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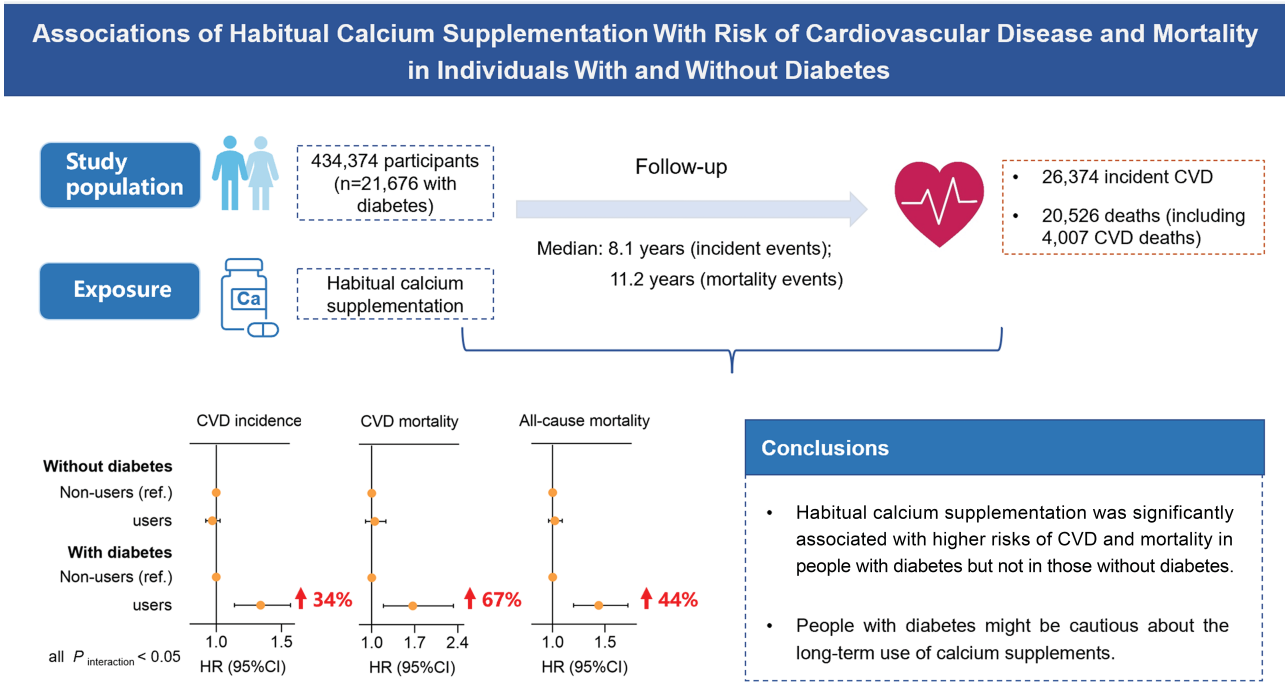

ARTICLE HIGHLIGHTS

- Although the association between calcium supplements and cardiovascular disease risk in the general population is debatable, evidence is scarce among people with diabetes who are at higher risk of both abnormal calcium metabolism and cardiovascular disease.
- This study examines whether the associations of habitual calcium supplementation with risk of cardiovascular disease and mortality are different between people with and without diabetes.
- Habitual calcium supplementation was associated with significantly higher risk of cardiovascular disease and mortality in individuals with diabetes but not in those without diabetes.
- People with diabetes might need to be cautious about the long-term use of calcium supplements.

Associations of Habitual Calcium Supplementation With Risk of Cardiovascular Disease and Mortality in Individuals With and Without Diabetes

Zixin Qiu,[1] Qi Lu,[1] Zhenzhen Wan,[1] Tingting Geng,[1] Rui Li,[1] Kai Zhu,[1] Lin Li,[1] Xue Chen,[1] An Pan,[2] JoAnn E. Manson,[3,4,5] and Gang Liu[1]

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OBJECTIVE

To prospectively examine the associations of habitual calcium supplementation with cardiovascular disease (CVD) events and mortality in individuals with and without diabetes.

RESEARCH DESIGN AND METHODS

The main analysis included 434,374 participants from the UK Biobank. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs. Interactions of calcium supplement use with diabetes status were tested on multiplicative and additive scales.

RESULTS

Over a median follow-up of 8.1 and 11.2 years, 26,374 incident CVD events and 20,526 deaths were documented, respectively. After multivariable adjustment, habitual calcium supplementation was significantly associated with higher risks of CVD incidence (HR 1.34; 95% CI 1.14, 1.57), CVD mortality (HR 1.67; 95% CI 1.19, 2.33), and all-cause mortality (HR 1.44; 95% CI 1.20, 1.72) in participants with diabetes, whereas no significant association was observed in participants without diabetes (HR 0.97 [95% CI 0.92, 1.03] for CVD incidence; HR 1.05 [95% CI 0.90, 1.23] for CVD mortality; HR 1.02 [95% CI 0.96, 1.09] for all-cause mortality). Significant multiplicative and additive interactions were found between habitual calcium supplementation and diabetes status on risks of CVD events and mortality (all $P_{interaction} < 0.05$). In contrast, no significant interactions were observed between dietary or serum calcium and diabetes status.

CONCLUSIONS

Habitual use of calcium supplements was significantly associated with higher risk of CVD events and mortality in people with diabetes but not in people without diabetes. Further studies are needed to balance potentially adverse effects of calcium supplement against likely benefits, particularly among patients with diabetes.

