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JIM Original Article

doi: 10.1111/joim.13643

All-cause and cause-specific mortality risks associated with calcium supplementation with or without vitamin D: A nationwide population-based study

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Abstract. Kim KJ, Choi J, Kim KJ, Kim NH, Kim SG. All-cause and cause-specific mortality risks associated with calcium supplementation with or without vitamin D: A nationwide population-based study. *J Intern Med.* 2023;**00**:1–13.

Background. Current evidence regarding the mortality outcomes associated with calcium supplementation with or without low-dose vitamin D is conflicting.

Objectives. To investigate the effects of calcium supplementation with or without vitamin D on all-cause and cause-specific mortalities in a large-scale cohort.

Methods. This study used data from the Korean National Health Insurance System database and National Death Registry. A total of 27,846 participants aged >55 years who had taken calcium supplements with or without vitamin D for at least 90 days (calcium supplementation only [CaO], n = 6256; calcium supplementation in combination with vitamin D [CaD], n = 21,590) were matched in a 1:1 ratio to those who did not take calcium or vitamin D supplements (control group) using propensity scores.

Results. No difference in all-cause mortality risk was found between the CaO and control groups: (adjusted hazard ratio [HR] = 1.00; 95% confidence interval [CI]: 0.92–1.10). However, all-cause mortality was lower in the CaD group (HR = 0.85; 95% CI: 0.80–0.89) compared with that in the control group. Mortality risk associated with cardiovascular disease (CVD) was decreased in the CaD group when the daily vitamin D dose received was less than 1000 IU (HR = 0.72; 95% CI: 0.64–0.81). Subgroup analysis showed significant effect of vitamin D with calcium in individuals who were female, aged ≥65 years or had previous history of cancer or CVD.

Conclusion. In combination with calcium, vitamin D supplementation provides better outcomes for all-cause mortality, particularly CVD-associated mortality, in a duration-dependent manner.

Keywords: calcium supplementation, cardiovascular mortality, cohort study, mortality, vitamin D

Abbreviations: BMI, body mass index; CaD, calcium and vitamin D supplements; CaO, calcium supplements only; CI, confidence intervals; CVD, cardiovascular disease; HR, hazard ratios; IRB, Institutional Review Board; NHIS, National Health Insurance Service; SD, standard deviation

Introduction

The extraskeletal effects of calcium and vitamin D supplements (CaD) on cardiovascular disease (CVD), cancer, and mortality remain unclear [1]. Ongoing concerns have been raised regarding the potential link between calcium supplementation and cardiovascular events [2–4]. Some studies have reported the cardioprotective effect of calcium supplementation by improving lipid profile and blood pressure [5, 6]. However, a recent epidemi-

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ological study showed that excess calcium intake alone increases the incidence of CVD, even among populations with lower daily calcium intake [7].

With regard to vitamin D supplements, there has been consistent evidence that vitamin D deficiency is associated with an increased risk of CVDs, all-cause mortality, and other chronic diseases [4]. Contrary to the beneficial effects of vitamin D, vitamin D-related mega-trials have failed to conclude that vitamin D supplementation prevents invasive cancer or major cardiovascular events [8, 9]. The reasons for this difference are uncertain; however, some experts have explained that most participants enrolled in randomized controlled trials (RCTs) for vitamin D already have sufficient levels of serum 25-hydroxyvitamin D3 (25(OH)D3) [10, 11]. Furthermore, based on the differential effects of vitamin D under various conditions, the associated risks of other health outcomes seem quite complex [8, 12].

There is still uncertainty regarding the benefits of CaDs, although many studies have been conducted, including epidemiological studies, meta-analyses, and Mendelian randomization analyses [1, 13–15]. However, most studies included only Caucasians, who generally consume moderate-to-high amounts of dietary calcium and have a relatively high body mass index (BMI), which potentially limits the generalizability of their results to other populations [4, 16]. Using the well-established Korean National Health Insurance Service (NHIS) database of populations with low daily calcium intake and a high prevalence of vitamin D deficiency [16, 17], we aimed to investigate the association between calcium supplementation with or without vitamin D and the risk of all-cause and cause-specific mortalities. Furthermore, we assessed the differential effects of supplementation on mortality outcomes according to BMI strata.

Methods

Data sources

The Korean NHIS claims, which cover 97% of the Korean population, require all insured employees and self-employed persons, as well as their dependents, to undergo a general health screening biannually. We used the Korean NHIS-Health Screening (NHIS-HEALS) Cohort (study number: NHIS-2021-2-247), which included 514,866 individuals aged 40–79 years who were enrolled in 2002 and followed up until 2019. The study cohort consisted of a random sample of 10% of the 5.15 million beneficiaries in 2002 who underwent health examinations between 2002 and 2003. This database includes anonymous identification numbers, individual sociodemographic information, diagnostic information defined by the International Classification of Diseases, 10th revision (ICD-10), prescribed drugs, medical procedures, hospitalization, and death records. The detailed cohort protocol has been described previously [18].

