The Association of Energy and Macronutrient Intake at Dinner Versus Breakfast With Disease-Specific and All-Cause Mortality Among People With Diabetes: The U.S. National Health and Nutrition Examination Survey, 2003–2014

Tianshu Han,[1,2] Jian Gao,[1] Lihong Wang,[2] Chao Li,[3] Lu Qi,[4] Changhao Sun,[1] and Ying Li[1]

Diabetes Care 2020;43:1442–1448 | https://doi.org/10.2337/dc19-2289

OBJECTIVE

This study aims to evaluate the association of energy and macronutrient intake at dinner versus breakfast with disease-specific and all-cause mortality in people with diabetes.

RESEARCH DESIGN AND METHODS

A total of 4,699 people with diabetes who enrolled in the National Health and Nutrition Examination Survey from 2003 to 2014 were recruited for this study. Energy and macronutrient intake was measured by a 24-h dietary recall. The differences (Δ) in energy and macronutrient intake between dinner and breakfast (Δ = dinner − breakfast) were categorized into quintiles. Death information was obtained from the National Death Index until 2015. Cox proportional hazards regression models were developed to evaluate the survival relationship between Δ and diabetes, cardiovascular disease (CVD), and all-cause mortality.

RESULTS

Among the 4,699 participants, 913 deaths, including 269 deaths due to diabetes and 314 deaths due to CVD, were documented. After adjustment for potential confounders, compared with participants in the lowest quintile of Δ in terms of total energy and protein, participants in the highest quintile were more likely to die due to diabetes (hazard ratio [HR]$_{\Delta energy}$ 1.92, 99% CI 1.08–3.42; HR$_{\Delta protein}$ 1.92, 99% CI 1.06–3.49) and CVD (HR$_{\Delta energy}$ 1.69, 99% CI 1.02–2.80; HR$_{\Delta protein}$ 1.96, 99% CI 1.14–3.39). The highest quintile of Δtotal fat was related to CVD mortality (HR 1.67, 99% CI 1.01–2.76). Isocalorically replacing 5% of total energy at dinner with breakfast was associated with 4% and 5% lower risk of diabetes (HR 0.96, 95% CI 0.94–0.98) and CVD (HR 0.95, 95% CI 0.93–0.97) mortality, respectively.

CONCLUSIONS

Higher intake of energy, total fat, and protein from dinner than breakfast was associated with greater diabetes, CVD, and all-cause mortality in people with diabetes.

[1]Department of Nutrition and Food Hygiene, National Key Discipline, School of Public Health, Harbin Medical University, Harbin, China
[2]Department of Endocrinology, The Second Affiliated Hospital of Harbin Medical University, Harbin, China
[3]Medical University of South Carolina, Charleston, SC
[4]Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA

Corresponding authors: Ying Li, liying_helen@163.com, and Changhao Sun, changhaosun2002@163.com

Received 15 November 2019 and accepted 4 April 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.12106815.

This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

Diabetes, as the ninth major cause of death, is a rapid growing public health concern worldwide (1). Diet is an important modifiable behavior that plays a critical role in the prevention and treatment of diabetes (2,3). In recent years, accumulating evidence shows that energy distribution across a day can influence the physiological metabolism; particularly, high energy intake at dinner may be associated with metabolic disorder through disrupted clock gene expression (4). Nowadays, people are still consuming a high proportion of daily energy at dinner (5); however, limited research has focused on the extent to which the distribution of energy and macronutrient intake in a day impacts the natural course of diabetes.

Energy intakes from dinner and breakfast have different impacts on postmeal glycemia due to its circadian effects (6–9), which are related to the internal synchrony of metabolic process (10,11). Recent animal studies and short-term randomized clinical trials have shown that altered proportion of energy intake from meals, such as skipping breakfast or high energy intake at dinner, was associated with disrupted clock gene expression, leading to dyslipidemia and hyperglycemia (6,12–15). On the other hand, high energy intake from breakfast or prolonged time-restricted feeding at dinner could reverse the disrupted clock gene expression (15–17) and have beneficial effects on body weight, glucose, and lipid control in patients with diabetes (18,19). Therefore, we hypothesized that energy intake distribution in meals is associated with long-term survival among people with diabetes. To test this hypothesis, this study assessed the association of differences in energy and macronutrient intake from dinner versus breakfast with diabetes, cardiovascular disease (CVD), and all-cause mortality among people with diabetes using data from the National Health and Nutrition Examination Survey (NHANES).