Calcium, the most abundant mineral in the body, is important for bone health and several major physiologic functions (1). The use of calcium supplements to prevent osteoporotic fractures is widespread, and thus, any beneficial or adverse effects of

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calcium supplements on health is of great public health importance. Recent evidence regarding the health effects of calcium supplements on cardiovascular disease (CVD) risk has been inconsistent and inconclusive (2–7). Previous experimental studies suggested that supplemental calcium, but not dietary calcium, could abruptly increase blood calcium levels, which may be harmful for cardiovascular health (8–10). As for epidemiological evidence, most studies revealed a null association in general populations (2,3), but others raised concerns about the cardiovascular safety of calcium supplement use, particularly in those at higher risk of CVD and impaired calcium metabolism (4,5,11).

Compared with the general population, patients with diabetes, who are characterized by insulin resistance and hyperglycosemia, have a two- to fourfold higher risk of developing CVD and premature death (12), and have relatively higher prevalence of abnormal calcium homeostasis such as elevated extra- and intracellular calcium levels (13–15). Such alteration in calcium homeostasis may further aggravate insulin resistance and hyperglycosemia and, in the long term, promote the development of CVD in patients with diabetes (16,17). Therefore, it is imperative to clarify the association between calcium supplements and risk of CVD and mortality in people with diabetes. However, evidence in this regard is scarce (18), and whether and the extent to which the associations differ between people with and without diabetes remains unknown.

To fill these knowledge gaps, based on a large-scale U.K. prospective cohort study, we primarily aimed to examine the associations between calcium supplements and CVD events and mortality in individuals with and without diabetes and further assess whether and the extent to which diabetes status would modify the associations of calcium supplements with these outcomes. Secondarily, we examined the associations of dietary and serum calcium with CVD events and mortality in participants with and without diabetes.

RESEARCH DESIGN AND METHODS

Study Population

The UK Biobank is a large, population-based cohort study, which recruited approximately half a million participants aged 40–69 years in 2006–2010 across the England, Scotland, and Wales. Each participant completed touchscreen questionnaires, underwent physical examinations, and provided biological samples (19).

Diabetes was defined on the basis of a validated algorithm that used UK Biobank self-reported medical history and medication information (diagnosis, age of diagnosis, diabetes type, diabetes medications, and diabetes complications) (20) or glycated hemoglobin A_{1c} (HbA_{1c}) $\geq$6.5% at baseline (21). For the present analyses, we excluded people who were self-reported as pregnant (n = 150) or having CVD (n = 28,079) or cancer (n = 38,614) at baseline, those with incomplete data on the use of calcium supplement (n = 3,235), and those who subsequently withdrew from the study (n = 1,298). After the exclusions, 434,374 participants (n = 21,676 with diabetes) were included in the main analyses (Supplementary Fig. 1).

The UK Biobank received ethical approval from the research ethics committee (REC reference 11/NW/0382) and participants provided written informed consent.

Ascertainment of Outcomes

The primary outcomes of the study were CVD incidence and all-cause mortality. The secondary outcomes were incidence of ischemic heart disease (IHD), heart failure (HF), and cerebrovascular disease. Information on death was obtained from death registry data. Incident CVD events were obtained from hospital admission data and death registry data. Outcomes were defined according to ICD-10 codes: CVD codes I21–I25, I50, I60–I69; IHD codes I21–I25; HF codes I50; cerebrovascular disease codes I60–I69; and CVD death codes I00–I99.

Assessment of Calcium Supplements

Information about the habitual use of calcium supplements was obtained from baseline touch-screen questionnaire. Participants were asked, "Do you regularly take any of the following?" and selected more than one answer from a list of supplements, which included calcium. We scored habitual use of calcium supplements as "1 = yes" or "0 = no." The definition was generally consistent with previous studies on habitual use of supplements (22,23).

Assessment of Covariates

Structured questionnaires were used to collect information through in-person interviews on sociodemographic characteristics, lifestyle factors (physical activity, smoking, alcohol consumption), usual diet, and medical history at the time of recruitment. Physical activity was defined as inactive (no documented moderate or vigorous physical activity), insufficient (moderate activity $<$150 min/week and vigorous activity $<$75 min/week), and active (moderate activity $\geq$150 min/week and/or vigorous activity $\geq$75 min/week). The Townsend deprivation index, used as an indicator of socioeconomic status, is provided directly from the UK Biobank. BMI was calculated from as weight (kg) divided by height squared (m^2). Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration formula considering creatinine, sex, age, and race (24). Dietary nutrients information was collected in a subsample of study participants (n = 182,387) who completed a web-based 24-h recall questionnaire on five occasions between 2009 and 2012. We calculated cumulative mean values from the available data to represent long-term dietary intake and reduce within-person variation.

Statistical Analysis

Sample characteristics are reported as mean ± SD for normally distributed continuous variables, medians (interquartile ranges) for nonnormally distributed continuous variables, and numbers with percentages for categorical variables. The difference between groups were compared by a Student t test, Wilcoxon test, or χ^2 test.

Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs for the associations of calcium supplement use with risk of CVD outcomes and all-cause mortality in individuals with and without diabetes. Schoenfeld residuals were used to test the proportional hazards assumption, and no violation was observed. In model 1, we adjusted for age and sex. Model 2 was further adjusted for race, BMI, education level, Townsend deprivation index, drinking frequency, smoking status, physical activity, vitamin supplementation, mineral and other dietary supplementation, and intakes of fresh fruit, fresh vegetables, red meat, poultry, fish, whole grain, and dairy. Model 3 (full model) was further adjusted for hypertension,

hypercholesterolemia, osteoporosis, aspirin use, serum vitamin D level, and eGFR. The full model for participants with diabetes was additionally adjusted for duration of diabetes, diabetes medicine use, and HbA_{1c}. Missing data were coded as a missing indicator category for categorical variables and with median values for continuous variables. Detailed information on the number of missing covariates is shown in Supplementary Table 1.

