

Association of Energy Intake and Dietary Glycemic Load in Different Time Periods With Cardiovascular Disease Mortality Among U.S. Adults With Type 2 Diabetes

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2,911 U.S. adults with diabetes from the National Health and Nutrition Examination Survey (2003–2014) and followed up for death through 2019

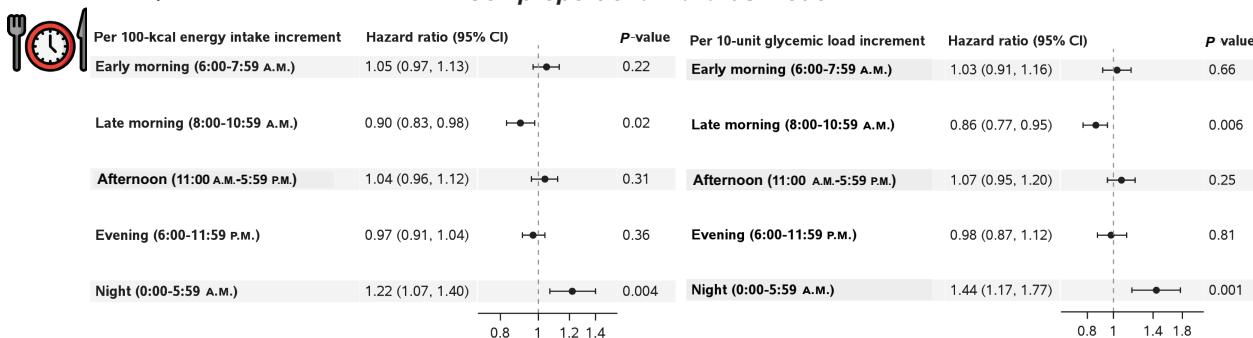
Covariates: total energy intake, diet quality, sociodemographic

Exposures: energy intake characteristics, lifestyle factors, and chronic conditions and dietary glycemic load in each time period

Outcome:
CVD death



Cox proportional hazards model



Conclusion: For U.S. adults with type 2 diabetes, late morning might be a protective eating time against cardiovascular disease mortality, whereas night might be a detrimental eating time.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
The favorable eating timing for lowering cardiovascular disease (CVD) mortality risk in adults with type 2 diabetes remains unknown.
- **What is the specific question(s) we wanted to answer?**
Is there an eating timing associated with CVD mortality risk in adults with type 2 diabetes?
- **What did we find?**
In 2,911 U.S. adults with diabetes, each 100-kcal of energy intake and 10-unit glycemic load increment in late morning (8:00–10:59 A.M.) were associated with 10–14% lower CVD mortality hazard, whereas the same increments at night (0:00–5:59 A.M.) were associated with 22–44% higher hazard.
- **What are the implications of our findings?**
For adults with type 2 diabetes, late morning eating timing may be protective against CVD mortality, whereas night eating timing may be detrimental.



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ORIGINAL ARTICLE

OBJECTIVE

To examine the associations of energy intake and glycemic load (GL) in different time periods during the day with cardiovascular disease (CVD) mortality risk in adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This cohort study included 2,911 adults with diabetes from who were part of the U.S. National Health and Nutrition Examination Survey 2003–2014 (baseline), and CVD mortality data obtained by linkage to the National Death Index through 2019. Energy intake and GL in early morning (6:00–7:59 A.M.), late morning (8:00–10:59 A.M.), afternoon (11:00 A.M.–5:59 P.M.), evening (6:00–11:59 P.M.), and night (0:00–5:59 A.M.) were derived from two 24-h dietary recalls at baseline. Cox models were used to estimate hazard ratios (HRs) for CVD mortality, adjusted for total energy intake, diet quality, sociodemographic and lifestyle characteristics, and medical conditions.

RESULTS

At baseline, the study population (51.8% female, 62.3% non-Hispanic White) had a mean age of 57.4 (SE, 0.4) years. Over a median follow-up of 9.3 (interquartile range = 6.8, 12.1) years, 190 CVD deaths were documented. Energy intake and GL in late morning were inversely associated with CVD mortality risk (per 100-kcal energy intake increment, HR 0.90 [95% CI 0.83–0.98]; per 10-unit GL increment, HR 0.86 [95% CI 0.77–0.95]). In contrast, energy intake and GL at night were positively associated with CVD mortality risk (per 100-kcal energy intake increment, HR 1.22 [95% CI 1.07–1.40]; per 10-unit GL increment, HR 1.44 [95% CI 1.17–1.77]).

CONCLUSIONS

For adults with type 2 diabetes, late morning may be a protective eating time against CVD mortality, whereas night may be a detrimental eating time.

