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Original article

Difference in association of carbohydrate intake with all-cause mortality between middle-aged and older Korean adults with and without diabetes mellitus: A prospective study

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SUMMARY

Background & aims: The relationship between diet and health, particularly the role of carbohydrates, has been extensively studied. However, carbohydrate intake based on individual health conditions remains unclear. Here, we aimed to investigate whether the association between carbohydrate intake and all-cause mortality varied between individuals with and without diabetes mellitus (DM).

Methods: This prospective cohort study used data from the Korean Genome and Epidemiology Study (KoGES). Overall, 143,050 participants were included, with 10.1% having DM. Dietary intake was assessed using a semiquantitative food frequency questionnaire. Cox proportional hazards regression models were used to assess the association between carbohydrate intake and mortality after adjusting for confounders.

Results: The study showed that 5436 deaths occurred during the median follow-up period of 10.1 years. A significant interaction between carbohydrate intake and DM was observed in the study population (interaction $p = 0.061$). Higher carbohydrate intake proportion was associated with an increased risk of all-cause mortality among individuals with DM (adjusted hazard ratio [HR], p-value = 1.10 [1.01–1.20], $p = 0.032$). Conversely, no association was observed between the proportion of carbohydrate intake and all-cause mortality in participants without DM. Additionally, both total sugar and added sugar intakes were associated with an increased risk of all-cause mortality in participants with DM (adjusted HR, p-value = 1.02 [1.01–1.04], $p < 0.001$ and 1.18 [1.13–1.24], $p < 0.001$).

Conclusions: High carbohydrate (%) and added sugar intake were associated with an increased mortality risk in individuals with DM. Reducing carbohydrate intake and opting for healthy carbohydrates to mitigate mortality risk may be beneficial for individuals with DM, particularly when compared with the general population.

1. Introduction

The relationship between diet and health has been extensively studied, and findings indicate that a well-balanced diet is closely associated with better health and longevity [1]. Carbohydrates are a macronutrient, along with protein and fat. When carbohydrates are consumed and digested, they are broken down into glucose, which is the body's primary fuel source [2]. Carbohydrates affect several physiological mechanisms, including energy production, insulin response, glycogen storage, and appetite control [2]. Dietary recommendations for carbohydrate intake by various working groups typically range between 45 and 65% [3–5]. However, this range is generally considered appropriate for most individuals, and research on adequate carbohydrate intake based on underlying health conditions is still limited.

Dietary carbohydrate restriction is recommended as a strategy to manage hyperglycemia in individuals with diabetes mellitus

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(DM), given that insulin resistance (IR) contributes to sustained elevated postprandial blood glucose levels subsequent to carbohydrate ingestion [6,7]. Investigations into dietary interventions that spanned over 2 years and aimed at ameliorating impaired glucose metabolism along with decreasing cardiovascular risk factors highlighted the potential advantages of adoption of a low-carbohydrate diet (LCD) by individuals diagnosed with DM [8–10]. These benefits include reduction in variables such as glycosylated hemoglobin (HbA1c), blood glucose, and triglycerides [8–10]. Additionally, the adoption of a LCD was shown to contribute to weight reduction [8–10].

However, prospective large-cohort studies examining the long-term effects of dietary carbohydrates on health outcomes have reported contrasting findings in different populations [11,12].

The Atherosclerosis Risk in Communities (ARIC) study from four US communities demonstrated that 50–55% of energy from carbohydrates was associated with the lowest mortality risk [12]. Additionally, a meta-analysis of eight cohort studies consisting of Asian countries demonstrated an association between both low (<40%) and high carbohydrate consumption (>70%) with increased mortality [12]. Conversely, according to the Prospective Urban Rural Epidemiology (PURE) study, increased consumption of carbohydrates (approximately 60% of energy) is linked to an elevated risk of total mortality [12]. These varying outcomes may be attributed to differences in dietary habits across countries, with the Asian population consuming more carbohydrates than Western populations. Racial and ethnic differences may also diversely influence the impact of carbohydrate consumption on mortality [13]. Additionally, the various types of carbohydrates may have distinct health effects depending on their sugar content [14]. There is a paucity of studies that have examined the influence of carbohydrate intake on mortality in the context of the presence or absence of DM.

Therefore, we hypothesized that individuals with DM might be more adversely affected by a high-carbohydrate diet than those without DM. Our study's objective was to examine whether the effect of carbohydrate intake on all-cause mortality varies between individuals with and without DM in a cohort of middle-aged and older Korean adults. In addition, we aimed to explore whether the association between types of carbohydrate intake (such as total sugar and added sugars) and all-cause mortality varies among individuals with and without DM.