To assess whether diabetes could modify the association of calcium supplements with the risk of CVD and all-cause mortality, we calculated interactions on multiplicative and additive scales. Multiplicative interaction was assessed by comparing models with and without a cross-product interaction term of calcium supplement use and diabetes status, using likelihood ratio tests. Additive interaction was evaluated by three indexes: the relative excess risk because of the interaction (RERI), the attributable proportion because of the interaction (AP), and synergy index (SI). In the absence of additive interaction, the CIs of the RERI, AP, and SI would include 0. To assess the joint associations, we further classified participants into four groups according to habitual calcium supplement use (nonuser or user) and diabetes status (without or with), and we calculated HRs of mortality and incident CVD in different groups compared with those without diabetes and without use of calcium supplement.

Stratified analyses were performed by age ($\leq$60, $>$60 years), sex (male, female), smoking status (current, past or never), BMI ($<$30, $\geq$30 kg/m^2), vitamin D supplements use (yes, no), serum vitamin D levels ($<$75, $\geq$75 nmol/L), heel bone mineral density (BMD) T-score (less than -1, at least -1), menopause status (yes, no), and eGFR ($<$60, $\geq$60 mL/min/1.73 m^2) in individuals with and without diabetes, respectively. In individuals with diabetes, we further stratified by diabetes duration ($<$3, $\geq$3 years), HbA_{1c} ($<$7%, $\geq$7%), hypertension (yes, no) and hypercholesterolemia (yes, no). Furthermore, several sensitivity analyses were also conducted. First, we repeated main analyses in a 1:4 propensity score–matched cohort to minimize confounding bias. Propensity scores were calculated with the use of a logistic regression model including all the covariates in model 3. Second, to minimize the potential influence of reverse causation, we excluded participants who died during the first 2 years of follow-up. Third, we restricted the analyses to participants with no missing covariate data. Fourth, we repeated main analyses in patients with type 2 diabetes. Fifth, instead of individual foods, we additionally adjusted for healthy diet score, which was constructed with reference to the dietary priorities for cardiometabolic health recommended by American Heart Association (AHA), with appropriate modifications (25). A healthy diet was defined as meeting at least five items of the recommendations. Sixth, an additional analysis with further adjustment for dietary energy, calcium, and other nutrients intake was performed. Seventh, to examine whether some medications commonly used by patients with diabetes might have interactions with calcium supplements, we performed stratified analyses according to use of insulin, metformin, ACE inhibitors, angiotensin-receptor blockers, and statins. Eighth, analyses were repeated accounting for death as a competing event, using the Fine and Gray competing risks model. Last, to assess whether the increased cardiovascular risk associated with calcium supplement use by patients with diabetes was conditioned on dietary calcium intake and serum calcium level, we further evaluated joint associations of calcium supplements use and dietary calcium intake or calcium supplement use and serum calcium level in patients with diabetes.

As secondary analyses, we investigated the association of calcium supplementation with risk of CVD subtypes (namely, cerebrovascular disease, IHD, and HF). We also examined the association of energy-adjusted dietary calcium intakes and serum albumin–adjusted calcium levels with CVD events and all-cause mortality by using the restricted cubic-spline regression model. Energy-adjusted dietary calcium intakes were calculated by using the residual method to improve the accuracy of nutrient measurements. An equation derived from UK Biobank data was used to calculate albumin-adjusted calcium to determine serum calcium levels (26) according to National Institute for Health and Care Excellence guidance recommendations (27).

All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Two-sided $P < 0.05$ was considered statistically significant.

Data Resource and Availability

The UK Biobank data are available from the UK Biobank on request (www.ukbiobank.ac.uk/).

RESULTS

Data from a total of 434,374 participants (mean age, 56.0 years; 45.0% male) were included in the analysis; of these participants, 21,676 had diabetes. Overall, 29,360 of the 434,374 participants (6.8%) reported habitual calcium supplementation at baseline. There was no significant difference in the prevalence of calcium supplement use between diabetic and nondiabetic populations (6.9% vs. 5.1%, respectively). Table 1 shows the baseline characteristics of study participants and compares those individuals who were taking calcium supplements with those who were not in the diabetic and nondiabetic populations. Patients with diabetes and those without who used calcium supplements, as opposed to nonusers, were more likely to be older, female, nonsmokers, and nonalcohol drinkers; tended to use other supplements; and had a higher prevalence of osteoporosis, healthier eating patterns, and higher serum vitamin D level.

Over a median follow-up of 8.1 and 11.2 years, 26,374 incident CVD events and 20,526 deaths (including 4,007 CVD deaths) were documented, respectively. After multivariable adjustment including dietary and lifestyle factors, other supplements use, and serum vitamin D levels, habitual calcium supplement use was significantly associated with higher risks of CVD incidence (HR 1.34; 95% CI 1.14, 1.57; $P < 0.001$), CVD mortality (HR 1.67; 95% CI 1.19, 2.33; $P = 0.003$), and all-cause mortality (HR 1.44; 95% CI 1.20, 1.72; $P < 0.001$) in participants with diabetes, whereas no significant association was observed in participants without diabetes (for CVD incidence, HR 0.97 [95% CI 0.92, 1.03]; for CVD mortality, HR 1.05 [95% CI 0.90, 1.23]; for all-cause mortality, HR 1.02 [95% CI 0.96, 1.09]) (Table 2). In addition, we repeated the analysis in a 1:4 propensity score–matched cohort. The standardized difference for all matching variables from model 2 was $<$0.1 (Supplementary Table 2). In Supplementary Fig. 2, the histograms shown after matching, on the right, are very similar between the groups, indicating good balance between calcium supplement users and nonusers. The results were almost unchanged in