Cardiovascular disease (CVD) remains the leading cause of death in the United States (1). Despite remarkable progress in CVD prevention and treatment in the past century, the decline in CVD mortality rates has leveled off in individuals without diabetes while continuing to decline in individuals with diabetes in the first

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decade of the 21st century (2), with more recent evidence indicating a national stall in this decline in the second decade of the 21st century (1,3). For instance, the annual decline rates for CVD mortality were 3.79% from 2000 to 2011, and only 0.65% from 2011 to 2014 (3). This alarming trend is partly fueled by the escalating prevalence of type 2 diabetes, which increases CVD risk two- to fourfold (4). Uncovering novel, modifiable protective factors against CVD mortality, particularly among individuals with type 2 diabetes, may provide alternative strategies for overturning this concerning mortality trend.

"When should we eat?" is a critical question prioritized by the National Institutes of Health (5). Yet, the optimal eating timing for lowering CVD mortality risk among individuals with type 2 diabetes remains unclear. Glucose tolerance exhibits a pronounced daily rhythm, peaking in the morning, declining in the afternoon and evening, and reaching its nadir at night (6,7). Furthermore, evidence adds a nuanced understanding of early-morning glucose tolerance, suggesting that it may be compromised due to high melatonin and cortisol levels (7–9). Because higher postprandial glucose levels are independent CVD risk factors in individuals with type 2 diabetes (10,11), assuming daily diet quality and quantity remain relatively constant, eating more in late morning may minimize a daily postprandial increase in glucose level, potentially reducing CVD mortality risk. Conversely, eating more at night may maximize daily postprandial increase in glucose level, potentially increasing CVD mortality risk in individuals with type 2 diabetes.

In this study, we evaluated the associations of energy intake and dietary glycemic load (GL) at different times of day with CVD mortality risk in a cohort of U.S. adults with diabetes. We used two dietary metrics: energy intake and GL. The interpretability of the former is straightforward, and the latter is a superior predictor of postprandial glycemia (12). We hypothesized that, while holding total energy intake and diet quality constant, greater energy intake or GL in late morning would be inversely associated with CVD mortality risk, whereas greater energy intake or GL at night would be positively associated with CVD mortality risk. Moreover, we hypothesized that women with diabetes (13) and individuals with diabetes

and adequate glycemic control might be more vulnerable to the adverse metabolic influence of diets inducing high postprandial glycemia, and the administration of glucose-lowering medications might obscure the associations of interest.

RESEARCH DESIGN AND METHODS

Study Design and Population

This population-based, prospective cohort study included adult participants from the National Health and Nutrition Examination Survey (NHANES) 2003–2014 (baseline), with passive follow-up on mortality through 2019, via linkage to the National Death Index. The NHANES is an ongoing, nationally representative, serial cross-sectional study monitoring the health and nutritional status of the civilian noninstitutionalized population in the United States (14). Using a stratified multistage probability sampling strategy, the NHANES has enrolled about 10,000 participants during every 2-year cycle since 1999. It comprises in-person interviews, physical examinations, and laboratory tests. The protocols of the NHANES were approved by the National Center for Health Statistics Ethics Review Board, with all participants providing written informed consent. This study received an exemption from the Institutional Review Board at the University of California, Los Angeles, and was conducted per the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (15).

Participants were included in this study if they were aged ≥ 20 years and had diabetes ($n = 5,571$) (Fig. S1). Diabetes was defined as having an HbA_{1c} value $\geq 6.5\%$ (48 mmol/mol), fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), 2-hour post-load plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during the physical examination, or self-reported physician-diagnosed diabetes. Participants with self-reported CVD (i.e., coronary heart disease, stroke, congestive heart failure, heart attack, or angina) at baseline ($n = 1,046$) were excluded because they may have adopted healthier diets after their diagnosis yet remained at a higher CVD mortality risk. Participants who were pregnant ($n = 12$) or without two reliable 24-h dietary recalls (i.e., daily energy intake < 600 or $> 3,500$ kcal for women, < 800 or $> 4,200$ kcal for men, or considered unreliable by interviewers) ($n = 1,150$) at baseline

were also excluded. Finally, the study population encompassed 2,911 adults with diabetes. Participants from the NHANES 2015–2018 were not included, because their cerebrovascular disease mortality data were unavailable and the symptom onset might precede their dietary assessment, due to the brief mortality follow-up ending in 2019 (16).

Assessment of Dietary Intake and Eating Timing

Dietary intake was assessed by trained staff at enrollment using two nonconsecutive, multiple-pass, time-stamped, 24-h dietary recalls. The first recall was administered in a mobile examination center, and the second via telephone 3–10 days later. Dietary data were analyzed using survey cycle-specific versions of the U.S. Department of Agriculture's Food and Nutrition Database for Dietary Studies (17). For each food item, its glycemic index (GI; with glucose as the reference) was assigned using a method outlined in the literature (18) based on the latest edition of the international tables of glycemic index and glycemic load values (19). GL was calculated by multiplying the amount of available carbohydrate (in grams) in the food by the GI value and dividing by 100 (19). The Healthy Eating Index 2015 score was calculated (20), with higher scores indicating better adherence to the 2015–2020 *Dietary Guidelines for Americans* (21).