2. Materials and methods

2.1. Study participants

Baseline data of participants aged ≥40 years were evaluated in the Korean Genome and Epidemiology Study (KoGES), Ansan-Ansung Study (2001–2002), KoGES Health Examinee Study (2004–2013), and KoGES Cardiovascular Disease Association Study (2005–2011). KoGES was a large-scale, prospective, longitudinal cohort study. The complete dataset of KoGES is present on the webpage https://nih.go.kr/ko/main/contents.do?menuNo=300569, and we accessed this data on April 4, 2023 to carry out our objectives.

Of the 211,571 participants included in the baseline data (2001–2013), we eliminated 68,521 individuals who were missing the following information: (1) age and personal traits of lifestyle (n = 2231); (2) results of a laboratory examination (n = 5387); (3) nutritional data and extreme total calorie consumption (<500 or >6000 kcal/day; n = 12,366); (4) mortality data (n = 48,476); and (5) those who passed away during the enrollment year (n = 61) (Fig. 1). Thus, a total of 143,050 individuals (128,726 participants without DM and 14,324 participants with DM) were included in the study.

All procedures performed in this study were in accordance with the tenets of the Declaration of Helsinki. Voluntary informed consent was obtained from all the participants prior to the commencement of the study. The study was approved by the Institutional Review Board (IRB), which is an independent ethics committee at Yongin Severance Hospital (IRB: 9-2021-0066).

2.2. Dietary evaluation

A semiquantitative food frequency questionnaire (FFQ), designed for a community-based cohort of the KoGES, was used to measure dietary intake. Trained personnel conducted the FFQ interviews in accordance with the standardized protocol. The FFQ was used to provide a measure of how frequently each type of food was consumed by each participant over the previous year.

The FFQ is a useful nutritional assessment instrument used in several prospective cohort studies. However, it includes fewer food items and is not always accurate in recording individuals' food intake [15–17]. The FFQ used in the KoGES included 103 food products validated in previous studies [18]. The FFQ used in this study encompassed various food items such as rice, other cereals, noodles, bread, potatoes, mushrooms, soy, soy products, beans, common fish, other fishes, shellfish, meat, seaweed, eggs, milk, dairy products, fruits, beverages, snacks, nuts, and fats. The Korea National Health and Nutrition Examination Survey data, which includes a representative sample of the Korean people, was used to calculate the serving size based on the median amount of every food item [19]. The serving sizes were categorized into the following three groups: small, medium, and large. The serving sizes of different foods were visually presented to aid participants' comprehension. Block's instrument (1: small = [standard amounts] × 0.5; 2: medium = [standard amounts] × 1.0; 3: large = [standard amounts] × 1.5) was used to calculate the portion size [20]. Food consumption frequency was classified into nine categories: never or rarely, once a month, twice or thrice a month, 1–2 times a week, 3–4 times a week, 5–6 times a week, once a day, twice a day, or ≥3 times a day. The reported FFQ frequency data were coded as daily frequencies to calculate the daily nutrient intakes. Nutrient intake was calculated by converting the determined weight based on the frequency of food consumption and portion sizes.

Calculations were conducted to estimate sugar content using the CAN-Pro 5.0 database developed by the Korean Nutrition Society (https://www.kns.or.kr/) and the database from the Korea Food and Drug Administration (KFDA) (https://various.foodsafetykorea.go.kr/nutrient/). In cases where total sugar values were unavailable in CAN-Pro 5.0, references were made to the KFDA database for estimation. When nutritional components differed between the databases, adjustments were made to align energy and carbohydrate values with those of CAN-Pro 5.0 as closely as possible. We considered sugars added to food ingredients (such as sugar and seasonings added during cooking processes) as added sugars and estimated the amounts of added sugars [21–23]. Total sugar is defined as the sum of added sugar and natural sugar in a food [21–23]. Food sources of total sugar and added sugar are presented in Supplementary Tables 1 and 2

The KoGES website provides additional in-depth resources and materials. https://nih.go.kr/ko/main/contents.do?menuNo=300569 (accessed on April 4, 2023).