This study was approved by the Institutional Review Board (IRB) of Korea University Anam Hospital in accordance with the Declaration of Helsinki of the World Medical Association (IRB number: 2019AN0284). Informed consent was not required because data from the NHIS cohort did not include any personally identifiable information. This study also followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study population

The process of selecting study participants is illustrated in Fig. 1. From the original NHIS-HEALS database, we excluded individuals younger than 55 years; those who had a diagnosis of hypoparathyroidism, hyperparathyroidism, or chronic kidney disease; those who had received active vitamin D supplementation; and those who had undergone any procedure affecting the neck during the study period. Among the 390,412 participants, individuals who had prescription records for calcium supplements were assigned to the "calcium group pool," whereas those who did not have any prescription records for calcium or vitamin D supplements were assigned to the "control group pool." The index date was defined as the first date of calcium supplement intake that lasted for at least 90 consecutive days in the calcium group. Propensity scores were calculated using index data from the calcium group and were derived from a multiple logistic regression model that included age, sex, BMI, systolic blood pressure, fasting blood glucose level, total cholesterol level, smoking status, alcohol intake, level of physical activity, socioeconomic status, comorbidities, concurrent drug treatment, and use of anti-osteoporotic agents. To avoid immortal time bias, the control groups were randomly selected from living individuals with the same propensity scores within the caliper of the calcium group at the index date and were matched using the propensity score matching method. The

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Fig. 1 *Flow diagram of participant selection.*

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index date of the matched control group was set to the middle of the day (July 1) of the same year as that of the calcium group. The participants who died or were lost to follow up within 1 year after the index date, as well as those with missing values required for our analysis, were excluded. The calcium group was further divided into two groups: those who had taken calcium supplements only (CaO) and those who had taken both CaD.

Definition of mortality outcomes and covariates

The primary cause and date of mortality were extracted from the database, and cause-specific mortalities were classified according to ICD-10 codes: CVD (I00–I99), cancer (C00–C97), respiratory disease (J00–J99), musculoskeletal disease (M00–M99), and trauma-related mortalities (S00–S99, T00–T14). Each patient was followed up from the index date until the earliest occurrence of death or until the end of the study period (December 31, 2019). Covariates for the analysis included patient age at the index date, sex, BMI, systolic blood pressure, fasting blood glucose level, total cholesterol level, smoking status (ever or never), alcohol consumption (none, ≤2 times per week, or ≥3 times per week), physical activity (<3 times per week or ≥3 times per week), socioeconomic status (lowest 30%, middle 40%, or highest 30%), comorbidities (diabetes mellitus, hypertension, dyslipidemia, osteoporosis, cancer, CVD, or respiratory disease), and concurrent medication (antihypertensive agents, statins, antithrombotic agents, and anti-osteoporotic agents) (Table S1).

Statistical analysis

Because the characteristics of the CaO and CaD groups differed considerably, we built two multiple logistic regression models that included all variables shown in Table 1. Using propensity score matching, each calcium group was separately matched in a 1:1 ratio with the control group. We used greedy nearest neighbor matching with a caliper width of 0.2 of the standard deviation (SD) of the propensity score logit. Data were summarized using the mean and SD for continuous variables or as frequencies with percentages for categorical variables. Demographic and clinical characteristics were compared by calculating the absolute standardized mean differences between groups. The mortality rate was calculated as the observed number of deaths divided by the sum of the follow-up time and presented as the number of deaths per 1000 person-years. The Kaplan–Meier analysis and log-rank tests were performed to compare the cumulative survival probabilities between the groups. Cox proportional hazards regression models were fitted to estimate the relative hazard for mortality in the calcium groups compared with the matched control group, and the relative hazards were presented as hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption was verified using graphical diagnostics based on scaled Schoenfeld residuals. Additionally, to evaluate the effect of the extent of exposure, we divided the patients into the following groups and performed subgroup analysis: (1) <500, (2) 500–999, and (3) ≥1000 mg based on the daily mean dose of calcium; and (1) <500, (2) 500–999, and (3) ≥1000 IU based on the daily dose of vitamin D. The mean dosage was calculated as the total intake of elemental calcium or vitamin D supplements during the study period divided by the duration of the intake (days). Furthermore, we conducted subgroup analyses stratified by age (≥65 and <65 years), sex (male and female), BMI (≥25 and <25 kg/m^2), and the presence of preexisting diseases (hypertension, diabetes mellitus, dyslipidemia, CVD, and cancer). An additional set of analyses divided the BMI into five categories (<18.5, 18.5–22.9, 23–24.9, 25–29.9, and ≥30 kg/m^2) to further explore its association with mortality outcomes. All statistical analyses were performed using SAS Enterprise Guide version 7.15 (SAS Institute Inc., Cary, NC, USA), and a two-sided p-value <0.05 was considered statistically significant.