RESEARCH DESIGN AND METHODS

Study Population

NHANES is a stratified, multistage study using a nationally representative sample of the noninstitutionalized civilian population of the U.S. Detailed information of NHANES has previously been provided (20). Briefly, adults (age ≥18 years) with diabetes who participated in NHANES from 2003 to 2014 were selected in this study. Diabetes was defined by a self-reported diagnosis, an HbA_{1c} level ≥6.5%, or a fasting plasma glucose level ≥7.0 mmol/L. After exclusion of participants who had missing information on any dietary intake and/or mortality, 4,699 participants with diabetes, including 2,413 men and 2,286 women, were included in the study. The institutional review board approval of the National Center for Health Statistics and written informed consent were obtained before data collection.

Dietary Assessment

Food intake was measured by a 24-h dietary recall for two nonconsecutive days. The first 24-h dietary recall was conducted in person, and the second 24-h dietary recall was conducted 3–10 days afterward via telephone. Dietary nutrients and energy intake were estimated by using the guidelines of the U.S. Department of Agriculture's Food and Nutrient Database for Dietary Studies (21). Dietary supplement usage was measured by a dietary supplement questionnaire. Based on the user guide of MyPyramid Equivalents Database, 2.0, for USDA Survey Foods (MPED 2.0), dietary intake components were integrated into 37 MyPyramid major groups and subgroups (22). In addition to the main meals, all other eating events were considered snacks. Five different snack patterns were derived based on when the snack was consumed in relation to a main meal. These snack patterns included *1*) snack before breakfast, *2*) snack between breakfast and lunch, *3*) snack between lunch and dinner, *4*) snack after dinner, and *5*) none of the above (23).

Main Exposure

The exposure variable of this study was the difference in total energy and macronutrient intake between dinner and breakfast (dinner − breakfast). The macronutrients assessed in this study included carbohydrate, fat (saturated fatty acids [SFA] and unsaturated fatty acids [USFA]), and protein (animal and plant).

Main Outcome

The outcome variable was mortality status, which was determined by using the National Death Index (NDI) by 31 December 2015 (24). The NDI is a highly reliable and widely used resource for death identification. The ICD-10 was used to determine disease-specific death. Death due to CVD was defined as ICD-10 codes I00–I09, I11, I13, I20–I51, or I60–I69. Death due to diabetes was defined as codes E10–E14. In total, 913 deaths, including 269 deaths due to diabetes and 314 deaths due to CVD, were documented.

Confounding and Effect Modification Measurements

Nondietary data included age (years), sex (men/women), race/ethnicity (non-Hispanic white/non-Hispanic black/Mexican American/other), education level (<9th grade, 9th–11th grade, high school graduate, GED or equivalent, some college or Associate in Arts degree, or college graduate or above), annual household income (<$20,000, $20,000–$45,000, $45,000–$75,000, or >$100,000), BMI ($kg/m^2$), systolic and diastolic blood pressure (mmHg), fasting plasma glucose (mmol/L), HbA_{1c} (%), HDL cholesterol (mmol/L), triglycerides (mmol/L), regular exercise (yes/no), current smoker (yes/no), current drinker (yes/no), family history of diabetes at first or second degree (yes/no), disease history of hypertension and dyslipidemia (yes/no), medication use for glucose or blood pressure or blood lipid control (yes/no), and duration of diabetes (years). Dietary measurements included dietary fiber (mg/day), whole grain (mg/day), dietary cholesterol (mg/day), energy (kcal/day), total dietary fat (g/day), protein (g/day), SFA (g/day), and USFA (g/day); breakfast skipping (yes/no); dietary supplement use (yes/no); and diet quality. Diet quality was calculated by the Alternative Healthy Eating Index (AHEI) (25).

Statistical Analysis

All analyses incorporated sample weights, stratification, and clustering to account for the complex survey design according to the NHANES analytic guidelines. Demographic characteristics, dietary nutrient intake, and anthropometric measurements were presented as mean (95% CI) for continuous variables and percentage (95% CI) for categorical variables. The differences in total energy and percentage of energy from macronutrients between dinner and breakfast (Δ = dinner − breakfast) were categorized into quintiles. General linear models adjusting for age and χ^2 tests were used to compare baseline characteristics as a function of Δ by quintiles.