We defined the five time periods as follows: early morning (6:00–7:59 A.M.), late morning (8:00–10:59 A.M.), afternoon (here, 11:00 A.M.–5:59 P.M.), evening (6:00–11:59 P.M.), and night (0:00–5:59 A.M.). Given that the exact clock times during which glucose tolerance peaks and nadirs have not been established, these time periods were determined based on the observed peaks in hourly energy intake throughout the day (Fig. S2) coupled with an exploratory analysis examining the directions of the crude associations between hourly energy intake and CVD mortality. For each time period, we calculated the mean energy intake in kilocalories and GL.

Ascertainment of Cardiovascular Mortality

Deaths due to CVD were identified by linkage with the National Death Index through 31 December 2019 (16). CVD mortality, including deaths from heart or cerebrovascular diseases, was defined

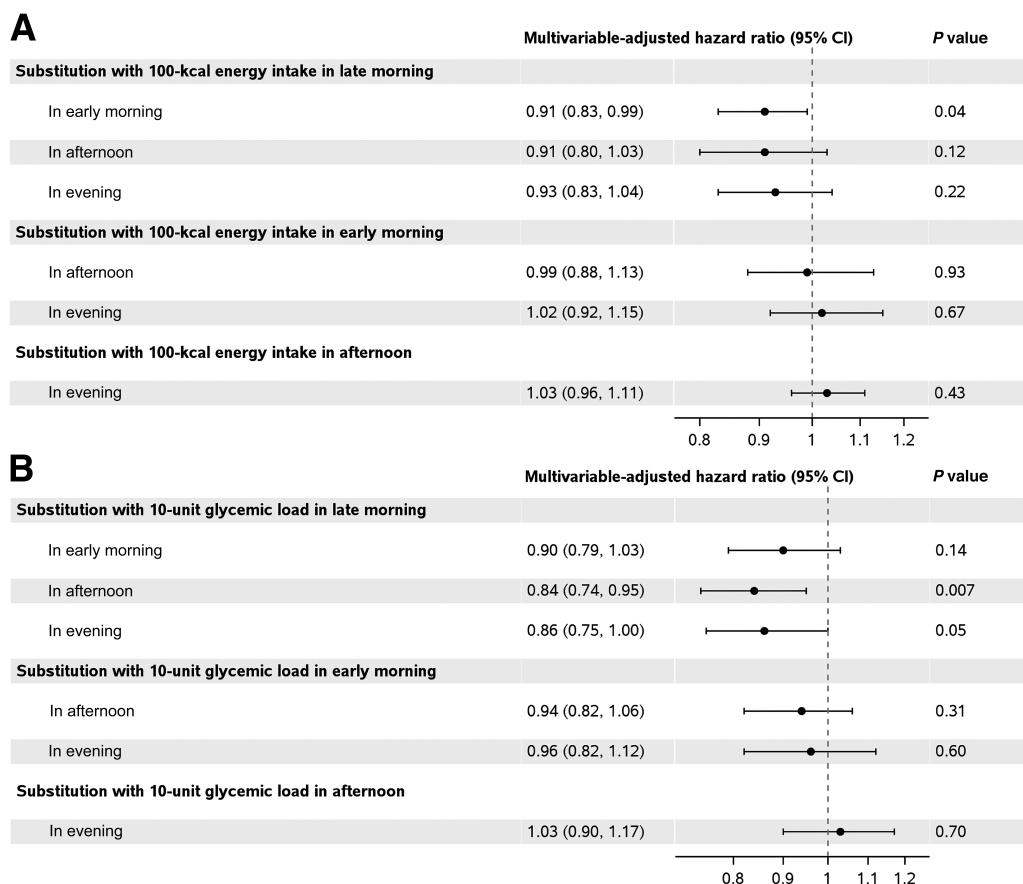


Figure 1—HRs of CVD mortality for substituting energy intake and GL across different time periods among U.S. adults with diabetes ($n = 2,911$), according to data from the NHANES 2003–2014. A) Substitution with 100-kcal energy intake. B) Substitution with 10-unit glycemic load. We defined the five time periods as follows: early morning (6:00–7:59 A.M.), late morning (8:00–10:59 A.M.), afternoon (11:00 A.M.–5:59 P.M.), evening (6:00–11:59 P.M.), and night (0:00–5:59 A.M.).

according to the recorded leading cause of death using ICD-10 codes I00–I09, I11, I13, I20–I51, and I60–I69.

Assessment of Covariates

Information on sociodemographic characteristics (i.e., age, sex, race/ethnicity, educational attainment, ratio of family income to poverty, and health insurance), lifestyle factors (i.e., smoking status, alcohol intake, and physical activity), and medical conditions (i.e., family history of heart disease, diabetes duration, and glucose-lowering medications) was collected through computer-assisted personal interviews at baseline.

Weight and height at baseline were directly measured at the mobile examination center and were used to calculate BMI (calculated as kg/m^2). Hypertension was defined as mean measured systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg, or antihypertensive medication use. Dyslipidemia was defined as measured low-density

lipoprotein cholesterol ≥ 160 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL, or triglycerides ≥ 200 mg/dL.