Results

The cohort included 27,846 individuals who received calcium supplements (the calcium group). Of these, 6256 and 21,590 were prescribed with CaO and CaD, respectively (Fig. 1). The baseline characteristics of the calcium and control groups were well matched, with absolute standardized differences of <0.1 (Table 1 and Fig. S1). The mean age of the participants was 66 years, of which 84.8% were women. Compared with the CaD group, individuals in the CaO group had more risk factors for mortality, including a higher proportion of men, higher systolic blood pressure, more smokers, greater alcohol consumption, and higher proportions of diabetes mellitus and hypertension (all p-values <0.05). However, the CaD group had more individuals with a history of dyslipidemia, osteoporosis, cancer, and CVD compared with the CaO group (all p-values <0.05). Individuals in the

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Table 1. *Baseline characteristics*

Characteristics	Total			CaO			CaD		
	Calcium group ($n = 27,846$)	Matched control ($n = 27,846$)	ASMD	CaO ($n = 6256$)	Matched control ($n = 6256$)	ASMD	CaD ($n = 21,590$)	Matched control ($n = 21,590$)	ASMD
Mean (SD) age (years)	66.0 (7.4)	65.9 (7.7)	0.014	66.7 (7.3)	66.7 (7.5)	0.006	65.8 (7.4)	65.7 (7.8)	0.016
Women, *n* (%)	23,612 (84.8)	23,612 (84.8)	0	4814 (77.0)	4814 (77.0)	0	18,798 (87.1)	18,798 (87.1)	0
Mean (SD) body mass index (kg/m^2)	23.9 (3.0)	24.0 (3.1)	0.012	24.1 (3.1)	24.1 (3.1)	0.013	23.9 (3.0)	23.9 (3.1)	0.012
Mean (SD) systolic blood pressure (mmHg)	127.4 (16.6)	127.1 (16.6)	0.013	129.2 (17.3)	128.7 (17.4)	0.027	126.8 (16.4)	126.7 (16.4)	0.008
Mean (SD) fasting glucose (mmol/L)	99.4 (24.5)	99.5 (23.8)	0.004	100.3 (27.6)	100.2 (26.4)	0.001	99.2 (23.5)	99.3 (23.0)	0.005
Mean (SD) total cholesterol (mmol/L)	202.6 (38.8)	202.9 (39.4)	0.008	203.0 (39.5)	203.1 (39.7)	0.005	202.5 (38.6)	202.8 (39.3)	0.009
Ever-smoker	2850 (10.2)	2871 (10.3)	0.003	909 (14.5)	884 (14.1)	0.011	1941 (9.0)	1987 (9.2)	0.007
Alcohol, *n* (%)			0.014			0.028			0.013
None	22,955 (82.4)	23,098 (82.9)		5053 (80.8)	5119 (81.8)		17,902 (82.9)	17,979 (83.3)	
≤Twice per week	3697 (13.3)	3569 (12.8)		818 (13.1)	781 (12.5)		2879 (13.3)	2788 (12.9)	
≥Three times per week	1194 (4.3)	1179 (4.2)		385 (6.1)	356 (5.7)		809 (3.8)	823 (3.8)	
Regular exercise, *n* (%)	18,786 (67.5)	18,994 (68.2)	0.016	3215 (51.4)	3255 (52.0)	0.013	15,571 (72.1)	15,739 (72.9)	0.017
Socioeconomic status, *n* (%)			0.018			0.018			0.026
Lower 30%	6867 (24.7)	6990 (25.1)		1732 (27.7)	1718 (27.5)		5135 (23.8)	5272 (24.4)	
Middle 40%	8313 (29.9)	8503 (30.5)		1828 (29.2)	1879 (30.0)		6485 (30.0)	6624 (30.7)	
Upper 30%	12,666 (45.5)	12,353 (44.4)		2696 (43.1)	2659 (42.5)		9970 (46.2)	9694 (44.9)	
Comorbidities, *n* (%)									
Diabetes mellitus	4394 (15.8)	4473 (16.1)	0.008	1042 (16.7)	1070 (17.1)	0.012	3352 (15.5)	3403 (15.8)	0.007
Hypertension	15,579 (55.9)	15,450 (55.5)	0.009	3630 (58.0)	3656 (58.4)	0.008	11,949 (55.4)	11,794 (54.6)	0.014
Dyslipidemia	10,996 (39.5)	10,768 (38.7)	0.017	2147 (34.3)	2178 (34.8)	0.010	8849 (41.0)	8590 (40.0)	0.025
Osteoporosis	17,605 (63.2)	17,605 (63.2)	0	3212 (51.3)	3212 (51.3)	0	14,393 (66.7)	14,393 (66.7)	0
Cancer	3754 (13.5)	3780 (13.6)	0.003	718 (11.5)	786 (12.6)	0.033	3036 (14.1)	2994 (13.9)	0.006
Cardiovascular disease	13,683 (49.1)	13,383 (48.1)	0.022	2998 (47.9)	2994 (47.9)	0.001	10,685 (50.0)	10,389 (48.1)	0.027
Concurrent drug treatment									
ARB/ACE inhibitor	9876 (35.5)	9797 (35.2)	0.006	2137 (34.2)	2195 (35.1)	0.020	7739 (35.9)	7602 (35.2)	0.013
β-Blocker	10,138 (36.4)	9912 (35.6)	0.017	2371 (37.9)	2320 (37.1)	0.017	7767 (36.0)	7592 (35.2)	0.017
CCB	14,033 (50.4)	13,867 (49.8)	0.007	3235 (51.7)	3198 (51.1)	0.012	10,798 (50.0)	10,669 (49.4)	0.012
Statin	10,693 (38.4)	10,475 (37.6)	0.016	2087 (33.4)	2128 (34.0)	0.014	8606 (39.9)	8347 (38.7)	0.025