Table 1—Baseline characteristics in terms of quintiles of differences in energy intake between dinner and breakfast: NHANES, 2003–2014

	Quintile 1 (N = 943)	Quintile 2 (N = 938)	Quintile 3 (N = 940)	Quintile 4 (N = 939)	Quintile 5 (N = 939)	P
Age, years	59.49 (58.28–60.71)	61.28 (60.19–62.37)	61.71 (60.53–62.89)	58.44 (57.18–59.69)	55.46 (54.32–56.61)	<0.001
Female, %	46.99 (43.21–50.80)	58.21 (53.85–62.45)	60.18 (56.09–64.12)	49.70 (45.20–54.20)	33.80 (29.90–37.90)	<0.001
Non-Hispanic white	44.80 (39.10–50.60)	59.82 (54.60–64.82)	65.28 (60.99–69.33)	67.67 (62.87–72.13)	68.73 (63.76–73.31)	<0.001
Current smoking, %	19.60 (16.28–23.40)	15.41 (12.77–18.49)	15.27 (12.64–18.33)	19.79 (16.57–23.46)	26.85 (22.96–31.14)	0.163
Current drinking, %	60.60 (56.52–64.53)	53.93 (48.80–58.97)	59.84 (55.99–63.58)	64.08 (59.60–68.33)	71.93 (67.40–76.06)	0.083
College graduate or above	11.82 (8.78–15.73)	28.21 (24.1–32.73)	17.84 (14.39–21.91)	20.08 (16.56–24.13)	20.88 (17.16–25.17)	<0.001
>$100,000 annual household income	7.28 (5.14–10.23)	9.03 (6.49–12.42)	9.09 (6.33–12.88)	9.29 (6.59–12.96)	12.57 (9.36–16.67)	<0.001
BMI, kg/m^2	31.63 (31.06–32.19)	31.59 (30.90–32.29)	32.55 (31.86–33.24)	32.88 (32.18–33.59)	33.47 (32.70–34.23)	0.001
Regular exercise, %	15.15 (11.98–18.98)	20.73 (17.58–24.27)	17.49 (13.53–22.32)	22.04 (18.45–26.10)	17.48 (13.79–21.91)	0.076
Dietary supplement use, %	47.88 (43.82–51.97)	55.56 (51.16–59.88)	55.55 (51.08–59.92)	59.36 (54.50–64.04)	51.31 (46.96–55.65)	0.342
Duration of diabetes, years	16.66 (0.97)	17.23 (1.02)	18.05 (1.12)	19.13 (1.17)	17.39 (1.45)	0.001
Family history of diabetes, %	2.08 (1.23–3.50)	2.77 (1.79–4.24)	1.90 (1.16–3.08)	3.77 (2.20–6.40)	3.50 (2.31–5.27)	0.186
Ever controlled diabetes, %	43.38 (39.11–47.76)	51.16 (46.24–56.05)	52.23 (48.04–56.38)	48.45 (44.00–52.92)	49.62 (44.98–54.27)	0.008
Prevalent hypertension, %	63.49 (58.68–68.05)	67.63 (63.29–71.68)	70.44 (66.64–73.98)	65.20 (60.72–69.42)	59.80 (55.92–63.55)	0.114
Ever controlled hypertension, %	55.92 (51.23–60.51)	62.01 (57.34–66.47)	63.78 (59.68–67.7)	58.20 (53.79–62.48)	52.29 (48.12–56.42)	0.003
Prevalent dyslipidemia, %	59.29 (54.73–63.7)	64.15 (60.33–67.79)	60.94 (56.53–65.18)	63.93 (59.74–67.91)	59.77 (55.84–63.59)	0.234
Ever controlled dyslipidemia, %	49.00 (45.08–52.93)	55.65 (51.34–59.88)	51.98 (47.28–56.63)	52.40 (48.20–56.57)	49.62 (45.79–53.46)	0.174
Total energy, kcal/day	1,789.7 (1,721.2–1,858.1)	1,611.0 (1,546.6–1,675.5)	1,694.7 (1,635.07–1,754.47)	1,902.8 (1,840.4–1,965.2)	2,400.3 (2,329.96–2,470.73)	<0.001
AHEI	44.72 (0.59)	43.30 (0.61)	44.98 (0.64)	49.34 (0.54)	55.12 (0.52)	<0.001
Energy at breakfast, kcal/day	656.62 (12.35)	420.16 (9.77)	366.37 (10.06)	333.66 (9.16)	290.08 (10.84)	<0.001
Energy at dinner, kcal/day	349.67 (10.33)	452.85 (9.90)	589.42 (10.08)	766.73 (9.44)	1,229.33 (18.67)	<0.001
SBP, mmHg	131.42 (129.72–133.12)	130.35 (128.69–132.01)	131.88 (129.88–133.88)	129.42 (127.77–131.07)	129.35 (127.91–130.78)	0.044
DBP, mmHg	68.95 (67.63–70.27)	68.56 (67.40–69.71)	66.90 (65.47–68.33)	69.82 (68.50–71.14)	70.63 (69.38–71.89)	<0.001
Serum glucose, mmol/L	8.73 (8.39–9.08)	8.39 (8.07–8.71)	8.03 (7.75–8.31)	8.32 (7.99–8.66)	8.57 (8.29–8.85)	0.917
Glycohemoglobin, %	7.37 (7.22–7.53)	7.22 (7.09–7.34)	7.13 (7.00–7.26)	7.12 (6.99–7.24)	7.32 (7.18–7.46)	0.745
Triglycerides, mmol/L	2.33 (2.13–2.52)	2.31 (2.02–2.60)	2.27 (2.06–2.49)	2.28 (2.09–2.47)	2.31 (2.16–2.45)	0.983
HDL cholesterol, mmol/L	1.21 (1.18–1.24)	1.26 (1.23–1.29)	1.24 (1.21–1.28)	1.23 (1.19–1.26)	1.19 (1.16–1.22)	0.007