Statistical Analysis

We accounted for the NHANES complex survey design, including sampling weights, clustering, and stratification in all analyses. We calculated energy-adjusted GL using the residual method (22). Person-years of follow-up were calculated from the date of visiting the mobile examination center to the date of death or 31 December 2019, whichever came first. We used Cox proportional hazards models to estimate hazard ratios (HRs) with 95% CIs of CVD mortality for a 100-kcal increment in energy intake and a 10-unit increment in energy-adjusted GL during different time periods. Model 1 was adjusted for age. Model 2 was adjusted for age, sex, race/ethnicity, educational attainment, ratio of family income to poverty, health insurance, smoking status, alcohol intake, physical activity, BMI, hypertension, dyslipidemia, family history

of heart disease, glucose-lowering medication use, and diabetes duration. For models with energy intake in different time periods as the exposure, model 3 was further adjusted for total energy intake and the Healthy Eating Index 2015. For models with energy-adjusted GL as the exposure, model 3 was further adjusted for total energy intake, energy-adjusted intake of total GL, fiber, total fat, saturated fat, monounsaturated fat, and polyunsaturated fat.

We tested the proportional hazards assumption by examining the significance of the cross-product term between time to event and each independent variable and found that physical activity violated the assumption. Thus, stratified Cox models were used to accommodate such violations (23). For time periods in which energy intake and GL were associated with CVD mortality risk, their dose-response relationship was investigated using restricted cubic spline functions with four knots at the 5th, 35th, 65th, and 95th percentiles (24).

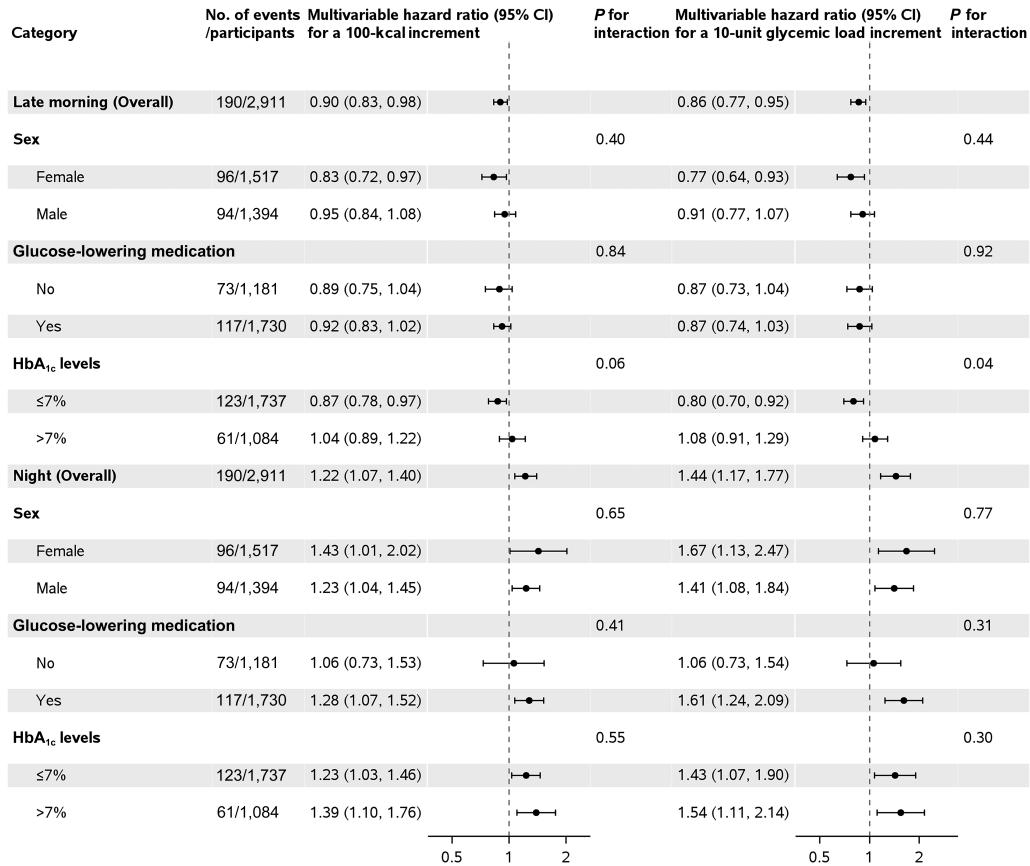


Figure 2—HRs of CVD mortality for energy intake and GL in late morning and at night among U.S. adults with diabetes stratified by selected characteristics, according to data from the NHANES 2003–2014.