Table 1—Baseline characteristics of participants*

Characteristic	Total participants	Participants without diabetes not using calcium supplements	Participants without diabetes using calcium supplements	*P* value†	Participants with diabetes not using calcium supplements	Participants with diabetes using calcium supplements	*P* value†
Participants, *n*	434,374	384,436	28,262		20,578	1,098	
Age (years)	56.0 ± 8.1	55.6 ± 8.1	58.3 ± 7.3	<0.001	58.8 ± 7.4	59.6 ± 7.3	<0.001
Male sex	195,464 (45.0)	177,840 (46.3)	4,578 (16.2)	<0.001	12,675 (61.6)	371 (33.8)	<0.001
White race	408,254 (94.0)	363,783 (94.6)	25,956 (91.8)	<0.001	17,729 (86.2)	786 (71.6)	<0.001
Education level				<0.001			<0.001
College or university degree	68,071 (16.0)	58,663 (15.6)	4,121 (14.7)		5,052 (25.3)	235 (21.8)	
A levels/AS levels or equivalent or O levels/GCSEs or equivalent	165,006 (38.7)	146,917 (39.0)	10,730 (38.4)		6,971 (34.9)	388 (36.0)	
Other professional qualifications	49,634 (11.7)	43,578 (11.6)	3,015 (10.8)		2,910 (14.6)	131 (12.1)	
Others	143,353 (33.7)	127,869 (33.9)	10,095 (36.1)		5,064 (25.3)	325 (30.1)	
Townsend deprivation index	−2.2 (−3.7, 0.5)	−2.2 (−3.7, 0.4)	−2.1 (−3.7, 0.5)	<0.001	−1.3 (−3.2, 1.9)	−1.1 (−3.1, 2.1)	0.03
Smoking status				<0.001			<0.001
Never	242,291 (56.1)	215,269 (56.3)	16,532 (58.7)		9,877 (48.4)	613 (56.3)	
Former	144,559 (33.5)	126,402 (33.1)	9,580 (34.0)		8,211 (40.3)	366 (33.6)	
Current	45,202 (10.5)	40,723 (10.7)	2,066 (7.3)		2,303 (11.3)	110 (10.1)	
Alcohol consumption (times/week)				<0.001			<0.001
Never	82,166 (19.0)	67,929 (17.7)	6,924 (24.5)		6,794 (33.2)	519 (47.4)	
1–2	161,175 (37.2)	143,454 (37.4)	10,011 (35.5)		7,373 (36.0)	337 (30.8)	
3–4	101,513 (23.4)	92,176 (24.0)	5,973 (21.2)		3,241 (15.8)	123 (11.2)	
≥5	88,322 (20.4)	79,795 (20.8)	5,334 (18.9)		3,076 (15.0)	117 (10.7)	
Physical activity				<0.001			0.22
Inactive	44,144 (10.9)	38,448 (10.7)	2,412 (9.0)		3,137 (16.6)	147 (14.6)	
Insufficient	95,221 (23.5)	83,707 (23.3)	6,125 (22.9)		5,117 (27.1)	272 (27.1)	
Active	266,706 (65.7)	237,345 (66.0)	18,176 (68.0)		10,600 (56.2)	585 (58.3)	
BMI (kg/m^2)	27.3 ± 4.8	27.2 ± 4.6	26.0 ± 4.5	<0.001	31.4 ± 5.9	30.4 ± 6.2	<0.001
Healthy diet	94,873 (21.8)	80,515 (20.9)	7,970 (28.2)	<0.001	6,015 (29.2)	373 (34.0)	<0.001
Mineral and other dietary supplementation	174,204 (40.1)	147,446 (38.4)	18,999 (67.2)	<0.001	7,145 (34.7)	614 (55.9)	<0.001
Vitamin supplementation	136,964 (31.5)	109,288 (28.4)	21,609 (76.5)	<0.001	5,249 (25.5)	818 (74.5)	<0.001
Hypertension	229,711 (52.9)	198,731 (51.7)	13,884 (49.1)	<0.001	16,285 (79.1)	811 (73.9)	<0.001
Hypercholesterolemia	63,767 (14.7)	45,724 (11.9)	3,392 (12.0)	0.59	13,925 (67.7)	726 (66.1)	0.15
Osteoporosis	6,293 (1.5)	2,730 (0.7)	3,342 (11.8)	<0.001	122 (0.6)	99 (9.0)	<0.001
Aspirin use	44,192 (10.3)	32,924 (8.7)	2,779 (9.9)	<0.001	8,082 (40.0)	407 (37.8)	0.15
Serum vitamin D levels (<25 nmol/L)	51,650 (13.3)	46,169 (13.5)	1,323 (5.2)	<0.001	4,030 (21.7)	128 (12.9)	<0.001
eGFR (<60 mL/min/1.73 m^2)	7,659 (1.9)	6,054 (1.7)	619 (2.3)	<0.001	919 (4.8)	67 (6.6)	0.03

*Normally distributed continuous variables are described as mean ± SD, and continuous variables without a normal distribution are described as median (interquartile range). Categorical variables are presented as number (%). GCSE, General Certificate of Secondary Education. †*P* difference in the baseline characteristic between calcium supplement users and calcium supplement nonusers in participants with and without diabetes.