Continuous variables are presented as weighted mean (95% CI). Categorical variables are presented as weighted percentages (95% CI). All data analyses conducted in the current study were based on estimates with sample weights provided by NHANES.

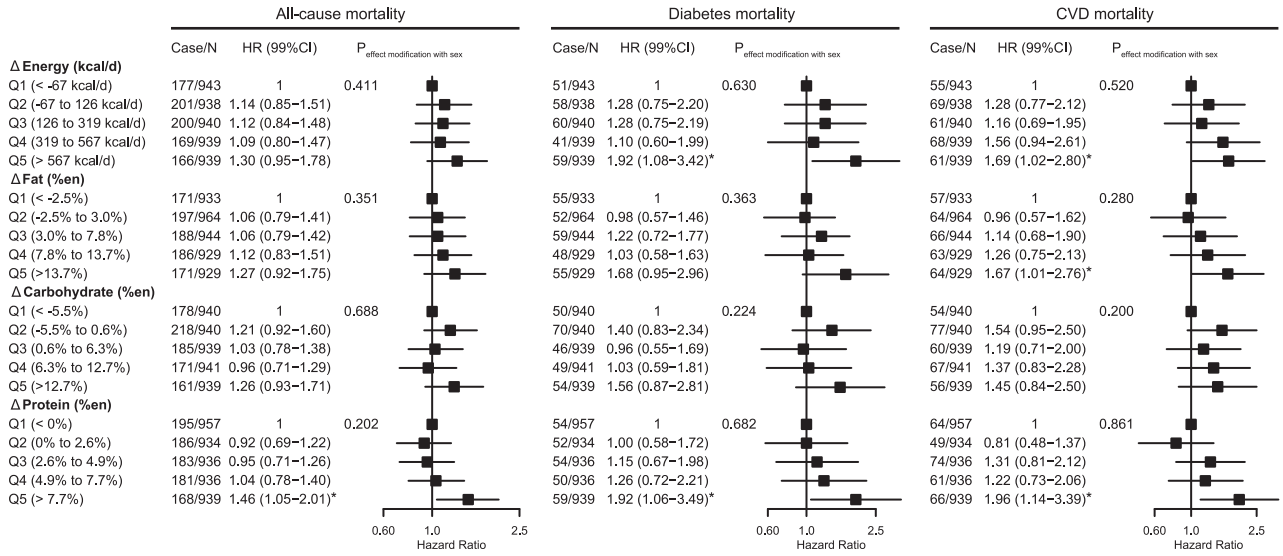

Figure 1—Adjusted HRs for the differences in total energy and macronutrient intake between dinner and breakfast and diabetes, CVD, and all-cause mortality. Adjustments included age, sex, ethnicity, income, education, exercise, smoking, alcohol intake, BMI, duration of diabetes, hypertension, dyslipidemia, nutrient supplement use, family history of diabetes, medication use for diabetes or hypertension or blood lipids, systolic and diastolic blood pressure, fasting plasma glucose, HbA_{1c}, HDL cholesterol, triglycerides, AHEI, and total intake of energy, fat, protein, cholesterol, SFA, USFA, whole grain, and dietary fiber. Case/N, number of case subjects/total; %en, percentage of energy provided by macronutrients; kcal/d, kcal/day; Q, quintile.