Nonlinearity was assessed by comparing models including only linear terms with those including linear and cubic spline terms, using design-adjusted Wald tests. Additionally, we performed substitution analysis to evaluate the HRs of CVD mortality for substituting 100 kcal of energy intake and 10 units of energy-adjusted GL across different time periods, using the leave-one-out modeling strategy (25). Moreover, we conducted stratified analyses by sex, glucose-lowering medication use, and baseline glycated hemoglobin (HbA_{1c}) levels, and we assessed the multiplicative effect modification by comparing models with and without interaction terms, using design-adjusted Wald tests. For primary data analysis, missing values were imputed as missing categories for categorical variables and medians for continuous variables. Details on missing values are shown in Table S1.

We conducted several sensitivity analyses. First, to mitigate residual confounding, we further adjusted for sleep duration; these data are available starting from the 2005–2006 cycle. Second, to account for

competing risk, we performed Fine-Gray subdistribution hazard model (26), in which noncardiovascular deaths ($n = 473$) were treated as competing events. Third, we examined the associations of energy intake and GL in each time period with the risk of death due to heart and cerebrovascular diseases separately. Fourth, we included adults in the NHANES who self-reported having CVD. Fifth, we included adults in the NHANES who had extreme energy intake (i.e., daily energy intake <600 or $>3,500$ kcal for women, <800 or $>4,200$ kcal for men). Sixth, we adjusted for baseline HbA_{1c} levels to alleviate potential confounding. Seventh, we adjusted for occupation and work hours to alleviate potential confounding. Lastly, to account for missing values, we performed multiple imputations using the fully conditional specification method to generate five imputed data sets (27).

We analyzed data using SAS, version 9.4 (SAS Institute, Cary, NC) and Stata 18.0 (Stata Corp., College Station, TX). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

At baseline, the study population had a mean age of 57.4 (95% CI 56.6–58.2) years; 51.8% of participants were women, 62.3% were non-Hispanic White, 16.2% were Hispanic, 15.0% were Black, and 57.7% were taking glucose-lowering medications (Table 1). The largest mean energy intake occurred during the afternoon (817.6 kcal) and evening (695.8 kcal), followed by late morning (269.8 kcal) and early morning (116.1 kcal), with few calories consumed at night (24.6 kcal). Energy intake and GL in each time period were strongly positively correlated, and energy intake and GL in adjacent time periods were weakly to moderately correlated (Fig. S3).

Energy Intake and GL in Different Time Periods and CVD Mortality

Over a median follow-up of 9.3 (interquartile range = 6.8, 12.1) years, 190 CVD deaths, including 154 heart disease deaths and 36 cerebrovascular disease deaths, were documented among individuals with diabetes. Greater energy intake and GL in the late morning were inversely associated

Table 1—Characteristics of U.S. adults with diabetes ($n = 2,911$) at baseline—the NHANES 2003–2014^a

Characteristic	% (95% CI) ^b
Age, y, mean (95% CI)	57.4 (56.6, 58.2)
Female sex	51.8 (48.7, 55.0)
Race/ethnicity	
Non-Hispanic White	62.3 (58.2, 66.4)
Non-Hispanic Black	15.0 (12.6, 17.5)
Hispanic	16.2 (13.1, 19.2)
Other	6.5 (5.0, 7.9)
Family-income to poverty ratio	
≤1.30	23.0 (20.2, 25.8)
1.31–3.50	38.5 (35.7, 41.2)
>3.50	38.6 (34.7, 42.4)
Educational attainment	
Less than high school	23.7 (21.1, 26.3)
High school graduate	25.6 (22.8, 28.5)
Some college or above	50.7 (46.7, 54.7)
Health insurance	
None	14.3 (12.2, 16.4)
Public	24.1 (21.8, 26.5)
Private	61.6 (58.4, 64.8)
Smoking status	
Never	51.3 (47.8, 54.8)
Former	31.6 (28.8, 34.5)
Current	17.1 (14.7, 19.4)
Alcohol intake ^c	
Never	40.5 (36.9, 44.0)
Moderate	53.3 (49.6, 57.0)
Heavy	6.2 (4.7, 7.7)
Leisure-time physical activity	
Inactive	56.1 (52.6, 59.6)
Insufficiently active	19.1 (16.5, 21.7)
Active	24.9 (22.3, 27.4)
BMI category, kg/m ²	
<25	13.3 (11.1, 15.4)
25 to <30	27.6 (24.9, 30.2)
30 to <35	25.6 (22.7, 28.4)
≥35	33.6 (30.1, 37.1)
Hypertension	74.1 (71.6, 76.7)
Dyslipidemia	36.3 (33.6, 39.1)
Family history of heart disease	14.4 (12.6, 16.2)
Diabetes duration, years	
≤5	31.1 (27.4, 34.7)
>5 and ≤10	19.5 (17.0, 22.1)
>10	49.4 (45.2, 53.6)
Glucose-lowering medication use	
None	42.3 (39.9, 44.7)
Noninsulin agents	40.6 (37.8, 43.3)
Insulin	17.1 (14.9, 19.3)
Healthy Eating Index 2015, mean (95% CI)	54.2 (53.4, 55.1)
Energy intake, kcal, mean (95% CI)	
Total	1924.0 (1884.1, 1963.9)
Early morning	116.1 (103.0, 129.2)
Late morning	269.8 (254.3, 285.3)
Afternoon	817.6 (794.3, 840.9)
Evening	695.8 (663.6, 728.0)
Night	24.6 (17.8, 31.5)