2.3. Covariates

Trained medical professionals conducted every step of health evaluation. Participants were seated, and their blood pressure was recorded twice. Blood investigations were performed after an 8-h

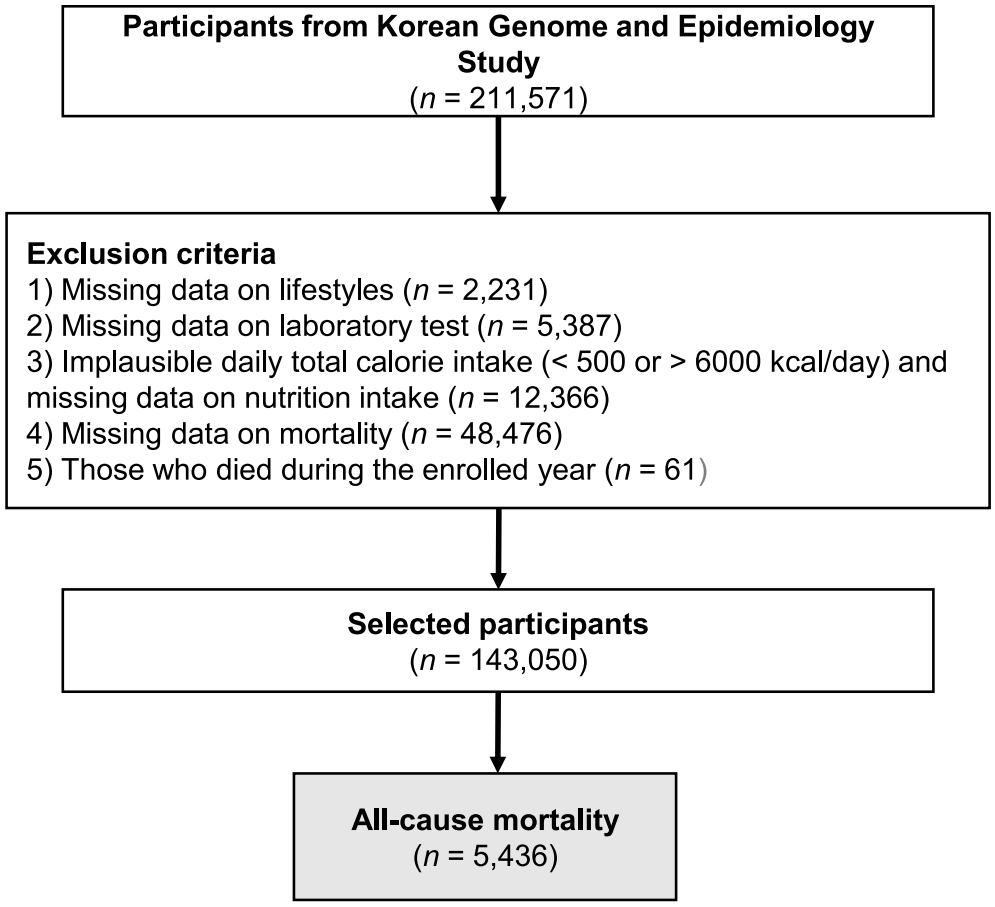

Fig. 1. Flow chart of the study population inclusion process.

fast. The levels of HbA1c, fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were assessed using a Laboratory Analyzer (Hitachi 7600, Tokyo, Japan until August 2002; and ADVIA 1650, Siemens, Tarrytown, NY from September 2002). The questionnaire asked respondents to self-report their status of tobacco smoking (never smoker, ex-smoker, and current smoker), alcohol consumption (never drinker, ex-drinker, and current drinker), and physical activity (frequent exercisers were those who routinely worked up a sweat).

Hypertension (HTN) was defined as systolic blood pressure (SBP) $\geq$140 mmHg, diastolic blood pressure (DBP) $\geq$90 mmHg, a diagnosis by a physician, or current treatment with antihypertensive medications [24]. DM was defined as FBG $\geq$126 mg/dL, HbA1c $\geq$ 6.5%, a diagnosis by a physician, or current treatment with antidiabetic medication therapy [25]. Dyslipidemia was defined as TC $\geq$ 240 mg/dL, TG $\geq$ 200 mg/dL, HDL-C <40 mg/dL, or current treatment with dyslipidemia medications [26]. Glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2, calculated by serum creatinine, was used to identify chronic kidney disease (CKD) based on the Chronic Kidney Disease Epidemiology Collaboration equation [27].

2.4. Study outcomes

The KoGES data is linked to national sources of information, such as the Korea National Statistics Office, which includes mortality records. To determine the participant's mortality status, a specific individual keycode identification system was used for information linkage. Participants were tracked from the time of initial research to their moment of death, completion of the study, or the last time they were contacted. The International Classification of Diseases (ICD) codes in the National Mortality Index were used to classify the reasons for participant's deaths, which was monitored from January 2001 to December 2019. All-cause mortality included both known and unidentified causes of death.