Cox Proportional Hazards Models

Cox proportional hazards (CPH) models were developed to evaluate the association between Δ and diabetes, CVD, and all-cause mortality. Survival time was months between NHANES interview date and death or census date (31 December 2015). We also controlled for a series of potential confounders and effect modifiers, which were age, sex, smoking, drinking, exercise, education, income, hypertension, dyslipidemia, family history of diabetes, duration of diabetes, medication use for glucose or blood pressure or blood lipids, systolic and diastolic blood pressure, fasting plasma glucose, HbA_{1c}, HDL cholesterol, triglycerides, BMI, dietary supplement use, AHEI, and dietary fiber, whole grain, cholesterol, energy, total fat, protein, SFA, and USFA, in all CPH models.

All statistical analyses were conducted by R 3.6.2, and two-sided $P < 0.01$ was considered to be statistically significant after Bonferroni correction for multiple comparisons in CPH models in order to reduce the likelihood of type 1 error. Accordingly, 99% CIs of hazard ratios (HRs) were provided.

Predicted Isocaloric Models

This study further built three sets of predicted isocaloric models to evaluate the extent to which a theoretical shift of total energy and energy from macronutrients would impact diabetes and CVD

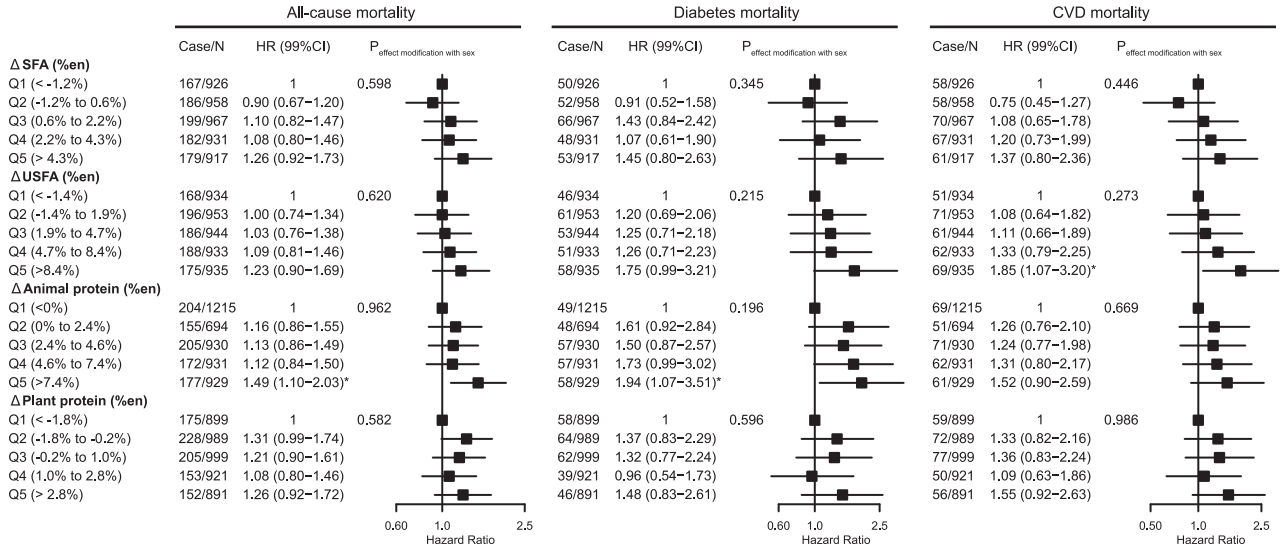

Figure 2—Adjusted HRs for the differences in SFA, USFA, and animal and plant protein intake between dinner and breakfast and diabetes, CVD, and all-cause mortality. Adjustments included age, sex, ethnicity, income, education, exercise, smoking, alcohol intake, BMI, duration of diabetes, hypertension, dyslipidemia, nutrient supplement use, family history of diabetes, medication use for diabetes or hypertension or blood lipids, systolic and diastolic blood pressure, fasting plasma glucose, HbA_{1c}, HDL cholesterol, triglycerides, AHEI, and total intake of energy, fat, protein, cholesterol, SFA, USFA, whole grain, and dietary fiber. Case/N, number of case subjects/total; %en, percentage of energy provided by macronutrients; Q, quintile.

