. Death and underlying causes of death were ascertained by linkage to death records through December 31, 2015.

Main outcome measures The outcomes were all-cause and CVD mortality.

Statistical analyses performed Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) of all-cause and CVD mortality.

Results During 185,398 person-years of follow-up period, 4,175 deaths occurred, including 878 cardiovascular deaths. Most participants ate three meals per day. Compared with participants eating three meals per day, the multivariable-adjusted HRs for participants eating one meal per day were 1.30 (95% CI 1.03 to 1.64) for all-cause mortality, and 1.83 (95% CI 1.26 to 2.65) for CVD mortality. Participants who skipped breakfast have multivariable-adjusted HRs 1.40 (95% CI 1.09 to 1.78) for CVD mortality compared with those who did not. The multivariable-adjusted HRs for all-cause mortality were 1.12 (95% CI 1.01 to 1.24) for skipping lunch and 1.16 (95% CI 1.02 to 1.32) for skipping dinner compared with those who did not. Among participants eating three meals per day, the multivariable-adjusted HR for participants with an average interval of ≤4.5 hours in two adjacent meals was 1.17 (95% CI 1.04 to 1.32) for all-cause mortality, comparing with those having a meal interval of 4.6 to 5.5 hours.

Conclusions In this large, prospective study of US adults aged 40 years or older, eating one meal per day was associated with an increased risk of all-cause and CVD mortality. Skipping breakfast was associated with increased risk of CVD mortality, whereas skipping lunch or dinner was associated with increased risk of all-cause mortality. Among participant with three meals per day, a meal interval of ≤4.5 hours in two adjacent meals was associated with higher all-cause mortality.

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CURRENTLY, THE INFLUENCE OF MEAL FREQUENCY, skipping, and intervals on health and disease is a topic of universal interest.[1] According to the US National Health and Nutrition Examination Survey (NHANES) in 2009-2010,[2] the proportion of adults who reported consuming all three standard meals (breakfast, lunch, and dinner) was 59% in men and 63% in women. The prevalence of skipping breakfast, lunch, and dinner was 19%, 22%, and 8% for men, and 19%, 21%, and 7% for women. This indicated that about 40% of Americans skipped meals, and at least one in five skipped breakfast or lunch among populations aged 20 to 74 years. As for meal intervals, the average meal interval between breakfast and lunch was about 5 hours, and the average interval between lunch and dinner was about 6 hours.[2] When compared with 1971-1974, the length of interval between the first and the last meal had

decreased by about 30 minutes.[2] However, the meal frequency, skipping, and intervals have not been addressed by the 2020-2025 Dietary Guidelines for Americans[3] because the Dietary Guidelines Advisory Committee "was unable to find sufficient evidence on which to summarize the evidence between frequency of eating and health."[4]

Prior observational and interventional evidence on the association between meal frequency and risk of obesity, diabetes, and cardiovascular disease (CVD) has been mixed and inconsistent.[5-8] Skipping breakfast has been associated with higher CVD risk and mortality in previous studies.[8-10] However, the association of meal frequency, skipping lunch or dinner, and meal intervals with mortality remains unknown. In this study, data from a nationally representative cohort was used to examine the associations of specific eating behaviors (meal frequency, skipping, and intervals) with all-cause and CVD mortality among US adults.

RESEARCH SNAPSHOT

Research Question: Are eating behaviors such as meal frequency, skipping, and intervals associated with all-cause and cardiovascular disease (CVD) mortality?

Key Findings: Eating one meal per day was associated with an increased risk of all-cause and CVD mortality. Skipping breakfast was associated with higher risk of CVD mortality, whereas skipping lunch or dinner was associated with higher risk of all-cause mortality. In addition, among participants with three meals per day, a shorter meal interval of $\leq$4.5 hours in two adjacent meals was associated with higher risk of all-cause mortality.

MATERIALS AND METHODS

Study Population

The study population consisted of participants from the NHANES 1999-2014. Briefly, NHANES is a large-scale, ongoing, nationally representative health survey of the noninstitutionalized US population. It is conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. Since 1999-2000, NHANES surveys have been organized in 2-year cycles; each cycle consists of approximately 10,000 participants.[11] Through in-house and telephone interviews, NHANES collects a wide range of health-related data to assess diet, nutritional status, general health, disease history, and health behaviors.[11] The surveys use multistage, probability clusters to develop a population sample that is nationally representative of the United States based on age, gender, and race and ethnicity. NHANES data along with documents on the survey methods and other information are publicly available on the NHANES website.[12] All participants gave written informed consent. The study protocol was approved by the NCHS Research Ethics Review Board.

For this analysis included 27,759 adult participants aged 40 years or older who had complete information on meal frequency, skipping, and intervals, and had linked mortality information, including underlying causes of death. After further exclusion of 534 women who are currently pregnant or breastfeeding, 3,136 participants with implausible total energy intake ($<$600 or $>$5000 kcal/day), and 78 participants who reported no meal consumption, 24,011 participants were left in the final analysis.