Continued on p. 6

with CVD mortality risk across all three models, with the magnitude of the association remaining stable (Table 2). In model 3, the HRs of CVD mortality were 0.90 (95% CI 0.83–0.98; $P = 0.02$) for a 100-kcal increment in energy intake and 0.86 (95% CI 0.77–0.95; $P = 0.006$) for a 10-unit increment in energy-adjusted GL in late morning. The hazard of CVD mortality declined approximately linearly with greater energy intake or GL in late morning ($P \geq 0.34$ for nonlinearity) (Fig. S4). In addition, greater energy intake and GL at night were positively associated with CVD mortality risk (for 100-kcal energy intake increment, HR 1.22 [95% CI 1.07–1.40], $P = 0.004$; for 10-unit GL increment, HR 1.44 [95% CI 1.17–1.77], $P = 0.001$). Energy intake and GL in other time periods were not associated with CVD mortality risk across three models among individuals with diabetes.

Substitution Analyses

Substituting 100-kcal energy intake from early morning with late morning equivalents was associated with a 9% (95% CI 1–17%; $P = 0.04$) lower CVD mortality risk (Fig. 1), whereas substituting 10-unit energy-adjusted GL from afternoon or evening with late morning equivalents was associated with 16% (95% CI 5–26%; $P = 0.007$) and 14% (95% CI 0.4–25%; $P = 0.05$) lower risks, respectively. Substituting energy intake and GL across other time periods was not associated with CVD mortality risk.

Stratified Analyses

The inverse associations of energy intake and GL in late morning with CVD mortality risk and the positive associations of energy intake and GL at night with CVD mortality risk appeared consistently stronger in female participants with diabetes, though no statistically significant heterogeneity by sex was detected ($P \geq 0.40$ for heterogeneity) (Fig. 2). In addition, the inverse associations of energy intake and GL in late morning with CVD mortality risk were only observed in adults with diabetes who had adequate baseline glycemic control (i.e., $\text{HbA}_{1c} \leq 7\%$) ($P \leq 0.06$ for heterogeneity). There was no significant heterogeneity by baseline glycemic control for the associations of energy intake and GL at night with CVD mortality risk ($P \geq 0.30$ for heterogeneity). The associations

Table 1—Continued

Characteristic	% (95% CI) ^b
Energy-adjusted glycemic load, mean (95% CI)	
Total	121.3 (119.5, 123.0)
Early morning	9.8 (8.9, 10.7)
Late morning	21.0 (19.8, 22.3)
Afternoon	52.2 (50.9, 53.5)
Evening	42.3 (41.0, 43.6)
Night	1.9 (1.5, 2.4)
Energy-adjusted intake, g, mean (95% CI)	
Fiber	17.1 (16.7, 17.5)
Total fat	80.6 (79.7, 81.5)
Saturated fat	26.1 (25.7, 26.5)
Monounsaturated fat	29.2 (28.9, 29.6)
Polyunsaturated fat	18.2 (17.8, 18.5)

^aData analyses accounted for the NHANES complex survey design. We defined the five time periods as follows: 1) early morning (6:00–7:59 A.M.); 2) late morning (8:00–10:59 A.M.); 3) afternoon (11:00 A.M.–5:59 P.M.); 4) evening (6:00–11:59 P.M.); and 5) night (0:00–5:59 A.M.).

^bUnless otherwise indicated. ^cNone: 0 drinks/week; moderate: >0 and ≤14 drinks/week for men, >0 and ≤7 drinks/week for women; heavy: >14 drinks/week for men and >7 drinks/week for women.

of energy intake and GL in late morning and at night with CVD mortality risk did not vary by glucose-lowering medication use ($P \geq 0.31$ for heterogeneity).

Sensitivity Analyses

The inverse associations of energy intake and GL in late morning with CVD mortality risk among individuals with diabetes remained robust across sensitivity analyses, with stronger associations observed when sleep duration was further adjusted for and a weaker association when including adults in the NHANES who had CVD (Table S2). Additionally, the strength of the associations was comparable when examining mortality risk attributed to heart diseases and cerebrovascular diseases separately. Likewise, the positive associations of energy intake and GL at night with CVD mortality risk remained unaltered across sensitivity analyses.