2.5. Statistical analysis

Data are presented as means (standard deviations, SD) for continuous variables or as numbers (proportions) for categorical variables. We created a density plot to confirm the total carbohydrate (%) distribution in groups with and without diabetes and added spline curves to confirm the mortality risk from carbohydrates (%). Univariable and multivariable Cox proportional hazards regression models were designed to evaluate the independent association between dietary carbohydrate consumption and outcomes. We included variables such as sex, age, body mass index (BMI), alcohol consumption, smoking, regular exercise, total calorie consumption, hypertension, dyslipidemia, CKD, and baseline glucose in multivariable Cox models that were adjusted for variables with $p < 0.05$ in the univariate analysis and previously reported variables. Harrell's C-index was used to estimate the ideal cut-off range of carbohydrate consumption from diet (%) for evaluating the clinical outcomes [28]. The most appropriate way to determine the cut-off point was to maximize mortality prediction. Survival rates in relation to dietary carbohydrate intake (%) were calculated using Kaplan–Meier curves and log-rank tests.

All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC, USA). All p-values were two-sided. Values of $p < 0.05$ were considered statistically significant except for interactions where $p < 0.1$ was considered statistically significant, based on previous studies [29–31].

3. Results

The study population comprised 143,050 participants. Among them, 128,726 (90.0%) participants did not have DM and 14,324 (10.1%) had DM. Table 1 shows the baseline characteristics of the study population according to the presence of DM. Compared with participants without DM, those with DM were more likely to be men ($p < 0.001$), to be older ($p < 0.001$), and to have a higher BMI ($p < 0.001$), waist circumference ($p < 0.001$), SBP ($p < 0.001$), DBP ($p < 0.001$), FBG ($p < 0.001$), HbA1c ($p < 0.001$), and TG ($p < 0.001$). Moreover, participants with DM were more likely to be smokers ($p < 0.001$), consume alcohol ($p = 0.007$), and engage in exercise ($p < 0.001$) compared with those without DM. The incidence of hypertension, dyslipidemia, and CKD was significantly higher in participants with DM than in those without DM. Participants with DM consumed fewer total calories (kcal/day), fat (%), and protein (%). However, their consumption of carbohydrates (%) was comparatively more.

Figure 2 shows the density plot of carbohydrate intake (%) and Cox proportional hazard spline curves in the unadjusted model. It illustrates the association between carbohydrate intake (%) and all-cause mortality in the entire population, participants without DM, and those with DM. A linear association was observed between carbohydrate intake (%) and all-cause mortality in individuals with >60% carbohydrate intake.

Table 1
Baseline characteristics of the study population.

Characteristics	Without DM	With DM	p-value
N	128,726	14,324	
Sex (male, n [%])	44,011 (34.2)	6933 (48.4)	<0.001
Age, years	53.4 ± 8.6	58.1 ± 8.1	<0.001
BMI, kg/m^2	23.8 ± 2.9	25.1 ± 3.2	<0.001
WC, cm	80.8 ± 8.7	86.0 ± 8.5	<0.001
Systolic BP, mmHg	122.1 ± 15.3	127.6 ± 15.6	<0.001
Diastolic BP, mmHg	76.0 ± 10.1	77.7 ± 9.7	<0.001
FBG, mg/dL	91.2 ± 10.0	135.4 ± 43.5	<0.001
HbA1c, %	5.5 ± 0.3	7.2 ± 1.3	<0.001
Total cholesterol, mg/dL	198.0 ± 35.0	192.0 ± 41.4	<0.001
HDL-C, mg/dL	53.1 ± 13.1	47.9 ± 11.8	<0.001
LDL-C, mg/dL	120.0 ± 32.0	111.3 ± 37.3	<0.001
Triglycerides, mg/dL	125.3 ± 85.4	166.6 ± 124.4	<0.001
Current smoker, n (%)	16,003 (12.4)	2375 (16.6)	<0.001
Current alcoholic, n (%)	63,447 (49.3)	7231 (50.5)	0.007
Regular exerciser, n (%)	64,173 (49.9)	7556 (52.8)	<0.001
Hypertension, n (%)	20,952 (16.3)	3455 (24.1)	<0.001
Dyslipidemia, n (%)	72,584 (56.4)	8635 (60.3)	<0.001
CKD, n (%)	2918 (2.3)	974 (6.8)	<0.001
Residential area, n (%)			<0.001
Urban	112,380 (87.3)	11,976 (83.6)	
Rural	16,346 (12.7)	2348 (16.4)	
Total energy intake, kcal/day	1739.8 ± 543.7	1699.4 ± 524.2	<0.001
Carbohydrate, g/day	310.1 ± 90.1	305.7 ± 86.7	<0.001
Carbohydrate, % from energy	71.9 ± 7.0	72.7 ± 7.1	<0.001
Fat intake, g/day	27.5 ± 17.2	25.3 ± 16.6	<0.001
Fat, % from energy	13.7 ± 5.5	12.8 ± 5.5	<0.001
Protein intake, g/day	58.6 ± 24.9	57.1 ± 24.5	<0.001
Protein, % from energy	13.3 ± 2.6	13.3 ± 2.7	0.007
Total sugar intake, g/day	85.6 ± 55.7	74.6 ± 50.5	<0.001
Added sugar intake, g/day	19.7 ± 15.1	13.1 ± 13.6	<0.001
Fiber intake, g/day	5.7 ± 2.9	5.6 ± 2.8	<0.001