Meal Frequency and Intervals

In all surveys, a trained dietary interviewer used a standardized protocol to administer a 24-hour recall of foods and beverages. One in-person dietary recall was collected in the 1999-2000, and 2001-2002 surveys. For the later six surveys in 2003-2014, a second recall was collected, via telephone, 3 to 10 days after the mobile exam center visit. This study used the first recall for all surveys. During the 24-hour recall interview, participants were asked to report the clock time when a food or beverage was consumed. For every food or beverage item recalled, participants also chose a name of the eating event from a list. All items reported in one event were given the same clock time and event name in the recall. Participants could choose from "breakfast," "brunch," "lunch," "dinner," "supper," "snack," "drink," or "extended consumption" or their equivalents in Spanish.

Reports of breakfast, lunch, and dinner or their equivalents in Spanish were considered as meals in this study. Breakfast consumption was defined based on self-reported consumption of morning meal, including "breakfast" and the Spanish equivalents. Lunch consumption was defined based on self-reported consumption of noon meal, including "lunch," "brunch," and the Spanish equivalents. Dinner consumption was defined based on self-reported consumption of afternoon meal, including "dinner," "supper," and the Spanish equivalents. All other eating events were considered as snack. All foods and beverages reported at one discrete clock time were considered as part of one eating event. Reports of two similarly named meals (eg, two breakfasts) but at different clock times were considered as two meals. Meal frequency was calculated as the sum of frequency of breakfast, lunch, and dinner consumption, and further categorized as one, two, three and four or more meals per day. Skipping breakfast, lunch, or dinner was defined as no reporting of breakfast, lunch, or dinner consumption during the 24-hour recall. Average intervals between meals were calculated as interval between the reported clock time (in hours) of the first and the last meal divided by (meal frequency $-$ 1). It was further categorized as $\leq$4.5, 4.6 to 5.5, and $>$5.5 hours, based on the average time required for complete emptying of the stomach.[13]

Ascertainment of Mortality Outcomes

Mortality status for each participant was determined using the NHANES Public-Use Linked Mortality File, which was created by the NCHS to permit a longitudinal study of participants in NHANES.[14] This file contains information based upon the results from a probabilistic match between NHANES and the National Death Index records to ascertain the vital status of each eligible NHANES subject through December 31, 2015. Underlying causes of death were classified according to the codes of the International Classification of Diseases 10th Revision.[15] The NCHS classified mortality from heart diseases, including acute rheumatic fever and chronic rheumatic heart diseases (codes I00-I09), hypertensive heart disease (codes I11), hypertensive heart and renal disease (codes I13), ischemic heart diseases (codes I20-I25) and other heart

diseases (codes I26-I51), and mortality from cerebrovascular disease (ie, stroke) (codes I60-I69) according to International Classification of Diseases 10th Revision. Deaths from CVD were defined as death from either heart disease or cerebrovascular disease. Persons who survived were administratively censored on December 31, 2015. Follow-up time for each person was calculated as the difference between the NHANES survey date and the last known date alive or censored from the NHANES mortality study.

Covariate Assessment

Information on age, gender, race and ethnicity, education, annual household income, smoking status, and physical activity was collected during the in-house interviews which were administered by trained interviewers.[16] Race and ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic (Mexican and non-Mexican Hispanic), and other race and ethnicity. Educational attainment was grouped as less than high school diploma, high school graduate/GED or equivalent, and college graduate or above. Family income-to-poverty ratios were categorized as <1.0, 1.0 to 1.99, 2.0 to 3.99, and ≥4.0 based on the federal poverty level for the survey year.[17] Individuals who smoked <100 cigarettes in their lifetime were defined as never smokers; those who had smoked >100 cigarettes but did not smoke at the time of survey were considered former smokers; those who had smoked >100 cigarettes and smoked cigarettes at the time of survey were current smokers.[18] Physical activity was assessed using the Global Physical Activity Questionnaire, and was classified into three groups (<600, 600 to 1,199, and ≥1,200 metabolic equivalent of task minutes per week).[19]

Dietary intake was assessed through 24-hour dietary recalls. Total energy intake was calculated using the Food and Nutrient Database for Dietary Studies and the Food Patterns Equivalents Database.[20,21] Alcohol intake was categorized as nondrinking (0 g/day), moderate drinking (0.1 to 27.9 g/day for men and 0.1 to 13.9 g/day for women), and heavy drinking (≥28 g/day for men and ≥14 g/day for women). Overall diet quality was assessed by the Healthy Eating Index (HEI) 2010, which is scored on the basis of the intake levels of 12 dietary components, including total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, and empty calories (ie, energy from solid fats, alcohol, and added sugars).[22] The Simple HEI Scoring Algorithm (Per Person) was used to calculate the individual HEI-2020 score.[23] Food insecurity was assessed by the Adult Food Security Survey Module, which is a standardized 10-item questionnaire developed by the US Department of Agriculture, validated and used in many national surveys.[24,25]