(*Continued*)

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Table 1. *Continued*

Characteristics	Total			CaO			CaD		
	Calcium group (n = 27,846)	Matched control (n = 27,846)	ASMD	CaO (n = 6256)	Matched control (n = 6256)	ASMD	CaD (n = 21,590)	Matched control (n = 21,590)	ASMD
Antithrombotic agent	11,278 (40.5)	11,101 (39.9)	0.013	2410 (38.5)	2425 (38.8)	0.005	8868 (41.1)	8,676 (40.2)	0.018
Mean (SD) daily calcium dose, mg/day	507.5 (283.5)			478.6 (325.8)			515.8 (269.4)		
Mean (SD) daily vitamin D dose, IU/day							660.2 (329.5)		

Note: Values are presented as the mean (standard deviation) and frequency (percentage).
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist; ASMD, absolute standardized mean difference; CaO, calcium only; CaD, calcium plus vitamin D; CCB, calcium channel blocker; IQR, interquartile range; n, number; SD, standard deviation.

CaD group received a higher dose of calcium (515.8 vs. 478.6 mg) and had a longer duration of ≥24 months (31.2% vs. 18.0%) of calcium supplementation compared with those in the CaO group.

Risk of all-cause and cause-specific mortality events

Table 2 shows the incidence rates (per 1000 person-years) and HRs of all-cause and cause-specific mortalities among individuals in the calcium group compared with their controls. During the median follow-up time of 100.2 months (interquartile range [IQR], 77.3–128.1) for the calcium group and 98.2 months (IQR, 78.1–126.2) for their matched controls, 2991 and 3192 mortality events occurred in the calcium and control groups, respectively. In the calcium group, 922 deaths resulted from cancer, 677 from CVD, 371 from respiratory diseases, and 150 from musculoskeletal and trauma-related causes. The association between calcium supplementation and all-cause mortality varied according to the concomitant use of vitamin D (p = 0.001), and the risk of all-cause mortality in the CaO group was comparable to that in the control group (HR: 1.00; 95% CI: 0.92–1.10). In contrast, the CaD group showed a lower risk of all-cause mortality compared with the control group (HR: 0.85; 95% CI: 0.80–0.89) (Fig. 2). Considering cause-specific mortality, the mortality risk from CVD (HR: 0.72; 95% CI: 0.64–0.81) was lower in the CaD group, whereas there was no significant difference between the CaO and control groups (HR: 0.93; 95% CI: 0.77–1.11; p = 0.020). No significant differences in the mortality risk from other causes were observed between the CaO and CaD groups and their respective control groups.

Analyses of the dose–response relationship

The association between the calcium supplementation dose and risk of all-cause mortality (Table 3) was further assessed. In the CaO group, this relationship did not change significantly with the calcium supplementation dose. However, patients taking CaD doses less than 1000 mg and 1000 IU, respectively, had the lowest risk of all-cause mortality (average calcium dose <500 mg/day [HR: 0.82; 95% CI: 0.76–0.89]; average vitamin D dose 500–999 IU/day [HR = 0.83; 95% CI: 0.77–0.90]).