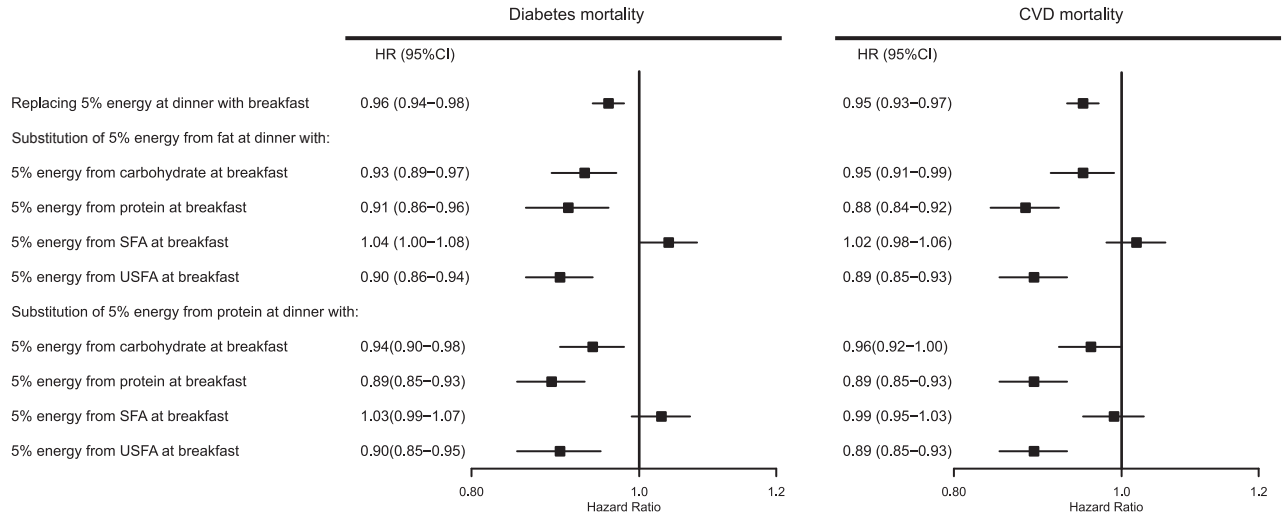

Figure 3—Adjusted HRs for diabetes and CVD mortality: isocaloric substitution of energy and macronutrients from dinner to breakfast. Adjustments included age, sex, ethnicity, income, education, exercise, smoking, alcohol intake, BMI, duration of diabetes, hypertension, dyslipidemia, nutrient supplement use, family history of diabetes, medication use for diabetes or hypertension or blood lipids, systolic and diastolic blood pressure, fasting plasma glucose, HbA_{1c}, HDL cholesterol, triglycerides, AHEI, and total intake of energy, fat, protein, cholesterol, SFA, USFA, whole grain, and dietary fiber.

mortality by holding total energy and all other macronutrient intake to be constant (26). In set 1, 5% of total energy intake was switched from dinner to breakfast; in set 2, 5% of energy intake from fat at dinner was substituted with 5% of energy intake from carbohydrate, protein, SFA, or USFA at breakfast; and in set 3, 5% of energy intake from protein at dinner was replaced with 5% of energy from carbohydrate, protein, SFA, or USFA at breakfast.

Sensitivity Analysis

Four sets of sensitivity analyses, by addition of breakfast skipping and energy from snack and lunch in all CPH models, were additionally performed as follows: in set 1, addition of skipped breakfast (yes/no) without snack consumption before lunch; in set 2, addition of skipped breakfast (yes/no) with snack consumption before lunch; in set 3, addition of energy intake from lunch; and in set 4, addition of snack consumption at breakfast and dinner.

RESULTS

Baseline Characteristics

The demographic and nutrition characteristics in terms of Δ in quintiles are presented in Table 1. Compared with those in quintiles 1–4, participants in quintile 5 were more likely to be younger, men, and non-Hispanic white and had higher income, BMI, total energy intake, and AHEI ($P < 0.05$). Other variables including smoking, drinking, exercise, nutritional supplements, family history of diabetes, prevalence of hypertension, and dyslipidemia were not significantly different across quintiles 1–5.

Cox Proportional Models

Association of Δtotal energy and macronutrients with all-cause, diabetes, and CVD mortality is presented in Figs. 1 and 2. As indicated by HR and 99% CI, participants in the highest quintile of Δenergy (quintile 5) were more likely to die due to diabetes (HR 1.92, 99% CI 1.08–3.42) and CVD (HR 1.69, 99% CI 1.02–2.80) than those in the lowest quintile of Δenergy (quintile 1). Also, energy intake from two macronutrients (fat and protein) was significantly related to mortality outcomes. For Δfat, participants in quintile 5 had significantly higher CVD mortality (HR 1.67, 99% CI 1.01–2.76) compared with those in quintile 1. Similarly, with regard to Δprotein, the highest quintile was significantly related to all-cause mortality (HR 1.46, 99% CI 1.05–2.01), diabetes mortality (HR 1.92, 99% CI 1.06–3.49), and CVD mortality (HR 1.96, 99% CI 1.14–3.39). Meanwhile, Δcarbohydrate was not significantly associated with all-cause, diabetes, and CVD mortality. Sex was not a significant effect modifier of the above association ($P_{\text{effect modification with sex}} > 0.01$ for all).