Table 2—Associations (HR, 95% CI) of habitual calcium supplementation with risk of cardiovascular outcomes and all-cause mortality in participants with and without diabetes

	CVD incidence	CVD mortality	All-cause mortality
Without diabetes (*n* = 412,698)			
No. cases/total	23,207/412,698	3,346/412,698	18,110/412,698
Model 1*	0.99 (0.94, 1.05)	1.05 (0.93, 1.19)	1.02 (0.97, 1.07)
P	0.35	0.41	0.53
Model 2†	1.02 (0.97, 1.08)	1.05 (0.90, 1.23)	1.04 (0.98, 1.10)
P	0.47	0.56	0.24
Model 3‡	0.97 (0.92, 1.03)	1.05 (0.90, 1.23)	1.02 (0.96, 1.09)
P	0.39	0.56	0.47
With diabetes (*n* = 21,676)			
No. cases/total	3,167/21,676	661/21,676	2,416/21,676
Model 1*	1.36 (1.17, 1.58)	1.51 (1.14, 2.01)	1.38 (1.17, 1.64)
P	<0.001	0.005	<0.001
Model 2†	1.34 (1.15, 1.56)	1.65 (1.21, 2.27)	1.50 (1.27, 1.78)
P	<0.001	0.002	<0.001
Model 3‡	1.34 (1.14, 1.57)	1.67 (1.19, 2.33)	1.44 (1.20, 1.72)
P	<0.001	0.003	<0.001

*Model 1: adjusted for age (continuous) and sex (male, female). †Model 2: further adjusted for race (White, others), BMI (continuous), education level (college or university degree, A levels/AS levels or equivalent or O levels/General Certificate of Secondary Education or equivalent, other professional qualifications, or others), the Townsend deprivation index (in quartiles), drinking frequency (never, 1–2, 3–4, or ≥5 times/week), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficient, or active), vitamin supplementation (yes, no), mineral and other dietary supplementation (yes, no), intakes of fresh fruit (mL [T] per day: <15 [<1.0], 15–28 [1.0–1.9], 30–43 [2.0–2.9], or ≥45 [≥3.0]), fresh vegetables (<2.0, 2.0–3.9, 4.0–5.9, or ≥6.0 pieces/day), red meat (<1.0, 1.0–1.9, 2.0–2.9, or ≥3.0 servings/day), poultry (<1, 1, or ≥2 servings/day), fish (<1.0, 1–1.9, 2.0–4.0, or ≥4.0 servings/week), whole grain (never, <3, or ≥3 servings/day), and dairy intakes (never, <1, 2–4, or ≥5 times/week). ‡Model 3: further adjusted for hypertension (yes, no), hypercholesterolemia (yes, no), osteoporosis (yes, no), aspirin use (yes or no), eGFR (in quartiles), and serum vitamin D level (in quartiles). The model for people with diabetes was additionally adjusted for duration of diabetes (<3.0, 3.0–9.9, or ≥10.0 years), diabetes medicine use (none, only oral medication, or insulin), and HbA_{1c} (<7%, ≥7%).

the propensity score–matched cohort (Supplementary Table 3).

Significant multiplicative and additive interactions were found between habitual calcium supplementation and diabetes status on the risk of CVD events and all-cause mortality (Table 3) (all $P_{interaction} < 0.05$). According to the three measures of additive interaction between calcium supplements and diabetes (i.e., RERI, AP, and SI), there is 0.44–1.11 relative excess risk of CVD events and mortality due to the additive interaction. In addition, the risk of CVD and mortality in individuals who had been exposed to both risk factors (habitual calcium supplementation and diabetes) is 2.18–2.96 times higher than the sum of risks in individuals exposed to a single risk factor alone, and 26–39% of the CVD events and mortality in individuals exposed to both risk factors is attributable to the additive interaction (Table 3). When compared with people without diabetes and without use of

Table 3—Multiplicative and additive interactions between habitual calcium supplementation and diabetes status on cardiovascular outcomes and all-cause mortality

	CVD incidence	CVD mortality	All-cause mortality
Multiplicative interaction			
HR (95% CI)	1.25 (1.19, 1.30)	1.63 (1.16, 2.30)	1.41 (1.18, 1.68)
P	0.001	0.007	<0.001
Additive interaction			
RERI (95% CI)	0.44 (0.19, 0.69)	1.11 (0.24, 1.99)	0.65 (0.28, 1.02)
AP (95% CI)	0.26 (0.15, 0.38)	0.39 (0.20, 0.59)	0.30 (0.18, 0.41)
SI (95% CI)	2.96 (1.81, 4.84)	2.54 (1.48, 4.37)	2.18 (1.56, 3.05)
P	<0.001	0.01	<0.001

Adjusted for age (continuous), sex (male, female), race (White, others), BMI (continuous), education level (college or university degree; A levels/AS levels or equivalent or O levels/General Certificate of Secondary Education or equivalent; other professional qualifications; or others), the Townsend deprivation index (in quartiles), drinking frequency (never, 1–2, 3–4, or ≥5 times/week), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficient, or active), hypertension (yes, no), hypercholesterolemia (yes, no), osteoporosis (yes, no), aspirin use (yes, no), serum vitamin D level (in quartiles), eGFR (in quartiles), vitamin supplementation (yes, no), mineral and other dietary supplementation (yes, no), intakes of fresh fruit (mL [T] per day: <15 [<1.0], 15–28 [1.0–1.9], 30–43 [2.0–2.9], or ≥45 [≥3.0]), fresh vegetables (<2.0, 2.0–3.9, 4.0–5.9, or ≥6.0 pieces/day), red meat (<1.0, 1.0–1.9, 2.0–2.9, or ≥3.0 servings/day), poultry (<1, 1, or ≥2 servings/day), fish (<1.0, 1–1.9, 2.0–4.0, or ≥4.0 servings/week), whole grain (never, <3, or ≥3 servings/day), and dairy intakes (never, <1, 2–4, or ≥5 times/week).

calcium supplement, people with diabetes and with calcium supplement use were associated with a particularly higher risk of CVD incidence (HR 1.67; 95% CI 1.43, 1.93), CVD mortality (HR 2.84; 95% CI 2.08, 3.87), and all-cause mortality (HR 2.20; 95% CI 1.87, 2.60) (Fig. 1).