DM, diabetes mellitus; BMI, body mass index; WC, waist circumference; BP, blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CKD, chronic kidney disease.

A total of 5436 mortalities occurred during the median follow-up period of 10.1 years. Table 2 shows the hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality according to carbohydrate intake proportion in participants without DM and in those with DM. The HRs (95% CI) for incidence of all-cause mortality per 10% increment of carbohydrate intake in participants without DM were 1.37 (1.31–1.44) and 1.00 (0.95–1.04) in the unadjusted and adjusted model, respectively. In participants with DM, the HRs (95% CI) for incidence of all-cause mortality per 10% increment of carbohydrate intake were 1.25 (1.15–1.36) and 1.10 (1.01–1.20) in the unadjusted and adjusted model, respectively. When the differential effect of carbohydrate intake (%) on all-cause mortality was tested according to the presence of DM, a significant interaction between carbohydrate intake and the presence of DM (interaction $p = 0.066$ and 0.061 in the unadjusted and adjusted models, respectively) was observed.

Table 3 presents the HR and 95% CI for all-cause mortality based on daily intake of total sugar (g/day), and added sugar (g/day) in participants with and without DM. A significant interaction was observed between total sugar intake and added sugar consumption (g/day) and the presence of DM (all interactions. $p < 0.001$) in the unadjusted model. Similar trends were noted in the adjusted models.

For the incidence of all-cause mortality corresponding to total sugar intake, the adjusted model revealed HRs (95% CIs) of 0.99 (0.98–1.00) and 1.02 (1.01–1.04) for participants without DM and those with DM, respectively. For the incidence of all-cause mortality corresponding to added sugar, the adjusted model indicated HRs (95% CIs) of 0.98 (0.95–1.02) and 1.18 (1.13–1.24) for participants without DM and those with DM, respectively.

We also determined the cut-off points for carbohydrate intake (%), which maximized Harrell's C-index values of all-cause mortality in the entire study population, participants without DM, and those with DM (Supplementary Fig. 1). The cut-off points at which the HR diverges the most for carbohydrate intake (%) were 73.2% for the whole study population, 73.3% for participants without DM, and 69.4% for those with DM for all-cause mortality. Supplementary Table 3 shows the baseline characteristics of the study population categorized according to the specified carbohydrate cut-off points for both the DM and non-DM groups. Supplementary Table 4 shows the association between carbohydrate intake proportion and all-cause mortality in the study population, participants without DM, and those with DM. These associations are delineated based on the designated carbohydrate cut-off points. Compared with HR and 95% CI for all-cause mortality for non-DM participants who consumed <73.3% carbohydrate, those for participants who consumed ≥73.3% carbohydrate were 1.47 (1.38–1.56, $p < 0.001$) in the unadjusted model, and 0.99 (0.93–1.06, $p = 0.294$) in model 3. In participants with DM, consumption of ≥69.4% carbohydrate was significantly associated with an increased risk of all-cause mortality than consuming <69.4% carbohydrate (HR 1.36, 95% CI 1.19–1.56, $p < 0.001$ in unadjusted model; 1.18, 1.03–1.36, $p = 0.017$ in model 1; and 1.18, 1.02–1.34, $p = 0.028$ in model 2). However, adjusting for HTN, dyslipidemia, CKD, and baseline glucose attenuated the statistical significance (HR 1.13, 95% CI, 0.98–1.30, $p = 0.090$).

4. Discussion

We observed an association between carbohydrate intake proportion and all-cause mortality in this large Korean population-based prospective cohort study, focusing on the differential effects on participants with and without DM.