CPH models in Fig. 2 showed that ΔUSFA was significantly associated with deaths due to CVD (HR 1.85, 99% CI 1.07–3.20). Participants who had the greatest Δanimal protein were more likely to die due to all causes (HR 1.49, 99% CI 1.10–2.03) and diabetes (HR 1.94, 99% CI 1.07–3.51) compared with participants who had the smallest Δanimal protein. Sex did not have an effect modification influence on the above association ($P_{\text{effect modification with sex}} > 0.01$ for all).

Isocaloric Substitution Analysis

Figure 3 shows risk of diabetes and CVD mortality in three sets of predicted isocaloric models via switching energy intake at dinner to breakfast. In set 1, HRs for diabetes and CVD decreased by 4% (HR_{diabetes} 0.96, 95% CI 0.94–0.98) and 5% (HR_{CVD} 0.95, 95% CI 0.93–0.97) in models with 5% of total energy at dinner being isocalorically switched to breakfast; in set 2, HRs for diabetes and CVD decreased by 7% (HR_{diabetes} 0.93, 95% CI 0.89–0.97) and 5% (HR_{CVD} 0.95, 95% CI 0.91–0.99) in models replacing 5% of total energy from fat at dinner with 5% of total energy from carbohydrate at breakfast. Similarly, for replacing 5% of total energy from fat at dinner with 5% of total energy from protein, HRs for diabetes and CVD decreased by 9% (HR_{diabetes} 0.91, 95% CI 0.86–0.96) and 12% (HR_{CVD} 0.88, 95% CI 0.84–0.92). Also, HRs for diabetes and CVD decreased by 10% (HR_{diabetes} 0.90, 95% CI 0.86–0.94) and 11% (HR_{CVD} 0.89, 95% CI 0.85–0.93) in models with 5% of total energy from fat at dinner being isocalorically replaced by 5% of total energy from USFA at

breakfast. In set 3, HRs for diabetes decreased by 6% ($HR_{diabetes}$ 0.94, 95% CI 0.90–0.98) in models with replacement of 5% of total energy from protein at dinner with 5% of total energy from carbohydrate at breakfast. Also, for replacing 5% of total energy from protein from dinner to breakfast, HRs for diabetes and CVD decreased by 11% ($HR_{diabetes}$ 0.89, 95% CI 0.85–0.93) and 11% (HR_{CVD} 0.89, 95% CI 0.85–0.93). Also, HRs for diabetes and CVD decreased by 10% ($HR_{diabetes}$ 0.90, 95% CI 0.85–0.95) and 11% (HR_{CVD} 0.89, 95% CI 0.85–0.93) when 5% of total energy from protein at dinner was isocalorically replaced by 5% of total energy from USFA at breakfast.

Sensitivity Analysis

After adjustment for breakfast skipping and snack consumption in the morning, the first and second sets of sensitivity analyses showed that the association between Δtotal energy and Δprotein and mortality outcomes was attuned, but still significant, whereas the association between Δfat and mortality outcomes became nonsignificant (Supplementary Figs. 1 and 2). Similarly, in the third set of sensitivity analysis, after addition of energy and macronutrients from lunch, only the association between Δfat and mortality outcomes became nonsignificant (Supplementary Fig. 3). The first three sets of sensitivity analyses indicated that breakfast skipping and total fat intake at lunch may only impact the relationship between Δfat and mortality outcomes. The fourth set of sensitivity analysis showed all of the above association was still significant after consideration of snack consumption at breakfast and dinner (Supplementary Fig. 4).

CONCLUSIONS

This study demonstrated that excessive energy consumption at dinner over breakfast was associated with elevated diabetes, CVD, and all-cause mortality among people with diabetes, mainly due to higher energy intake from fat and protein at dinner. Moreover, isocalorically replacing 5% of energy intake at dinner with breakfast reduced risk of diabetes and CVD mortality by 4% and 5%, respectively.