Subgroup analysis for the risk of all-cause mortality

Figure 3 shows the results of the subgroup analyses of the association between CaD and the risk of all-cause mortality. Significant protective effects

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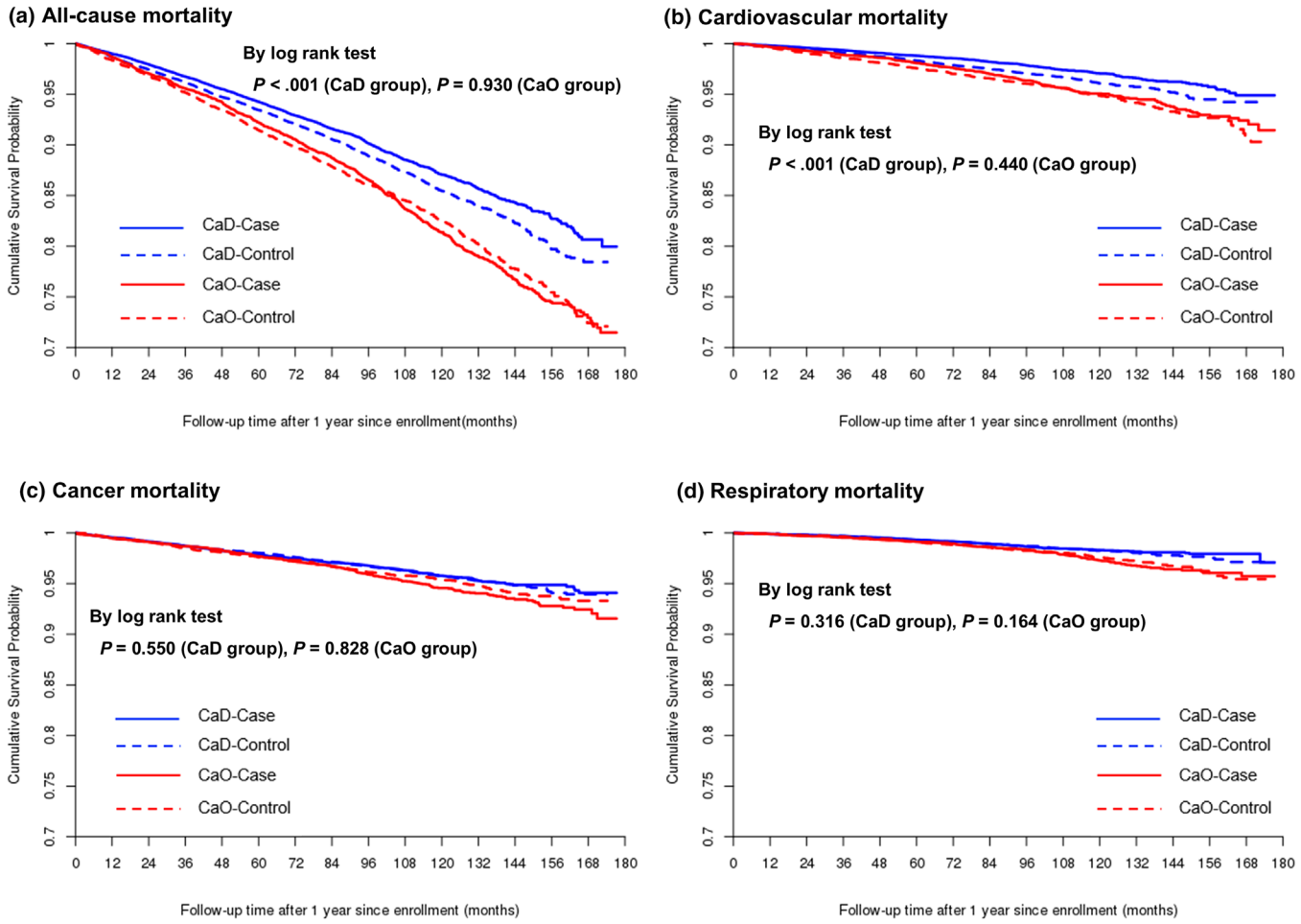

Fig. 2 *Kaplan–Meier survival curves for all-cause and cause-specific mortalities in each calcium group with matched control groups used for comparison.*