DISCUSSION

In this study, we found that in U.S. adults with diabetes, greater energy intake and GL in late morning (8:00–10:59 A.M.) were associated with lower CVD mortality risk, whereas greater energy intake and GL at night (0:00–5:59 A.M.) were associated with higher CVD mortality risk. Replacing energy intake from early morning, or GL from afternoon or evening, with the late morning equivalents was inversely associated with CVD mortality risk. Additionally, the point estimates of the

associations of energy intake and GL in late morning and at night with CVD mortality risk appeared consistently stronger in women with diabetes than in men, though heterogeneity tests were not statistically significant. Moreover, the associations of energy intake and GL in late morning with CVD mortality risk were only significant in individuals with appropriate glycemic control (i.e., $\text{HbA}_{1c} \leq 7\%$). To our knowledge, this is the first study to indicate late morning might be a favorable eating time associated with CVD mortality risk in individuals with type 2 diabetes.

To date, to our knowledge, no study reports favorable eating timing for CVD mortality. Using the NHANES data, a recent study examined the timing of consuming specific foods in relation to CVD mortality risk among individuals with diabetes (28). Those who consumed potatoes and starchy vegetables in the forenoon (defined as breakfast plus snack between breakfast and lunch) were reported to have lower CVD mortality risk than those not eating at corresponding periods (28). These findings support our findings, because potatoes and starchy vegetables typically have a high energy content and GI (19). Our study differs from that study and provides additional data in several major respects, including using GL (a metric capturing the postprandial increase in glucose level induced by all food intake), defining eating time periods by clock time (more objective than self-defined eating occasions), and modeling the exposures as continuous

variables and exploring the dose-response relationship. Another study reported a positive association of differences in energy intake between dinner and breakfast (i.e., calories consumed at dinner minus calories consumed at breakfast) with CVD mortality risk among NHANES participants with diabetes (29). Although the results of that study seem to support our findings, the authors' analysis did not differentiate between early and late morning time periods nor did it control for the combined energy intake from dinner and breakfast. Therefore, a greater difference in energy intake between dinner and breakfast does not necessarily indicate a high-energy dinner coupled with a low-energy breakfast.

Consistent with literature indicating the harmful consequences of nighttime eating (30,31), we found that greater energy intake or GL at night (0:00–5:59 A.M.) was positively associated with CVD mortality risk in adults with diabetes. However, given that >90% of individuals reported no eating between 0:00–5:59 A.M. and eating at night may be determined by unmeasured conditions (e.g., night eating syndrome, poor sleep quality), interpreting this association should be cautious. Confirming this association in a cohort of people with habitual nighttime eating (e.g., night-shift workers) may be warranted.

Research on the daily rhythm of glucose tolerance in individuals with type 2 diabetes has been scarce, with findings contradicting each other (32–35). For example, some studies indicated almost identical glucose tolerance between morning and afternoon (32,33), whereas others indicated higher glucose tolerance in the afternoon (34,35). This inconsistency may be explained by the lack of control over factors influencing postprandial glucose levels, such as sleep patterns and physical activity. Furthermore, because chronotherapy is attracting increasing interest (36), the timing of glucose-lowering medication administration might also account for the inconsistency. Nevertheless, we did not observe heterogeneity in the associations stratified by glucose-lowering medication use. Considering that the circadian rhythm in glucose tolerance in individuals without diabetes is partly attributed to a more robust pancreatic β-cell response in the morning (37,38), we infer that this rhythm may be attenuated among individuals with diabetes who have appropriate glycemic control and may diminish among those with poor glycemic control, because the

Table 2—HRs of CVD mortality for energy intake and GL in different time periods among U.S. adults with diabetes (*n* = 2,911)—the NHANES 2003–2014^a

	Model 1 ^b HR (95% CI)	P	Model 2 ^c HR (95% CI)	P	Model 3 ^d HR (95% CI)	P
For a 100-kcal increment in energy intake						
Early morning	1.08 (0.99, 1.19)	0.09	1.03 (0.96, 1.11)	0.39	1.05 (0.97, 1.13)	0.22
Late morning	0.89 (0.81, 0.97)	0.008	0.90 (0.83, 0.97)	0.006	0.90 (0.83, 0.98)	0.02
Afternoon	1.02 (0.94, 1.11)	0.62	1.01 (0.94, 1.09)	0.79	1.04 (0.96, 1.12)	0.31
Evening	0.98 (0.93, 1.03)	0.46	0.96 (0.91, 1.01)	0.13	0.97 (0.91, 1.04)	0.36
Night	1.17 (1.03, 1.32)	0.02	1.19 (1.06, 1.35)	0.004	1.22 (1.07, 1.40)	0.004
For a 10-unit increment in energy-adjusted GL						
Early morning	1.05 (0.93, 1.19)	0.45	1.02 (0.91, 1.14)	0.74	1.03 (0.91, 1.16)	0.66
Late morning	0.84 (0.74, 0.96)	0.01	0.87 (0.78, 0.97)	0.01	0.86 (0.77, 0.95)	0.006
Afternoon	1.06 (0.94, 1.20)	0.35	1.06 (0.96, 1.18)	0.25	1.07 (0.95, 1.20)	0.25
Evening	0.99 (0.88, 1.11)	0.83	0.98 (0.89, 1.09)	0.75	0.98 (0.87, 1.12)	0.81
Night	1.34 (1.10, 1.64)	0.004	1.40 (1.16, 1.69)	0.001	1.44 (1.17, 1.77)	0.001