Notably, higher carbohydrate intake proportion was found to increase all-cause mortality in participants with DM in both unadjusted and adjusted models. Specifically, each 10% increase in

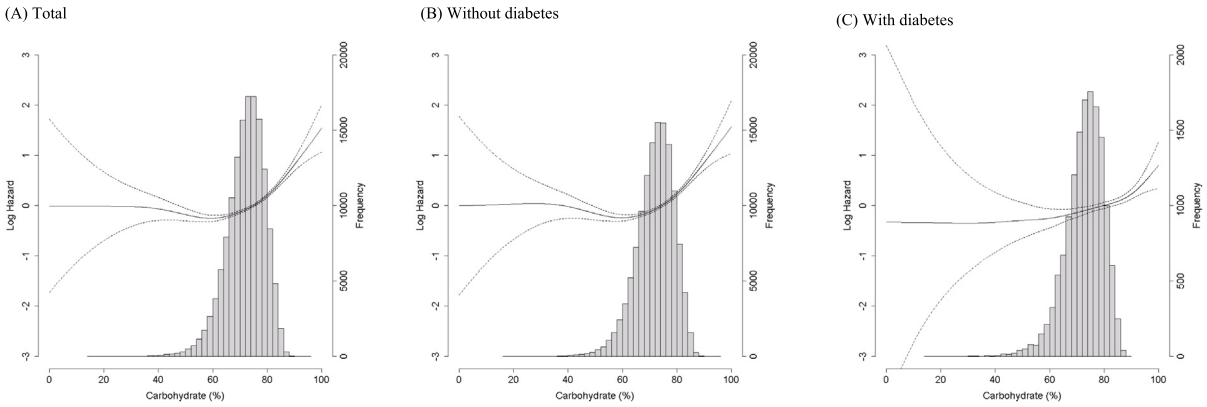

Fig. 2. Density plot of carbohydrate intake (%) and Cox proportional hazard spline curves in unadjusted model. (A) Total population, (B) participants without diabetes, and (C) those with diabetes.

Table 2
Hazard ratios and 95% confidence intervals for all-cause mortality based on carbohydrate intake (%).

	Total N = 143,050		Without DM N (%) = 128,726 (90.0)		With DM N (%) = 14,324 (10.0)		
Carbohydrate (%)							
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	p for interaction
Unadjusted	1.17 (1.15–1.19)	<0.001	1.37 (1.31–1.44)	<0.001	1.25 (1.15–1.36)	<0.001	0.066
Model 1	1.02 (1.00–1.04)	0.081	1.02 (0.97–1.06)	0.475	1.13 (1.03–1.23)	0.008	0.102
Model 2	1.01 (0.99–1.03)	0.255	1.01 (0.96–1.05)	0.805	1.10 (1.00–1.20)	0.042	0.102
Model 3	1.01 (0.99–1.03)	0.372	1.00 (0.95–1.04)	0.889	1.10 (1.01–1.20)	0.032	0.061

DM, diabetes mellitus; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index.
Model 1: adjusted for age, sex, and BMI.
Model 2: adjusted for age, sex, BMI, smoking, alcohol consumption, exercise, and total calorie intake.
Model 3: adjusted for age, sex, BMI, smoking, alcohol consumption, exercise, total calorie intake, hypertension, dyslipidemia, CKD, baseline glucose level.

Table 3
Hazard ratios and 95% confidence intervals for all-cause mortality based on the different sugar intake (g).

	Total N = 143,050		Without DM N = 128,726 (90.0)		With DM N = 14,324 (10.0)		
Total sugar, g/day							
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	p for interaction
Unadjusted	0.96 (0.96–0.97)	<0.001	0.96 (0.95–0.97)	<0.001	1.01 (0.99–1.02)	0.353	<0.001
Model 1	0.99 (0.98–1.00)	0.002	0.98 (0.97–0.99)	<0.001	1.02 (1.01–1.03)	0.004	<0.001
Model 2	0.99 (0.99–1.00)	0.135	0.99 (0.98–1.00)	0.010	1.02 (1.01–1.04)	0.002	<0.001
Model 3	1.00 (0.99–1.00)	0.358	0.99 (0.98–1.00)	0.017	1.02 (1.01–1.04)	<0.001	<0.001
Added sugar, g/day							
Unadjusted	0.93 (0.91–0.95)	<0.001	0.90 (0.88–0.93)	<0.001	1.12 (1.07–1.17)	<0.001	<0.001
Model 1	0.99 (0.97–1.02)	0.623	0.96 (0.93–0.99)	0.011	1.16 (1.11–1.21)	<0.001	<0.001
Model 2	0.99 (0.96–1.01)	0.257	0.96 (0.93–0.98)	0.003	1.14 (1.09–1.19)	<0.001	<0.001
Model 3	1.00 (0.97–1.02)	0.703	0.98 (0.95–1.02)	0.326	1.18 (1.13–1.24)	<0.001	<0.001