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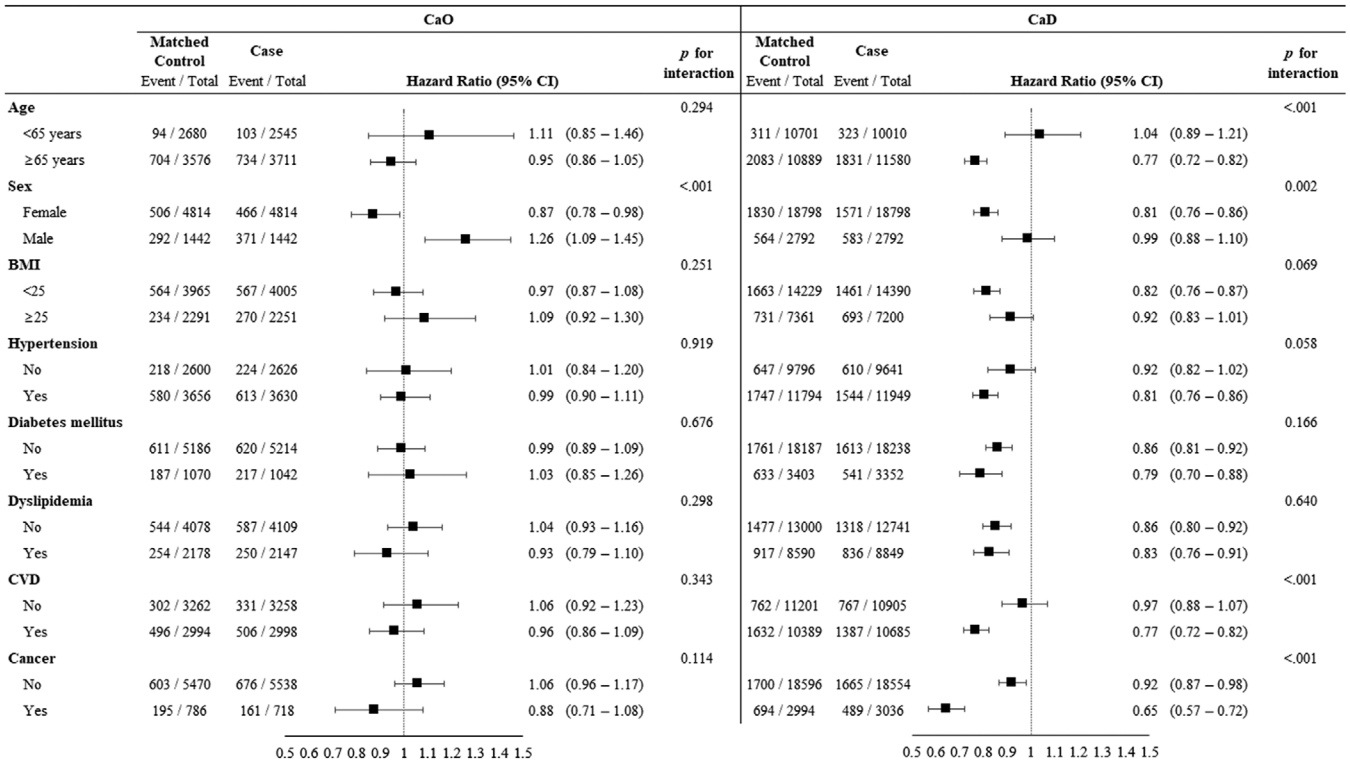

Fig. 3 *Subgroup analysis of the incidence of all-cause mortality.*

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Table 2. *Mortality rates and hazard ratios (HRs) in the calcium groups compared with those in the matched control groups*

	CaO			CaD			
	Matched control ($n = 6256$)	CaO ($n = 6256$)	p-Value[a]	Matched control ($n = 21,590$)	CaD ($n = 21,590$)	p-Value[a]	p For interaction
All-cause mortality							
No. of events (IR)	798 (17.4)	837 (17.6)		2394 (13.1)	2154 (11.3)		
Hazard ratio (95% CI)	1.00 (Ref)	1.00 (0.92–1.10)	0.923	1.00 (Ref)	**0.85 (0.80–0.89)**	**<0.001**	**0.001**
Cause-specific mortality							
Cardiovascular disease							
No. of events (IR)	220 (4.8)	214 (4.5)		604 (3.3)	463 (2.4)		
Hazard ratio (95% CI)	1.00 (Ref)	0.93 (0.77–1.11)	0.425	1.00 (Ref)	**0.72 (0.64–0.81)**	**<0.001**	**0.020**
Cancer (C00–97)							
No. of events (IR)	213 (4.6)	227 (4.8)		681 (3.7)	695 (3.6)		
Hazard ratio (95% CI)	1.00 (Ref)	1.02 (0.85–1.22)	0.822	1.00 (Ref)	0.97 (0.87–1.07)	0.542	0.586
Respiratory disease (J00–J99)							
No. of events (IR)	88 (1.9)	112 (2.4)		264 (1.4)	259 (1.4)		
Hazard ratio (95% CI)	1.00 (Ref)	1.22 (0.93–1.59)	0.147	1.00 (Ref)	0.92 (0.77–1.09)	0.310	0.079
Musculoskeletal disease/trauma							
No. of events (IR)	29 (0.6)	40 (0.8)		98 (0.5)	110 (0.6)		
Hazard ratio (95% CI)	1.00 (Ref)	1.34 (0.83–2.17)	0.232	1.00 (Ref)	1.07 (0.81–1.41)	0.637	0.431

Abbreviations: CaD, calcium plus vitamin D; CaO, calcium only; CI, confidence interval; IR, incidence rate; Ref, reference.
[a]p-Value for each calcium group versus their matched control group.

of CaD were observed in patients aged ≥65 years, who were female, or who had a history of CVD or cancer. Calcium supplementation was associated with lower all-cause mortality in women but higher all-cause mortality in men.

Association between BMI strata and mortality outcomes

Table S2 presents the HRs for all-cause, CVD-, and cancer-related mortality according to the BMI categories. For all-cause and cancer-related mortality, the BMI classification did not affect the outcome in either the CaO or CaD groups. However, the risks of CVD-related mortality were lower in patients with a BMI of 18.5–25 kg/m^2 in the CaD group compared with their controls.