Trained technicians measured weight and height. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and was categorized as <25, 25 to 29.9, and ≥30.[26] Baseline diabetes was defined based on a self-reported physician diagnosis, plasma fasting glucose levels of 126 mg/dL (to convert to mmol/L, multiply by 0.0555) or higher, glycated hemoglobin level 6.5% or higher, or 2-hour plasma glucose levels of 200 mg/dL or higher.[27] Baseline hypertension was defined based on a self-reported physician diagnosis, currently taking antihypertensive medications, mean systolic blood pressure ≥130 mm Hg, or mean diastolic blood pressure ≥80 mm Hg.[28] Baseline hypercholesterolemia was defined based on self-reported physician diagnosis, currently taking cholesterol-lowering medications, plasma levels of total cholesterol ≥240 mg/dL (to convert to mmol/L, multiply by 0.0259), or plasma levels of low-density lipoprotein-cholesterol ≥160 mg/dL.[29] Baseline CVD status was defined based on self-reported physician diagnosis of congestive health failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke. Baseline cancer status was defined based on a self-reported physician diagnosis of cancer or malignancy.

Statistical Analysis

This study followed the NHANES Analytic Guidelines developed by the NCHS when conducting and reporting this study.[17] All statistical analyses accounted for the complex, multistage, stratified, cluster-sampling design of NHANES by using sample weights, strata, and primary sampling units embedded in the NHANES data. Comparisons of characteristics among participants across categories of meal frequency were performed using analysis of variance for continuous variables and chi-square test for categorical variables.

Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs of mortality in relation to meal frequency and intervals. Model 1 adjusted for age, gender, and race and ethnicity. Model 2 additionally adjusted for education, income, smoking status, alcohol intake, physical activity levels, total energy intake, HEI-2010 score, household adult food insecurity status, and snacks frequency. Model 3 further adjusted for baseline diabetes, hypertension, hypercholesterolemia, CVD, cancer, and BMI status, because these variables may be mediators between meal frequency, intervals and timing, and mortality.[30,31]

For sensitivity analyses, the analyses were repeated by excluding participants with CVD or cancer at baseline. All analyses were performed using survey procedures in SAS 9.4.[32] Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

During 185,398 person-years of period, 4,175 deaths occurred, including 878 CVD deaths. Most participants (56.7%) ate three meals per day. As shown in Table 1, compared with participants with three meals per day, participants eating fewer than three meals per day were more likely to be younger, men, non-Hispanic Black, with less education and lower family income, current smokers, heavy alcohol drinkers, higher physical activity levels, lower total energy intake and lower diet quality, food insecure, and higher frequency of snacks. They were less likely to have diabetes, and cancer at baseline. The characteristics for participants who ate more than three meals per day were comparable to those for participants with three meals per day, except participants who ate more than three meals per day were more likely to be with higher physical activity levels, higher total energy intake, and higher diet quality, lower BMI, lower frequency of snacks, and less likely to have CVD at baseline.

Table 1. Characteristics of 24,011 US adults aged 40 years or older according to meal frequency, National Health and Nutrition Examination Survey, 1999-2014