To the best of our knowledge, this was the first study to examine the association of energy distribution across meals throughout the day with diabetes, CVD, and all-cause mortality among people with diabetes. The most important finding of this study was that higher intake of energy at dinner than breakfast was significantly associated with diabetes and CVD mortality, and this association was independent of a series of traditional dietary risk factors, in particular, breakfast skipping and diet quality (27,28). This study provides evidence of adverse effects of high energy intake at dinner and emphasized the importance of energy distribution across meals. Previous studies reported that each 10% increase in the proportion of energy consumed in the evening resulted in a 3% increase in C-reactive protein concentrations (29), and late-night eating was related to elevated risk of coronary heart disease (30). A randomized clinical trial conducted by Jakubowic et al. (18) indicated that high-energy breakfast with reduced dinner consumption could increase insulin sensitivity, decrease glucose excursions and HbA_{1c} levels, and reduce body weight. Another randomized clinical trial found that early time-restricted feeding (finishing dinner before 3:00 P.M.) could improve cardiometabolic health (19), which is consistent with the findings from this study. The alteration of circadian pattern could be a possible mechanism explaining the above association. Animal studies also suggested that consumption of high-energy breakfast determined the circadian phasing of peripheral clocks in liver with improved blood lipids (31,32), whereas high energy consumption at dinner was tightly related to lipid metabolism and adipose tissue accumulation (16,33). Also, increasing energy content at breakfast and reducing it at dinner could restore clock gene expression, leading to decreased glucose, blood lipid levels, and body weight (15–17). Taken all together, the accumulated findings of studies consistently demonstrate the potential beneficial effects of high energy intake at breakfast and low energy intake at dinner.

Another key finding of this study is that higher energy intake from fat and protein at dinner than breakfast is associated with diabetes, CVD, and all-cause mortality. Moreover, we observed in this study that replacing 5% energy from total fat or protein at dinner with the energy from carbohydrate, USFA, or protein at breakfast could significantly decrease the risk of diabetes and of CVD mortality among people with diabetes. One possible mechanism could be that the timing of macronutrient consumption influences the circadian clock machinery and metabolism (34–36) that control lipid and amino acid homeostasis (37–39). This hypothesis is supported by a series of mouse studies, which reported adverse health effects, including increased adiposity, decreased glucose tolerance, dyslipidemia, and metabolic syndrome, when mice consumed a high proportion of calories from fat in an ad libitum high-fat diet during the sleep phase, and protective health effects, including reduced body weight, cholesterol levels, and increased insulin sensitivity, with consumption of an isocaloric high-fat diet at the first meal during the activity phase (17,35). Our study suggests that not only nutritional values but also timing of meals need to be taken into consideration for dietary recommendations for patients with diabetes.

Strengths and Limitations

This study has several strengths. First, this was the first study to examine the association of energy and macronutrient distribution throughout the day with diabetes, CVD, and all-cause mortality using high-quality dietary data from a well-designed population-based study (NHANES). Second, the association reported in this study was relatively robust with adjustment for a variety of important dietary confounders, including breakfast skipping and diet quality. We also recognize that this study has certain limitations. First, although the self-reported 24-h dietary recall is the most valid and commonly used instrument to capture diet information in observational studies, it is subject to measurement error due to day-to-day variations in food intake. Second, we had the opportunity to control a series of potential confounders, but this study still was observational in nature, and other unmeasured confounding factors cannot be ruled out. Third, this study was not able to distinguish different types of diabetes. Future studies are needed to examine this association in terms of type 1 and type 2 diabetes in order to provide more comprehensive evidence. Last, we only used two dietary measurements in 2 weeks to predict long-term survival status for people with diabetes who may change dietary habits over time. Therefore,

future research is needed to evaluate the longitudinal effect of energy and macronutrient distribution on mortality outcomes.

Clinical Implications

Nutritional therapy is a critical element of diabetes treatment. Nutritional guidelines and intervention strategies should integrate and emphasize the importance of energy and macronutrient distribution across meals in a day. Diabetes care professionals should be aware of the current findings from this study regarding beneficial effects of high energy and macronutrient intake from breakfast and low energy and macronutrient intake from dinner. This information is of importance in providing individualized nutritional treatment plans for patients with diabetes.

In conclusion, higher intake of energy, total fat, and protein at dinner than at breakfast is associated with greater diabetes, CVD, and all-cause mortality in people with diabetes.

Acknowledgments. The authors thank the participants and staff of the NHANES 2003–2014 for valuable contributions.

Funding. This research was supported by funds from the National Key R&D Program of China (2017YFC1307401 to C.S.) and the National Natural Science Foundation (81803227 to T.H.).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.H., C.S., and Y.L. conceived the study design. T.H., J.G., and L.W. did the statistical analysis. C.L. and L.Q. repeated and validated the statistical analysis. T.H., C.S., and Y.L. wrote the manuscript. All authors provided critical insights of the manuscript. Y.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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