Discussion

This propensity-matched cohort study of individuals with low daily calcium intake and a high prevalence of vitamin D deficiency indicated that vitamin D supplementation with calcium is more likely to be beneficial than harmful, considering the reduced risk of all-cause mortality, especially that associated with CVD. However, calcium supplementation without vitamin D did not demonstrate this relationship, indicating the differential effects of calcium supplementation alone versus vitamin D supplementation. We also observed a protective effect of daily dose equivalents of <1000 mg calcium and <1000 IU vitamin D on the risk of all-cause mortality. Additionally, the associations between vitamin D supplementation combined with calcium and lower all-cause mortality were stronger in women, those aged ≥65 years, and those with a history of cancer or CVD.

Previous observational studies have linked low vitamin D levels with various illnesses, including osteoporosis, autoimmune disorders, CVDs, and cancers, as well as their mortality risk [5, 19]. However, large vitamin D supplementation clinical trials have presented disappointing results, showing no benefits in the incidence of cancer, CVD, or type 2 diabetes mellitus [20]. Given this uncertainty, a recent Mendelian randomization analysis reported a causal relationship between 25(OH)D3 concentrations and all-cause mortality in selected participants with vitamin D deficiency (serum [25(OH)D3] <25 nmol/L), suggesting that some individuals may benefit from vitamin D supplementation [13]. In South Korea, vitamin D insufficiency (defined as serum [25(OH)D] <50 nmol/L) is highly prevalent, reaching 75.2%

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Table 3. *Hazard ratio (hazard ratio) for all-cause mortality associated with the daily dose of calcium and/or vitamin D supplementation*

	n	Total person-years	No. of events (IR)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
CaO					
Control	6256	45,951	798 (17.4)	1 (Ref)	1 (Ref)
Daily average dose of calcium					
<500 mg	4005	29,613	450 (15.2)	0.87 (0.79–0.97)	0.96 (0.85–1.08)
500–999 mg	1710	13,836	306 (22.1)	1.24 (1.10–1.40)	1.03 (0.90–1.18)
≥1000 mg	541	4054	81 (20.0)	1.13 (0.90–1.42)	1.08 (0.86–1.37)
p For trend				0.018	0.626
CaD					
Control	21,590	182,439	2394 (13.1)	1 (Ref)	1 (Ref)
Daily average dose of calcium					
<500 mg	8917	76,945	826 (10.7)	0.81 (0.75–0.88)	**0.82 (0.76–0.89)**
500–999 mg	11,015	99,294	1156 (11.6)	0.87 (0.81–0.93)	**0.88 (0.81–0.94)**
≥1000 mg	1658	14,545	172 (11.8)	0.89 (0.77–1.04)	0.90 (0.77–1.05)
p For trend				<0.001	**<0.001**
Daily average dose of vitamin D					
<500 IU	8903	82,147	964 (11.7)	0.86 (0.80–0.93)	**0.86 (0.80–0.93)**
500–999 IU	9228	82,571	891 (10.8)	0.81 (0.75–0.87)	**0.83 (0.77–0.90)**
≥1000 IU	3,459	26,067	299 (11.5)	0.92 (0.82–1.04)	0.92 (0.85–1.04)
p For trend				<0.001	**<0.001**

Abbreviations: CaO, calcium only; CaD, calcium plus vitamin D; CI, confidence interval; IR, incidence rate; Ref, reference.
[a]Calculated using multiple Cox proportional hazards regression analysis further adjusted for age, sex, body mass index, systolic blood pressure, fasting blood glucose level, total cholesterol level, smoking status, alcohol intake, level of physical activity, socioeconomic status, comorbidities, concurrent drug treatment, and use of anti-osteoporotic agents.
Using time-dependent Cox proportional hazards regression analysis.

in men and 82.5% in women [17]. Therefore, our findings of favorable mortality outcomes could be explained by the beneficial effects of vitamin D on a vitamin D-deficient population compared with those of other trials with various vitamin D levels.

The Vitamin D and Omega-3 trial (VITAL) suggested that vitamin D supplementation had a protective effect against cancer mortality, which was also supported by the results from a meta-analysis of RCTs. [8, 14]. However, several Mendelian randomization studies have indicated no association between vitamin D levels and overall cancer outcomes, which would be consistent with our findings [21, 22]. Another aspect to be considered is vitamin D receptor polymorphism, which could explain the different effects of vitamin D supplementation on various types of cancer [19]. In our study, the cardioprotective roles of vitamin D may lower the risk of cardiovascular mortality among patients in the CaD group. Several mechanistic observations, including anti-hypertrophic, anti-fibrotic, and anti-inflammatory properties and improvement in myocyte contractility by vitamin D, directly support its beneficial effects on the cardiovascular system [23–26]. Vitamin D can directly modify cardiovascular risk factors such as systemic hypertension, dyslipidemia, and type 2 diabetes [12, 27].