^aWe defined the five time periods as follows: 1) early morning (6:00–7:59 A.M.); 2) late morning (8:00–10:59 A.M.); 3) afternoon (11:00 A.M.–5:59 P.M.); 4) evening (6:00–11:59 P.M.); and 5) night (0:00–5:59 A.M.). ^bModel 1 was adjusted for age in the Cox proportional hazards model, accounting for the NHANES complex survey design. ^cModel 2 was model 1 further adjusted for sex, race/ethnicity, educational attainment, ratio of family income to poverty, health insurance, smoking status, alcohol consumption, leisure-time moderate to vigorous physical activity, BMI categories, family history of heart disease, hypertension, dyslipidemia, glucose-lowering medications, and diabetes duration. ^dFor energy intake in different time periods as the exposure, model 3 was model 2 further adjusted for total energy intake and Healthy Eating Index 2015. For energy-adjusted GL in different time periods as the exposure, model 3 was model 2 further adjusted for total energy intake, energy-adjusted intake of total GL, fiber, total fat, saturated fat, monounsaturated fat, and polyunsaturated fat.

latter are more likely to have severely compromised β -cell function. This inference is corroborated by our findings that the associations of energy intake and GL in late morning with CVD mortality were only significant in individuals with appropriate glycemic control. Rigorous mechanistic studies are warranted to explore the circadian rhythm of glucose tolerance across the spectrum of β -cell functions. Additionally, women with diabetes appear to be more susceptible to the influences of eating timing than are men. This potential modification by sex is supported by literature showing that diabetes imposes a greater CVD risk on women. This increased risk might be attributed to the fact that women tend to accumulate more subcutaneous fat compared with liver fat, leading to a higher BMI at the onset of type 2 diabetes, than do men. Consequently, women might experience prolonged insulin resistance and metabolic dysfunction before being diagnosed with type 2 diabetes, which elevates their CVD risk (13,39,40).

Our study has several strengths. First, the rigorous and comprehensive data collection procedure of NHANES allows us to control for various confounders, thereby mitigating confounding bias. Second, using a nationally representative sample makes our findings readily generalizable to the broader U.S. adult population with diabetes. Third, the incorporation of GL

enables us to examine the hypothesis more accurately, and the use of energy intake is easily understandable by the public.

We acknowledge several limitations. First, energy intake and GL in each time period were collected by two 24-h dietary recalls at baseline, without repeated measurements during follow-up, potentially resulting in exposure measurement error. Nonetheless, considering the temporal sequence of the exposure assessment (i.e., energy intake and dietary GL in each time period) prior to the outcome assessment (i.e., deaths due to CVD) in the prospective cohort design, the potential measurement errors of exposure would primarily lead to nondifferential measurement error of the exposures (41). Given that the exposures were treated as continuous variables and averaged from two 24-h dietary recalls, the potential non-differential measurement error would likely attenuate the estimated associations of energy intake and GL in each time period with CVD mortality risk, biasing the associations toward the null (41). Second, we used clock time to approximate internal circadian time. Considering the interpersonal differences in internal circadian time (6), the late morning period defined by clock time may solely represent the overlap of the population's internal circadian time when glucose tolerance peaks and may vary across populations. Because our hypothesis relies on the daily rhythm of

glucose tolerance inherently controlled by the circadian system, subsequent studies with accurate internal circadian time measurements are necessary to confirm our findings. Third, we were unable to adjust for sleep duration in our primary analyses, due to the absence of sleep duration data before the NHANES 2005–2006 cycle. The stronger associations of energy intake and GL in late morning and at night with CVD mortality risk after adjusting for sleep duration in the sensitivity analyses with a subsample (i.e., among participants from NHANES 2005–2014) indicated that sleep duration might be a strong confounder that warrants adjustment in future studies. Fourth, our sample size is relatively small, especially for examining heterogeneity by sex and baseline glycemic control, which warrants confirmation by larger cohort studies. Fifth, given our observational study design, residual confounding (e.g., chronotype) cannot be ruled out, and causality cannot be established.

In conclusion, this study revealed that late morning might be a protective eating time against CVD mortality risk, and night might be a detrimental eating time associated with higher CVD mortality risk among U.S. adults with diabetes. These findings shed new light on the circadian regulation of glucose metabolism in type 2 diabetes. In response to the increasing burden of type 2 diabetes and CVD mortality in the United States, our study explores a novel

hypothesis that eating in alignment with the daily rhythm of glucose tolerance may be associated with lower CVD mortality risk among individuals with diabetes, and this carries substantial public health implications, particularly in a society with 24-h food availability. Further mechanistic studies are needed to advance our understanding of the circadian rhythm of glucose tolerance in individuals with diabetes, and additional epidemiologic studies with larger sample sizes and repeated measurements of eating timing are warranted to validate our findings.

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