Characteristic	Meal frequency				*P* value[a]
	1	2	3	≥4	
No. of participants	1,116	6,315	13,626	2,954	
	←——— *mean (SE)* ———→				
Age (y)	53.1 (0.3)	55.8 (0.2)	57.5 (0.2)	55.7 (0.3)	< 0.001
Total energy intake (kcal/d)	1,732 (33)	1,945 (14)	2,090 (10)	2,229 (24)	< 0.001
Heealthy Eating Index-2010 score	43.2 (0.6)	47.2 (0.3)	52.5 (0.2)	53.0 (0.4)	< 0.001
Snacks frequency (times/d)	2.8 (0.1)	2.4 (0.03)	2.1 (0.02)	2.0 (0.04)	< 0.001
Body mass index	28.9 (0.3)	29.5 (0.1)	29.0 (0.1)	28.5 (0.2)	< 0.001
	←——— *% (SE)*[b] ———→				
Male gender (%)	55.9 (1.9)	49.9 (0.8)	45.5 (0.5)	49.6 (1.2)	< 0.001
Race and ethnicity					
Non-Hispanic White	61.7 (2.7)	69.3 (1.5)	78.7 (1.0)	74.9 (1.2)	< 0.001
Non-Hispanic Black	24.6 (2.1)	15.1 (1.0)	7.4 (0.5)	7.6 (0.6)	
Hispanic	8.8 (1.2)	11.3 (0.9)	8.8 (0.7)	10.9 (0.8)	
Other[c]	4.8 (1.1)	4.3 (0.4)	5.1 (0.3)	6.5 (0.6)	
Education					
Less than high school diploma	30.6 (1.7)	22.7 (0.8)	15.9 (0.5)	18.2 (1.1)	< 0.001
High school graduate/GED or equivalent	28.1 (1.9)	25.6 (0.7)	23.9 (0.7)	24.6 (1.2)	
College graduate or above	41.4 (2.2)	51.7 (1.0)	60.3 (0.9)	57.1 (1.5)	
Ratio of family income to poverty					
<1.0	22.2 (1.6)	12.9 (0.6)	8.0 (0.4)	8.4 (0.6)	< 0.001
1.00-1.99	22.7 (1.9)	20.0 (0.8)	16.5 (0.6)	17.1 (1.0)	
2.00-3.99	26.5 (2.1)	27.5 (0.9)	27.6 (0.7)	26.7 (1.1)	
≥4	22.1 (2.1)	32.4 (1.0)	41.3 (1.0)	41.4 (1.4)	
Missing	6.5 (0.9)	7.2 (0.5)	6.6 (0.4)	6.3 (0.5)	
Smoking status					
Never smoker	37.9 (2.0)	44.8 (0.9)	52.7 (0.6)	48.8 (1.4)	< 0.001
Former smoker	19.7 (1.7)	29.2 (0.8)	32.1 (0.5)	34.4 (1.2)	
Current smoker	42.4 (2.3)	26.0 (0.9)	15.3 (0.4)	16.8 (1.0)	
Alcohol intake[d]					
Non-drinking	69.8 (2.2)	72.1 (0.9)	73.4 (0.8)	64.2 (1.4)	< 0.001
Moderate drinking	8.0 (1.3)	9.9 (0.6)	11.0 (0.4)	13.7 (1.0)	
Heavy drinking	22.1 (1.7)	17.9 (0.7)	15.7 (0.6)	22.1 (1.3)	
Physical activity (MET-min/wk)					
<600	51.0 (2.0)	47.2 (0.9)	41.3 (0.7)	37.9 (1.4)	< 0.001
≥600-1,199	9.8 (1.5)	11.8 (0.5)	14.0 (0.4)	15.2 (0.8)	
≥1,200	39.2 (1.8)	41.0 (0.8)	44.7 (0.7)	46.9 (1.4)	
Food insecurity	18.2 (1.4)	11.9(0.5)	7.1 (0.3)	8.7 (0.7)	< 0.001
Baseline diabetes	14.2 (1.2)	16.7 (0.5)	17.5 (0.5)	15.3 (0.8)	0.01
Baseline hypertension	59.7 (1.9)	60.6 (0.9)	59.7 (0.6)	57.7 (1.2)	0.18
Baseline hypercholesterolemia	46.9 (2.2)	51.1 (0.8)	50.2 (0.6)	51.0 (1.2)	0.20

(*continued on next page*)

Table 1. Characteristics of 24,011 US adults aged 40 years or older according to meal frequency, National Health and Nutrition Examination Survey, 1999-2014 (*continued*)

Characteristic	Meal frequency				*P* value[a]
	1	2	3	≥4	
Baseline cardiovascular disease	12.3 (1.1)	13.8 (0.5)	12.4 (0.4)	10.0 (0.7)	< 0.001
Baseline cancer	8.7 (1.1)	11.1 (0.6)	14.4 (0.4)	12.7 (0.8)	< 0.001
Body mass index status					
Normal weight and underweight	29.2 (1.9)	24.5 (0.7)	27.5 (0.6)	28.5 (1.1)	< 0.001
Overweight	36.5 (1.8)	34.7 (0.9)	35.2 (0.5)	37.1 (1.3)	
Obesity	33.2 (2.0)	39.1 (0.9)	35.9 (0.6)	33.2 (1.2)	
Missing	1.1 (0.2)	1.7 (0.2)	1.3 (0.1)	1.2 (0.2)	

[a]*P* values indicated comparisons of characteristics among participants across categories of meal frequency. The comparisons were performed using analysis of variance for continuous variables and χ^2 test for categorical variables.
[b]The numbers in the table were unweighted and the percentages of values were weighted.
[c]Other included other races and multiracial.
[d]Nondrinker = 0 g/day alcohol; moderate drinking = 0.1 to 27.9 g/day alcohol for men and 0.1 to 13.9 g/day alcohol day for women; and heavy drinking: ≥28 g/day alcohol for men and ≥14 g/day alcohol for women.

The association between meal frequency and all-cause and CVD mortality were shown in Table 2. After adjustment for age, gender, race and ethnicity, socioeconomic status, lifestyle factors, and baseline history of diseases, compared with participants with three meals per day, the multivariable-adjusted HRs all-cause mortality for participants eating one meal and two meals were 1.30 (95% CI 1.03 to 1.64), and 1.07 (95% CI 0.98 to 1.16), respectively. For CVD mortality, the multivariable-adjusted HRs for participants eating one meal and two meals were 1.83 (95% CI 1.26 to 2.65), and 1.10 (95% CI 0.90 to 1.35), respectively. Eating more than three meals per day was not associated with all-cause or CVD mortality compared with eating three meals per day. The multivariable-adjusted HRs for the participants who ate more than three meals per day were 0.91 (95% CI 0.79 to 1.04) for all-cause mortality, and 0.92 (95% CI 0.67 to 1.25) for CVD mortality.