With regard to the dose of supplementation, a daily dose of calcium ≥1000 mg and a daily dose of vitamin D ≥1000 IU showed no benefit in lowering mortality risk. These results are supported by previous findings that calcium intake >1000 mg/day increases the incidence of CVDs [7, 19]. A transient rise in serum calcium levels upon an ingestion of a higher dose of calcium supplements can trigger the coagulation cascade, vascular deposition of calcium, vascular smooth muscle contraction, or atherosclerosis [28]. A large population-based cohort study also suggested a possible "U-shaped" association between serum 25(OH)D levels and

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all-cause mortality, indicating the risks of both vitamin D deficiency and toxicity [29–31]. A recent meta-analysis reported a significant protective effect of vitamin D supplementation on the risk of acute respiratory infections in patients with a daily dose equivalent of 400–1000 IU, but not in those taking doses outside this range, which was consistent with our findings [32]. The hypothesis that higher doses of vitamin D may not be effective for health outcomes can be explained by biological mechanisms with threshold-mediated anti- and pro-inflammatory properties, promoting the intestinal absorption of phosphorous and a significant increase in fibroblast growth factor 23 [33]. Although appropriate doses have not yet been established, excess doses of CaD are not generally recommended owing to the potential harm from high doses of supplementation.

Interestingly, the risks of all-cause mortality were not different according to BMI strata; however, patients with a BMI of 18.5–24.9 in the CaD group had a lower risk of CVD mortality. The VITAL trial reported that patients with a BMI ≥30 did not benefit from vitamin D [8]. According to the Vitamin D and Type 2 Diabetes trial, vitamin D supplementation reduced the incidence of type 2 diabetes in patients with BMI <30, but not in those with BMI ≥30 [34]. The reasons for the different results regarding the association between vitamin D levels and health outcomes as measured by BMI remain unclear. Further studies are needed to determine whether BMI alone affects health outcomes. Our subgroup analysis also demonstrated a stronger effect of vitamin D supplementation in patients aged ≥65 years or those with a history of CVD or cancer. These findings could be explained by the benefits of vitamin D supplementation among frail patients with a high prevalence of vitamin D deficiency [35]. Additionally, the decreased risk of all-cause mortality in both calcium groups was more prominent in women than in men. Taking calcium with or without vitamin D supplements can prevent critical fractures in women with a high prevalence of osteoporosis, although this issue remains controversial [36, 37]. Therefore, further research on sex-specific differences related to supplements should be conducted.

The current study has several limitations. First, it was based on secondary analyses of the claims database, which lacked clinical information such as the dietary calcium and vitamin D intake of each patient because the NHIS did not have a nutrition questionnaire. However, according to a well-designed epidemiological study, the mean calcium intake in Korea is 490 mg/day [16]. Second, the status of mineral deficiency could not be considered because data on serum calcium and vitamin D levels were not available for this cohort. Third, owing to the retrospective observational study design, we could not determine any causal relationship, and there may still be residual confounding by unknown factors. Lastly, we included only Koreans with a low daily calcium intake, high prevalence of vitamin D deficiency, and relatively low obesity rate. Furthermore, our study included a greater proportion of women than men (84.8% vs. 15.2%) because we assigned patients who had received calcium supplementation to the calcium group. CaD are generally recommended to prevent worse outcomes in postmenopausal women with low bone mineral density who are at risk of fractures due to osteoporosis. Therefore, our findings may not be generalizable to other ethnic groups with different characteristics. However, this study had the principal strength of a population-based propensity-matched design with a sufficient sample size. Moreover, the follow-up duration was long enough to evaluate mortality outcomes. Another strength of our study is that various BMI classes, including underweight, were considered.

In conclusion, this propensity-weighted cohort study supports the beneficial role of vitamin D in combination with calcium supplementation for a substantial period in all-cause mortality risk reduction among populations with a high prevalence of vitamin D deficiency.

Author contributions

Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing—original draft; writing—review and editing: Kyoung Jin Kim and Sin Gon Kim. Data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization; writing—original draft; writing—review and editing: Jimi Choi. Conceptualization-supporting; data curation-supporting; formal analysis-supporting; investigation-supporting; methodology-supporting; project administration-supporting; supervision-supporting; validation-supporting; visualization-supporting; writing—original draft-supporting: Kyeong Jin Kim. Conceptualization-

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supporting; data curation-supporting; formal analysis-supporting; investigation-supporting; methodology-supporting; supervision-supporting; validation-supporting: Nam Hoon Kim.

Acknowledgments

We thank the participants of the Korean Health Insurance Cohort Study and the National Health Insurance Service.

Conflict of interest statement

The authors have nothing to disclose.

Data availability statement

Additional data are available after approval and oversight by the Korean National Health Insurance Service.

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