As for CVD subtypes, habitual calcium supplementation was significantly associated with higher risk of cerebrovascular disease, IHD, and HF in individuals with diabetes but not in those without (HR range: 1.26–2.26) (Supplementary Table 4). Significant multiplicative and additive interactions were also observed for

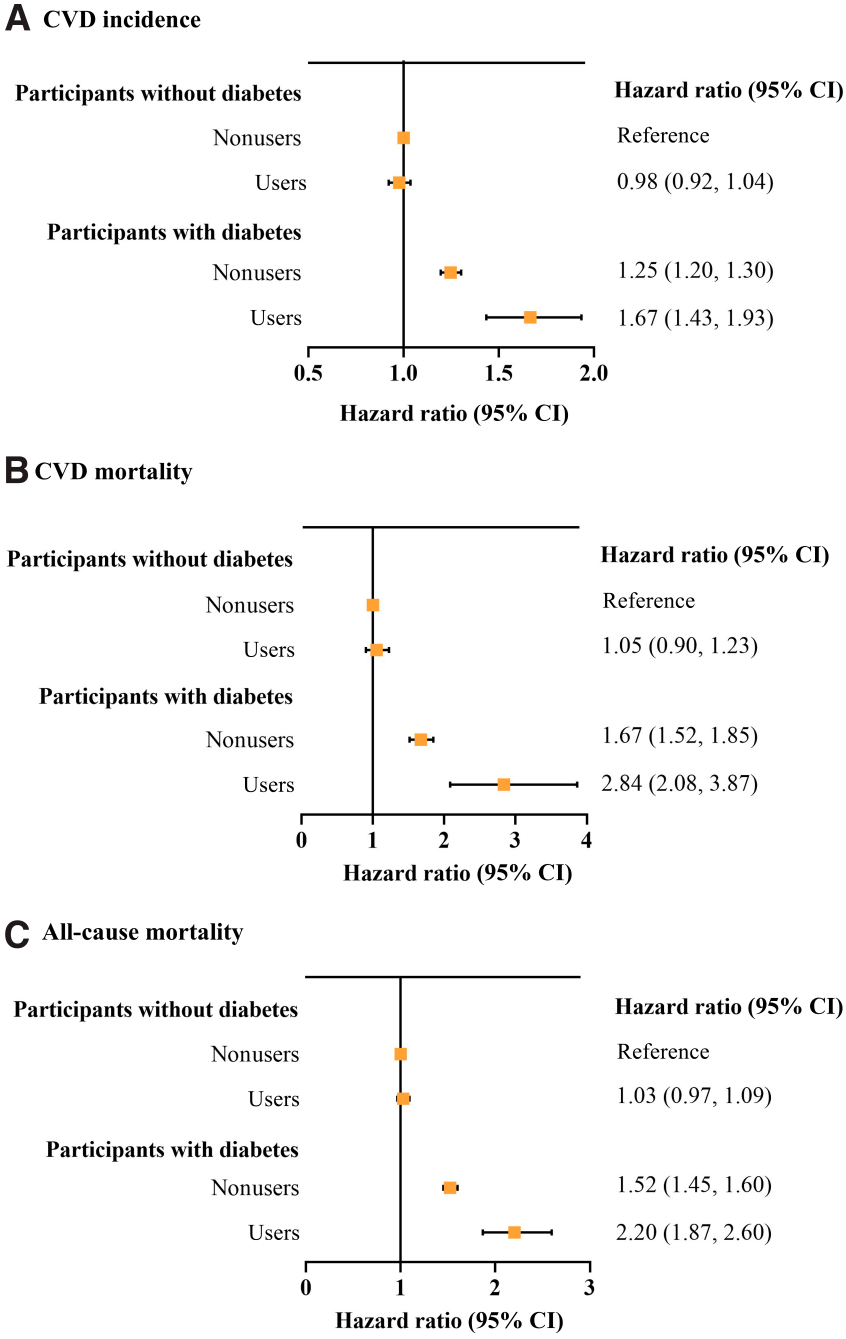

Figure 1—Joint associations (HR, 95% CI) of habitual calcium supplement use (nonuser or user) and diabetes status (without or with) with CVD incidence (*A*), CVD mortality (*B*), and all-cause mortality (*C*). HRs were adjusted for age (continuous), sex (male or female), race (White or others), BMI (continuous), education level (college or university degree; A levels/AS levels or equivalent or O levels/General Certificate of Secondary Education or equivalent; other professional qualifications; or others), the Townsend deprivation index (in quartiles), drinking frequency (never, 1–2, 3–4, or ≥5 times/week), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficient, or active), hypertension (yes, no), hypercholesterolemia (yes, no), osteoporosis (yes, no), aspirin use (yes, no), serum vitamin D level (in quartiles), eGFR (in quartiles), vitamin supplementation (yes, no), mineral and other dietary supplementation (yes, no), intakes of fresh fruit (mL [T] per day: <15 [<1.0], 15–28 [1.0–1.9], 30–43 [2.0–2.9], or ≥45 [≥3.0]), fresh vegetables (<2.0, 2.0–3.9, 4.0–5.9, or ≥6.0 pieces/day), red meat (<1.0, 1.0–1.9, 2.0–2.9, or ≥3.0 servings/day), poultry (<1, 1, or ≥2 servings/day), fish (<1.0, 1–1.9, 2.0–4.0, or ≥4.0 servings/week), whole grain (never, <3, or ≥3 servings/day), and dairy intakes (never, <1, 2–4, or ≥5 times/week).

cerebrovascular disease, IHD, and HF incidence (RERI, 0.34–1.61; AP, 0.30–0.48; and SI, 2.35–4.36; all $P_{interaction} < 0.05$) (Supplementary Table 5).