The associations of skipping a specific meal with mortality were shown in Table 3. In the fully adjusted model, skipping breakfast was associated with higher risk of CVD mortality, whereas skipping lunch or dinner was associated with higher risk of all-cause mortality. Compared with participant who did not skip breakfast, the multivariable-adjusted HRs for participants who skipped breakfast were 1.11 (95% CI 0.98 to 1.26) for all-cause mortality, and 1.40 (95% CI 1.09 to 1.78) for CVD mortality. Compared with participant who did not skip lunch, the multivariable-adjusted HRs for participants who skipped lunch were 1.12 (95% CI 1.01 to 1.24) for all-cause mortality, and 1.15 (95% CI 0.94 to 1.40) for CVD mortality. Compared with participant who did not skip dinner, the multivariable-adjusted HRs for participants who skipped dinner were 1.16 (95% CI 1.02 to 1.32) for all-cause mortality, and 1.19 (95% CI 0.89 to 1.59) for CVD mortality.

The associations of meal intervals with mortality were shown in Table 4. Among those eating 3 meals/day, compared with an average interval between two daytime meals of 4.6 to 5.5 hours, the fully adjusted HRs associated with an average interval of ≤4.5 hours were 1.17 (95% CI 1.04 to 1.32) for all-cause mortality and 1.22 (95% CI 0.94 to 1.59) for CVD mortality. An interval >5.5 hours between two daytime meals was not associated with all-cause or CVD mortality, with the multivariable-adjusted HRs as 0.98 (95% CI 85 to 1.12), and 0.98 (95% 0.74 to 1.29), respectively.

Some of the results became statistically insignificant in the sensitivity analyses by excluding participants with CVD or cancer at baseline (Tables 5 through 7, available at www.jandonline.org), probably due to reduced sample size because similar HRs were observed.

DISCUSSION

In this large, prospective study of a nationally representative sample of US adults, eating 1 meal/day was associated with higher risk of all-cause and CVD mortality compared with eating 3 meals/day, whereas eating two meals per day or four or more meals per day was not associated with mortality in fully adjusted models. Specifically skipping breakfast was associated with higher risk of CVD mortality, whereas skipping lunch or dinner was associated with higher risk of all-cause mortality. Furthermore, meal intervals ≤4.5 hours was associated with higher risk of all-cause mortality, compared with meals intervals of 4.6 to 5.5 hours, whereas meal intervals >5.5 hours was not associated with mortality.

The findings that eating one meal per day was associated with higher risk of all-cause and CVD mortality were consistent with the findings of the only previous study on eating frequency and mortality. It was found that a decreasing trend in mortality was observed to be associated with increasing eating frequency.[33] The findings of this study were also consistent with findings from previous studies that greater eating frequency was related to improved risk status for coronary heart disease.[8,34] A meta-analysis of 21 randomized controlled trials found that higher meal frequency, not less meal frequency, could improve total cholesterol and low-density lipoprotein cholesterol levels in human.[35] Furthermore, evidence from animal experimental studies also showed that increased feeding frequency could also improve the postprandial glucose and insulin concentrations,

Table 2. Association of meal frequency with mortality among 24,011 US adults aged 40 years or older with meals at least 1 per day, National Health and Nutrition Examination Survey, 1999-2014

	Meal Frequency			
	1	2	3	≥4
	←——————————Hazard ratio (95% CI)——————————→			
All-cause mortality				
No. of cases/participants	224/1,116	1,137/6,315	2,424/13,626	390/2,954
Model 1[a]	1.69 (1.34-2.13)	1.24 (1.14-1.34)	Ref[b]	0.87 (0.76-0.99)
Model 2[c]	1.21 (0.95-1.55)	1.06 (0.98-1.15)	Ref	0.89 (0.78-1.03)
Model 3[d]	1.30 (1.03-1.64)	1.07 (0.98-1.16)	Ref	0.91 (0.79-1.04)
CVD mortality				
No. of cases/participants	54/1,116	242/6,315	504/13,626	78/2,954
Model 1[a]	2.21 (1.46-3.33)	1.24 (1.01-1.53)	Ref	0.84 (0.62-1.14)
Model 2[c]	1.67 (1.11-2.51)	1.09 (0.89-1.34)	Ref	0.89 (0.65-1.21)
Model 3[d]	1.83 (1.26-2.65)	1.10 (0.90-1.35)	Ref	0.92 (0.67-1.25)

[a]Model 1 was adjusted for age, gender, and race and ethnicity.
[b]Ref = reference category.
[c]Model 2 was model 1 + education, income, smoking status, alcohol intake, physical activity levels, total energy intake, overall diet quality indicated by Healthy Eating Index 2010 score, food insecurity status, and snacks frequency.
[d]Model 3 was model 2 + baseline diabetes, baseline hypertension, baseline hypercholesterolemia, baseline cardiovascular disease, baseline cancer, and body mass index status.

which might decrease cardiometabolic risk of hyperglycemia, glucosuria, and excessive insulinemia.[36]