Abbreviations; T2DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CKD, chronic kidney disease.
Model 1: adjusted for age, sex, and BMI.
Model 2: adjusted for age, sex, BMI, smoking, alcohol consumption, exercise, and total calorie intake.
Model 3: adjusted for age, sex, BMI, smoking, alcohol consumption, exercise, total calorie intake, hypertension, dyslipidemia, CKD, baseline glucose level.

carbohydrate intake was associated with a 25% and 10% higher risk of all-cause mortality in the unadjusted and adjusted models, respectively. Conversely, no association was observed between the proportion of carbohydrate intake and all-cause mortality in participants without DM. Additionally, the adjusted model showed that elevated total sugar and added sugar intakes were associated with an increased risk of all-cause mortality in participants with DM. In participants without DM, total sugar intake was associated with a decreased risk of all-cause mortality, whereas added sugar intake showed no association with all-cause mortality.

In participants without DM, no significant association was observed between carbohydrate intake proportion and all-cause mortality; however, a negative association was observed between total sugar intake and all-cause mortality in those without DM. This could be attributed to the inclusion of natural sugar, commonly found in fruits, within total sugar. Interestingly, added sugar showed no association with all-cause mortality in participants without DM. Furthermore, our subsequent analysis, delineating complex carbohydrates as total carbohydrates excluding added sugar, revealed no association with all-cause mortality in participants without DM. The negative association between fiber intake and all-cause mortality could support these findings (Supplementary Table 5). However, no significant interactions were observed between complex carbohydrates, fiber, and all-cause

mortality based on the presence of DM. Further research on the influence of carbohydrate types based on the presence of DM is warranted.

There is a strong physiological rationale supporting the role of carbohydrate restriction in the management of type 2 DM [32]. However, evidence linking low carbohydrate diet with mortality has not been unified. A large-scale study involving a national representative sample of American adults demonstrated that LCD is linked to a higher risk of all-cause and cause-specific mortality [33]. The study reported that ≤39% carbohydrate intake can elevate the risk of all-cause mortality [33]. The ARIC study revealed a U-shaped relationship between carbohydrate intake and all-cause mortality, indicating that both low (<40%) and high (>70%) carbohydrate consumption confer a greater mortality risk than moderate carbohydrate intake [34]. Another study showed a U-shaped relationship between carbohydrate intake and all-cause mortality in patients with type 2 DM, with the lowest risk at 43–52% carbohydrate intake [35]. The PURE study [36] reported that higher carbohydrate intake is associated with an increased risk of total mortality (quintile 5 [77.2%] vs quintile 1 [46.4%]; HR 1.28 [95% CI 1.12–1.46]). Similarly, a study among the Asian population with 29 years of follow-up found a beneficial association of a low carbohydrate diet with the occurrence of CVD and overall mortality [9,37]. This discrepancy could be attributed to the differences in participants' characteristics, race, amount and source of carbohydrate intake [4]. Moreover, it seems critical to consider the important covariates, such as the presence of DM.

Whether dietary recommendations for people with DM should differ from those for the general public still remains unclear. Moreover, there are no separate recommendations regarding carbohydrate intake for adults with DM in most countries [38]. We found a significant interaction between dietary intake of carbohydrates and DM in terms of all-cause mortality (p for interaction = 0.061). Furthermore, we conducted pre-specified analyses based on DM status. Notably, we observed that increased carbohydrate consumption was associated with higher mortality risk among participants with DM, whereas no significant association was observed in those without DM. These findings highlight the differential impact of carbohydrate intake on mortality depending on the presence or absence of DM.

In the present study, total sugar and added sugar intakes were associated with an increased risk of all-cause mortality in participants with DM. Conversely, in participants without DM, total sugar intake was associated with a decreased risk of all-cause mortality, whereas added sugar intake showed no association with all-cause mortality. Epidemiologic studies have generated somewhat mixed results regarding the association between fruits consumption and risk of type 2 DM [39,40]. Consumption of whole fruits has been associated with a lower risk of DM, while consumption of fruit juices may be associated with an increased risk of DM [39,40]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study reported that intake of several food groups is more strongly associated with mortality risk in individuals with diabetes than in those without diabetes [41]. Ma et al. [14]. reported that a higher intake of sugar-sweetened beverages is associated with higher all-cause mortality and CVD incidence and mortality among adults with type 2 DM.

These findings align with the existing understanding that excessive sugar consumption can exacerbate metabolic dysregulation and increase the risk of complications in individuals with DM.