Consistent results were observed when analyses were stratified by age, sex, BMI, smoking status, supplemental vitamin D use, serum vitamin D levels, BMD T-score, menopause status, eGFR, diabetes duration, HbA_{1c}, hypertension, or hypercholesterolemia, and no significant interactions were detected in individuals with and without diabetes after taking multiple testing into account (Supplementary Table 6).

The results were largely unchanged when we excluded participants who died during the first 2 years of follow-up (Supplementary Table 7) or excluded those with missing covariate data (Supplementary Table 8). Similar results were also observed when we restricted the analyses to type 2 diabetes (Supplementary Table 9), adjusted for the healthy diet score instead of individual foods (Supplementary Table 10), additionally adjusted for energy and dietary calcium intakes in the subsample with dietary data collected from the 24-h dietary recalls (Supplementary Table 11), stratified by some medications commonly used by patients with diabetes (Supplementary Table 12), or controlled for death as a competing risk (Supplementary Table 13).

In the joint analysis, although no significant interactions were observed, we found that calcium supplement use with low intake of dietary calcium was strongly associated with higher risk of CVD events and mortality, compared with no use of calcium supplements and low intake of dietary calcium (HR range: 1.72–2.92) (Supplementary Fig. 3). Greatest relative risk increase was observed in those using calcium supplements who also had high serum calcium levels, compared with participants who did not use calcium supplements and who had low serum calcium levels (HR range: 1.60–1.99) (Supplementary Fig. 4).

According to restricted cubic spline, associations between dietary calcium intakes and CVD events and all-cause mortality were approximately U-shaped, with decreased risk confined to people with moderate intakes (approximately 900–1,000 mg/day) in individuals without diabetes ($P_{nonlinearity} < 0.05$) (Supplementary Fig. 5). Higher concentrations of serum calcium were significantly associated with greater risk of CVD incidence in a linear fashion ($P_{nonlinearity} > 0.05$), whereas the association tended to be nonlinear for CVD and all-cause mortality ($P_{nonlinearity} < 0.05$) in individuals without diabetes (Supplementary Fig. 6). The results for dietary and serum calcium were similar in individuals with diabetes, although some results did not reach statistical significance, probably due to limited sample size. No interactions were observed between dietary calcium and serum calcium and diabetes status (Supplementary Figs. 5 and 6).

CONCLUSIONS

To our knowledge, this prospective study is among the first to find a significant heterogeneity in the association of habitual calcium supplementation with CVD events and all-cause mortality in participants with and without diabetes. Specifically, habitual use of calcium supplements was associated with increased risk of CVD events and all-cause mortality among participants with diabetes but not among those without diabetes. A variety of stratified analyses and sensitivity analyses demonstrated the robustness of these associations. In addition, our study also provided quantitative data on the effect of the additive interaction between habitual calcium supplementation and diabetes status on CVD outcomes and all-cause mortality.

To date, evidence regarding the association of calcium supplements with CVD risks remains controversial, with most studies showing null associations (2,3) and others demonstrating adverse (6) or protective (7) association. For example, a recent meta-analysis of six large randomized controlled trials (RCTs) found no relationship between supplemental calcium intake and risk of CVD and mortality in general healthy populations (2). More recently, a systematic review that was conducted for the U.S. Preventive Services Task Force also revealed no overall benefit or harm of calcium supplementation on CVD risk (3). However, many intervention trials launched with patients with renal impairment demonstrated adverse cardiovascular effect of calcium, either as a phosphate binder or as a supplement (5,11,28). A possible explanation is that these patients are at higher risk of CVD and abnormal calcium and phosphate metabolism, and thus they tended to be more susceptible to the adverse effects of acute increment in serum calcium after supplement ingestion (5).

Compared with individuals without diabetes, people with diabetes are more likely to experience disturbed calcium homeostasis and have higher risk of CVD and renal impairment (12,17). An important question that arises is whether calcium supplement use would be associated with higher risk of CVD in this specific population. However, data in this regard are limited. To our knowledge, only one study has evaluated cross-sectional associations of calcium supplements with vascular calcified plaque, as well as all-cause and CVD mortality (18). That study was conducted with 720 patients with diabetes, and researchers found no association between calcium supplements and risk of calcified plaque and CVD mortality in men and women, while a modest protective association with all-cause mortality was observed in women (18). Of note, this study had small sample sizes and did not adjust for several key confounders such as socioeconomic, dietary, and diabetes-related factors.