Consistent with previous studies, this study confirmed that skipping breakfast was associated with higher CVD mortality.[9,37] However, to our best knowledge, there has not been a previous study that has investigated the association of skipping lunch or dinner with mortality. There was only one study that found a significant association between skipping dinner and increased risk of obesity, which provides support for the findings of this current study that skipping dinner was related with increased risk of all-cause mortality.[38] The association of skipping lunch with mortality disappeared with the adjustment for some lifestyle factors, which indicated that these lifestyle factors, such as diet quality, might have important role in the influence of skipping meals on mortality. Evidence from previous studies showed that people who skipped lunch had lower diet quality, less consumption of fruits and vegetables, and more consumption of sodium and refined grains, and these were also risk factors for mortality.[39]

There are several possible reasons that skipping meals is a probable risk factor of disease and mortality. First, skipping meals was an indicator of the inability to acquire adequate food, which has been shown to be associated with higher CVD risk among adults.[40,41] Second, skipping meals, in particular skipping breakfast, might also be a behavioral marker for unhealthy dietary and lifestyle habits.[39] However, the results remained significant after adjustment for food insecurity status, and a variety of dietary and lifestyle factors including smoking, alcohol use, physical activity levels, total energy intake and overall diet quality, making them less likely explanations for the observed association between skipping meals and mortality. Third, skipping meals usually means eating meals with a larger energy load, which could aggravate the burden of glucose metabolism regulation, and thus might lead to subsequent metabolic deterioration.[33] This could also explain the association between a shorter meal interval; for example, ≤4.5 hours, and mortality, as a shorter waiting time in between meals also means a larger energy load in a given period of time. In addition, skipping meals, in particular skipping breakfast, which is related to changes in appetite and decreased satiety, might lead to subsequent overeating later and impairment in insulin sensitivity.[42] By contrast, eating meals regularly has a beneficial effect on appetite regulation and also improves the glycemic response at the next eating occasion with increased sensitivity to insulin.[43,44] Fourth, skipping meals may reflect psychosocial conditions which are associated with elevated CVD risk; for example, anorexia nervosa.[45-48]

To our best knowledge, there were no prior study that has examined the association of duration of the daily postprandial period with cardiometabolic health. This study is the first to show that among participants with three meals per day, an average meal interval between two daytime meals of ≤4.5 hours was associated with a higher risk of all-cause mortality.

Strengths and Limitations

The strengths of this study include the use of detailed dietary information obtained from a 24-hour dietary recall in a large representative sample of US adults.[2] It was based on a nationally representative sample of US adults, the findings of which could be more directly translated to the general population. Furthermore, the reported clock time of each meal made it possible to calculate the intervals between meals. There are also several limitations. First, the measures of eating behaviors were self-reported, which might lead to

Table 3. Association of skipping meal with mortality among 24,011 US adults aged 40 years or older with meals at least one per day, National Health and Nutrition Examination Survey, 1999-2014

	Skipping Breakfast	
	No	Yes
	←——————Hazard ratio (95% CI)——————→	
All-cause mortality		
No. of cases/participants	3,736/21,217	439/2,794
Model 1[a]	Ref[b]	1.38 (1.22-1.57)
Model 2[c]	Ref	1.10 (0.96-1.25)
Model 3[d]	Ref	1.11 (0.98-1.26)
Cardiovascular disease mortality		
No. of cases/participants	779/21,217	99/2,794
Model 1[a]	Ref	1.68 (1.32-2.15)
Model 2[c]	Ref	1.36 (1.05-1.75)
Model 3[d]	Ref	1.40 (1.09-1.78)
	Skipping lunch	
All-cause mortality		
No. of cases/participants	2,970/17,830	1,205/6,181
Model 1[a]	Ref	1.26 (1.16-1.38)
Model 2[c]	Ref	1.07 (0.97-1.18)
Model 3[d]	Ref	1.12 (1.01-1.24)
Cardiovascular disease mortality		
No. of cases/participants	614/17,830	264/6,181
Model 1[a]	Ref	1.28 (1.06-1.55)
Model 2[c]	Ref	1.09 (0.89-1.34)
Model 3[d]	Ref	1.15 (0.94-1.40)
	Skipping dinner	
All-cause mortality		
No. of cases/participants	3726/21,722	449/2,289
Model 1[a]	Ref	1.22 (1.07-1.38)
Model 2[c]	Ref	1.13 (0.99-1.29)
Model 3[d]	Ref	1.16 (1.02-1.32)
Cardiovascular disease mortality		
No. of cases/participants	779/21,722	99/2,289
Model 1[a]	Ref	1.22 (0.91-1.63)
Model 2[c]	Ref	1.16 (0.87-1.56)
Model 3[d]	Ref	1.19 (0.89-1.59)

[a]Model 1 was adjusted for age, gender, and race and ethnicity.
[b]Ref = reference category.
[c]Model 2 was model 1 + education, income, smoking status, alcohol intake, physical activity levels, total energy intake, overall diet quality indicated by Healthy Eating Index 2010 score, food insecurity status, snacks frequency, and mutual adjustment for each other (skipping breakfast, skipping lunch and slipping dinner).
[d]Model 3 was model 2 + baseline diabetes, baseline hypertension, baseline hypercholesterolemia, baseline cardiovascular disease, baseline cancer, and body mass index status.