Several pathophysiological mechanisms can be used to explain why reducing carbohydrate intake is beneficial for individuals with DM. Patients with T2DM experience IR, leading to impaired gluconeogenesis control and reduced capacity to prevent hepatic glucose release [42]. This IR serves as the precursor for several pathological conditions, including obesity, HTN, dyslipidemia, inflammation, oxidative stress, and endothelial dysfunction, all of which are predisposing factors for atherosclerosis and CVDs [43]. A recent meta-analysis of prospective cohort studies reported that higher intake of carbohydrates is independently associated with an increased risk of CVD, particularly in Asian populations, where carbohydrate intake outpaces Western countries [44,45]. Conversely, a tiny decline in insulin secretion capacity can lead to a rapid decrease in the threshold level of IR in the Asian population [46,47]. Specifically, the postprandial surge in blood glucose and insulin levels following the intake of added high-fructose corn syrup and sucrose could potentially result in hyperinsulinemia, lipogenesis, and IR over an extended period [48]. This is particularly concerning for individuals with DM [14]. The differential effects of sugar intake on mortality rates highlight the importance of considering individual metabolic status and dietary patterns in assessing health outcomes. Further research is warranted to elucidate the mechanistic pathways underlying these contrasting effects and to inform evidence-based dietary guidelines for diverse populations.

Furthermore, the cut-off points for carbohydrate intake (%), which maximized the Harrell's C-index values of all-cause mortality, were determined as 73.2% in the total study population, 73.3% in participants without DM, and 69.4% in those with DM. In individuals without DM, after adjusting for confounding variables, no significant association was observed between the carbohydrate cut-off ratio and overall mortality. However, in individuals with DM, consuming less than 69.4% carbohydrates significantly reduced overall mortality in model 2. In Model 3, which additionally adjusted for underlying conditions and baseline glucose, statistical significance diminished, yet a trend towards decreased overall mortality was observed. In our study, carbohydrate intake exceeded 70% of total energy in the middle-aged and older population, surpassing the acceptable macronutrient distribution range for carbohydrates (typically 45–65%) to reduce the risk of chronic diseases [3]. As dietary recommendations for carbohydrate intake by various working groups typically range between 45 and 65%, the optimal cut-off points identified in this study appear notably higher. Koreans have a relatively higher carbohydrate intake than Western populations. Additionally, the baseline survey for this study was conducted in 2001–2002, focusing on the middle-aged and older population. These factors may have contributed to the observed results.

Therefore, carbohydrate restriction may be the most effective method to improve glycemic control, mitigate IR and address CVD concerns in Asians with DM [49]. Although physical activity can affect biochemical parameters associated with diabetes, including HbA1c and blood glucose level, statistically significantly identical results in the DM group were found even after correcting for physical activity.

Our study had a few limitations. First, we relied on the FFQ to collect information on dietary carbohydrate intake. In our study, the carbohydrate and sugar intakes were relatively low compared to those of recent KNHANES data (https://knhanes.kdca.go.kr/knhanes/main.do). Utilizing the FFQ may have led to inaccuracies in absolute nutrient values and the potential for over- or under-reporting of specific meals. Moreover, recall bias may have influenced participants' ability to accurately recall their dietary intake. However, the FFQ remains a practical and effective tool, particularly in large-scale epidemiological cohort studies. Additionally, there is a discrepancy in the years of examination. Our baseline survey was conducted almost 20 years ago in 2001, which may introduce differences from present-day circumstances. Second, nutritional evaluation was only performed using the questionnaire at the baseline. Therefore, the current study could not account for the

varying time effects of dietary carbohydrate consumption or any changes in dietary practices during the follow-up period. Third, observational studies have inherent limitations, including the potential for residual confounding bias and the absence of causal inference.

Finally, as we only included middle-aged and older Korean adults, future studies involving different age groups and ethnicities are required to establish more generalizable recommendations.

Nevertheless, our study is the first to utilize a large population-based prospective Korean cohort to investigate the significant interaction between carbohydrate intake (%) and the presence of DM. Moreover, our study investigated the association between types of carbohydrate intake and all-cause mortality among individuals with and without DM.

5. Conclusion

We conclude that the effect of carbohydrate consumption on mortality differs for individuals with DM from that of those without DM. Individuals with DM may benefit more from reducing their carbohydrate intake and adopting healthier choices. Nevertheless, those without DM should also be cautious about consuming excessive carbohydrates. Future research involving diverse populations would be valuable for confirming and refining these findings.

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Author contribution

YHP, HSL, JY, and JWL contributed to the conception and design of the work. YHP, HSL, LRL, JY, and JWL contributed to the acquisition, analysis, and interpretation of data and drafting of the manuscript. All authors critically revised the manuscript, provided final approval and are accountable for all aspects of the work, ensuring integrity and accuracy.

Conflict of interest

All authors declare that they do not have any conflict of interest regarding this publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.03.024.

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