Using a large population-based cohort with uniform data collection protocols and comprehensive data, we found an overall null association between habitual use of calcium supplements and CVD outcomes in participants without diabetes, which is consistent with the findings of most previous studies that were conducted in generally healthy populations (2,3). When restricting analyses to people with diabetes, interestingly, we found a different scenario from that observed in people without diabetes: habitual use of calcium supplements is significantly associated with higher risk of CVD outcomes and all-cause mortality in patients with diabetes. These findings were somehow consistent with a recent patient-level analysis of nine RCTs showing that calcium supplements increased calcium indices, a surrogate measurement of cardiovascular risk, only in people with plaque progression but not in those without (29). Additionally, it is questionable whether patients with diabetes with inadequate dietary calcium intake may benefit from supplements (30). However, when we evaluated the joint association of calcium supplement use and dietary calcium intake by patients with diabetes, no significant interaction was observed, and the highest risk of CVD and mortality was found among calcium supplement users with low intakes of dietary calcium.

Furthermore, we quantified the additive interactions between calcium supplements and diabetes status to assess the public health significance of interaction.

The RERI, AP, and SI were greater than zero, indicating the interactive effect of diabetes risk and habitual calcium supplements use was greater than the sum of the two individual effects. We estimated that the interaction itself accounted for 26–39% higher risk of CVD events and all-cause mortality in patients with diabetes who use calcium supplements. Our study, if replicated, underscores the need to balance the potentially adverse effects of calcium supplements against the likely benefits, particularly among people with diabetes.

As for dietary calcium intakes, our findings were in accordance with the results of several previous studies that found a similar U-shaped association between dietary calcium intakes and risk of CVD, with the decreased risk confined to people with moderate intakes (approximately 900–1,000 mg/day) (31,32). The association did not differ between participants with and without diabetes in our study. Collectively, our results suggest that patients with diabetes might need to be cautious about habitual use of calcium supplements, but moderate calcium intakes from food sources are still recommended. These findings, in line with recent guidelines from the AHA, reinforce the advice to adopt a "natural" way via eating a good diet instead of using supplements for the prevention of CVD (33) and have public health significance in the context of widespread use of calcium supplements and the presence of high CVD risk among patients with diabetes.

Although mechanisms underlying the complex association between calcium and CVD risk are not definitively clear, there are several possible explanations. Adequate calcium intake could prevent CVD by playing an important role in lipid metabolism, insulin secretion, and regulation of body weight (1). It is reported that dietary and supplemental calcium have different impacts on circulating calcium. Several interventional studies found that dietary calcium intake (800 or 2,000 mg/day) did not substantially change serum calcium level (34), whereas calcium intake from supplements, either in small or large doses (500 mg or 1,500 mg), can cause instantaneous increase in serum calcium levels, even above the normal range up to 8 h or more (8). Such abrupt changes in serum calcium levels were suggested to increase the risk of hypercoagulability (35) and vascular calcification (36). Because diabetes itself carries a high risk of developing cardiovascular complications (12) and is susceptible to altered calcium homeostasis (13,17), the potential adverse cardiovascular effect caused by calcium supplements thus may be manifested or exacerbated by diabetes status and finally converted into event occurrence in this particular population (17,37). Nevertheless, more studies are warranted to clarify the potential mechanisms underlying the associations.

This study has several strengths. First, it included nearly half a million participants, which allowed us to retain power when analyses were conducted in participants with and without diabetes. Second, we investigated not only calcium supplementation but also dietary calcium and serum calcium. Third, the availability of complete data on confounding factors, including serum vitamin D levels, use of other supplements, and dietary and lifestyle factors, enabled us to minimize the possibility of confounding. Finally, the well-validated outcome events and consistent results in sensitivity analyses demonstrated the robustness of the study findings.

However, several limitations should also be considered. First, detailed information on calcium supplements such as the dosage, formulation, and duration of use was not available, which may preclude us from further evaluating the dose-response relationship and effects of different calcium supplement forms and supplementation duration. Previous studies found that both high and low doses (1,500 mg vs. 500 mg) of calcium supplements could abruptly change serum calcium to a similar level (38), which can be explained by saturation of the calcium absorption mechanism at around 500 mg (39). Although there may be lack of a dose-response effect of calcium supplements on CVD risk when taking ordinary daily doses (500 or 600 mg) (8,40), more studies with detailed information on dosage, formulation, and duration of use are needed. Second, misclassification bias should be considered because information on calcium supplementation was based on a single, self-reported assessment. Misclassification of exposure is likely to be nondifferential with respect to outcome because of the prospective design. However, we cannot rule out differential misclassification with respect to diabetes status. Third, we cannot rule out potential effects of changes in the use of calcium supplements during the follow-up period on the results. Studies are needed to deeply analyze the temporal relationships between the exposure and outcome. Fourth, although we have accounted for diabetes duration, HbA_{1c} levels, diabetes medication use, and some complications in the analyses, more diabetes-specific information is needed to lend more insights into the relationship between calcium supplement use and CVD outcomes among patients with diabetes. Fifth, these results are based on U.K. adults who are predominantly White, which may limit the generalizability to other populations. Last, although we carefully adjusted for a series of confounders in our analyses, residual or unknown confounding cannot be excluded.

Conclusion

Based on data from a large, prospective cohort, we found that habitual use of calcium supplements was significantly associated with higher risk of CVD outcomes and all-cause mortality in people with diabetes but not in those without diabetes. This finding indicates that people with diabetes might need to be cautious about the long-term use of calcium supplements. Further studies are warranted to balance the potentially adverse effects of calcium supplements against the likely benefits, particularly among people with diabetes.

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Author Contributions. G.L. conceived the study design. Z.Q. conducted analyses and wrote the first draft of the manuscript. Q.L., Z.W., T.G., R.L., K.Z., L.L., X.C., A.P., and J.E.M. contributed to interpretation of the results and critical revision of the manuscript. All authors approved the final version of the manuscript. G.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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