Table 4. Association of average meal intervals with mortality among 13,626 US adults aged 40 years or older with three meals per day, National Health and Nutrition Examination Survey, 1999-2014

	Meal Intervals (h)		
	≤4.5	4.6-5.5	>5.5
	←——————Hazard ration (95% CI)——————→		
All-cause mortality			
No. of cases/participants	666/3,270	1111/5,770	647/4,586
Model 1[a]	1.28 (1.14-1.45)	Ref[b]	0.94 (0.82-1.08)
Model 2[c]	1.19 (1.06-1.33)	Ref	0.98 (0.84-1.13)
Model 3[d]	1.17 (1.04-1.32)	Ref	0.98 (0.85-1.12)
Cardiovascular disease mortality			
No. of cases/participants	136/3,270	230/5,770	138/4,586
Model 1[a]	1.40 (1.08-1.82)	Ref	0.96 (0.73-1.28)
Model 2[c]	1.27 (0.98-1.64)	Ref	0.99 (0.75-1.31)
Model 3[d]	1.22 (0.94-1.59)	Ref	0.98 (0.74-1.29)

[a]Model 1 was adjusted for age, gender, and race and ethnicity.
[b]Ref = reference category.
[c]Model 2 was model 1 + education, income, smoking status, alcohol intake, physical activity levels, total energy intake, overall diet quality indicated by Healthy Eating Index 2010 score, and food insecurity status.
[d]Model 3 was model 2 + baseline diabetes, baseline hypertension, baseline hypercholesterolemia, baseline cardiovascular disease, baseline cancer, and body mass index status.

recall bias. This may bias the results towards the null. Second, the lack of information on sleep such as sleep duration or bedtime makes it impossible to evaluate the role of sleep as a potential confounder for the association between meal patterns and mortality. Third, because only one in-person dietary recall was collected in the 1999-2000, and 2001-2002 cycles, this study used the first recall for all surveys. Fourth, despite the adjustment for a wide range of potential factors that were both related to meal consumption and mortality, there is still a possibility of residual confounding by unmeasured factors, such as neighborhood characteristics, detailed housing condition, or occupational environment. Fifth, this study focused on meal skipping regardless of snack consumption, thus the evidence provided for healthy effects of intermittent fasting is limited.

This study has significant public health implications. Previous dietary studies and Dietary Guidelines for Americans have focused mainly on dietary components and food combinations. Little is known about the association of eating behaviors such as meal skipping and meal intervals with health. The findings have contributed to the current evidence regarding the association between eating behaviors and mortality by examining the association between meal skipping and mortality, in the context of meal timing and duration of the daily prandial period.

CONCLUSIONS

In this large, prospective study of US adults aged 40 years or older, eating one meal per day was significantly associated with an increased risk of all-cause and CVD mortality compared with eating three meals per day. Skipping breakfast was associated with increased risk of CVD mortality, whereas skipping lunch or dinner was associated with higher risk of all-cause mortality. Moreover, among participant with 3 meals/day, a shorter interval between meals (≤4.5 hours) was associated with higher risk of all-cause mortality. The results support the role of eating at least three meals per day and a >4.5 hours of waiting time in between two daytime meals in relation to better cardiovascular health. These findings need replication and assessment in other populations.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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Y. Sun, S. Rong, and W. Bao contributed to the conception and design of the study. Y. Sun and S. Rong analyzed data and wrote the manuscript. All authors contributed to the acquisition, analysis, or interpretation of the data, and revised the manuscript for important intellectual content. W. Bao and Y. Sun primary responsibility for final content. All authors read and approved the final manuscript.

Table 5. Association of meal frequency with mortality among 17,901 US adults aged 40 years or older with meals at least 1 per day (baseline cardiovascular disease [CVD] and cancer excluded), National Health and Nutrition Examination Survey, 1999-2014

	Meal Frequency			
	1	2	3	≥4
	←——— Hazard ratio (95% CI) ———→			
All-cause mortality				
No. of cases/participants	136/884	607/4,776	1,192/9,961	212/2,280
Model 1[a]	1.66 (1.25-2.19)	1.22 (1.08-1.38)	[b]Ref	0.90 (0.75-1.08)
Model 2[c]	1.19 (0.89-1.59)	1.08 (0.96-1.21)	Ref	0.88 (0.73-1.07)
Model 3[d]	1.26 (0.94-1.68)	1.10 (0.98-1.23)	Ref	0.88 (0.73-1.07)
CVD mortality				
No. of cases/participants	27/884	125/4,776	226/9,961	35/2,280
Model 1[a]	1.57 (0.96-2.58)	1.23 (0.92-1.65)	Ref	0.80 (0.54-1.17)
Model 2[c]	1.20 (0.77-1.86)	1.12 (0.83-1.50)	Ref	0.80 (0.53-1.19)
Model 3[d]	1.31 (0.85-2.02)	1.15 (0.85-1.55)	Ref	0.80 (0.54-1.19)

[a]Model 1 was adjusted for age, gender, and race and ethnicity.
[b]Ref = reference category.
[c]Model 2 was model 1 + education, income, smoking status, alcohol intake, physical activity levels, total energy intake, overall diet quality indicated by Healthy Eating Index 2010 score, food insecurity status, and snacks frequency.
[d]Model 3 was model 2 + baseline diabetes, baseline hypercholesterolemia, baseline hypertension, and body mass index status.

Table 6. Association of skipping meal with mortality among 17,901 US adults aged 40 years or older with meals at least 1 per day (baseline cardiovascular disease [CVD] and cancer excluded), National Health and Nutrition Examination Survey, 1999-2014

	Skipping Breakfast	
	No	Yes
	←——————Hazard ratio (95% CI)——————→	
All-cause mortality		
No. of cases/participants	1882/15,657	265/2,244
Model 1[a]	Ref[b]	1.42 (1.22-1.66)
Model 2[c]	Ref	1.15 (0.98-1.35)
Model 3[d]	Ref	1.18 (0.99-1.39)
CVD-mortality		
No. of cases/participants	352/15,657	61/2,244
Model 1[a]	Ref	1.99 (1.44-2.74)
Model 2[c]	Ref	1.70 (1.22-2.36)
Model 3[d]	Ref	1.77 (1.28-2.45)
	Skipping lunch	
All-cause mortality		
No. of cases/participants	1512/13,303	635/4,598
Model 1[a]	Ref	1.25 (1.10-1.41)
Model 2[c]	Ref	1.07 (0.94-1.21)
Model 3[d]	Ref	1.10 (0.96-1.25)
CVD mortality		
No. of cases/participants	286/13,303	127/4,598
Model 1[a]	Ref	1.18 (0.87-1.61)
Model 2[c]	Ref	1.01 (0.73-1.40)
Model 3[d]	Ref	1.05 (0.76-1.45)
	Skipping dinner	
All-cause mortality		
No. of cases/participants	1884/16,137	263/1,764
Model 1[a]	Ref	1.27 (1.04-1.54)
Model 2[c]	Ref	1.18 (0.97-1.43)
Model 3[d]	Ref	1.20 (0.99-1.46)
CVD mortality		
No. of cases/participants	362/16,137	51/1,764
Model 1[a]	Ref	1.09 (0.69-1.70)
Model 2[c]	Ref	1.01 (0.64-1.59)
Model 3[d]	Ref	1.02 (0.65-1.60)

[a]Model 1 was adjusted for age, gender, and race and ethnicity.
[b]Ref = reference category.
[c]Model 2 was model 1 + education, income, smoking status, alcohol intake, physical activity levels, total energy intake, overall diet quality indicated by Healthy Eating Index 2010 score, food insecurity status, snacks frequency, and mutual adjustment for each other (skipping breakfast, skipping lunch and skipping dinner).
[d]Model 3 was model 2 + baseline diabetes, baseline hypertension, baseline hypercholesterolemia, baseline CVD, and body mass index status.

Table 7. Association of average meal intervals with mortality among 9,961 US adults aged 40 years or older with 3 meals per day (baseline cardiovascular disease [CVD] and cancer excluded), National Health and Nutrition Examination Survey, 1999-2014

	Meal Interval (h)		
Variable	**≤4.5**	**4.6-5.5**	**>5.5**
	←——————————Hazard ratio (95% CI)——————————→		
All-cause mortality			
No. of cases/participants	317/2,303	532/4,096	343/3,562
Model 1[a]	1.30 (1.09-1.57)	Ref[b]	0.95 (0.78-1.17)
Model 2[c]	1.21 (1.02-1.45)	Ref	1.00 (0.81-1.22)
Model 3[d]	1.19 (0.99-1.43)	Ref	0.97 (0.79-1.19)
CVD mortality			
No. of cases/participants	58/2,303	99/4,096	69/3,562
Model 1[a]	1.45 (0.93-2.28)	Ref	1.10 (0.71-1.68)
Model 2[c]	1.38 (0.88-2.15)	Ref	1.16 (0.76-1.78)
Model 3d[c]	1.35 (0.85-2.14)	Ref	1.12 (0.74-1.71)

[a]Model 1 was adjusted for age, gender, and race and ethnicity.
[b]Ref = reference category.
[c]Model 2 was model 1 + education, income, smoking status, alcohol intake, physical activity levels, total energy intake, overall diet quality indicated by Healthy Eating Index 2010 score, and food insecurity status.
[d]Model 3 indicates model 2 + baseline diabetes, baseline hypertension, baseline hypercholesterolemia, baseline CVD, and body mass index status.