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ARTICLE

Calcium, vitamin D and dairy intake in relation to type 2 diabetes risk in a Japanese cohort

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Abstract
Aims/hypothesis Calcium and vitamin D have been implicated in the development of type 2 diabetes, but epidemiological evidence is limited. We examined prospectively the relation of calcium and vitamin D intake to type 2 diabetes risk in a Japanese cohort.
Methods Participants were 59,796 middle-aged and older men and women, who participated in the Japan Public Health Center-based Prospective Study and had no history of type 2 diabetes or other serious diseases. Dietary intake of calcium and vitamin D were estimated using a validated food frequency questionnaire. Logistic regression was used to assess the association between intake of these nutrients and self-reported newly diagnosed type 2 diabetes.
Results During a 5 year follow-up, 1,114 cases of type 2 diabetes were documented. Overall, calcium intake was not associated with a significantly lower risk of type 2 diabetes; the multivariable odds ratio for the highest vs lowest quartiles was 0.93 (95% CI 0.71–1.22) in men and 0.76 (95% CI 0.56–1.03) in women. However, among participants with a higher vitamin D intake, calcium intake was inversely associated with diabetes risk; the odds ratio for the highest vs lowest intake categories was 0.62 (95% CI 0.41–0.94) in men and 0.59 (95% CI 0.38–0.91) in women. Dairy food intake was significantly associated with a lower risk of type 2 diabetes in women only.
Conclusions/interpretation Calcium and vitamin D may not be independently associated with type 2 diabetes risk. Our finding suggesting a joint action of these nutrients against type 2 diabetes warrants further investigation.

Keywords Calcium · Cohort studies · Type 2 diabetes · Vitamin D

Abbreviations

25-OHD	25-Hydroxyvitamin D
JPHC	Japan Public Health Center-based Prospective Study

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Introduction

The number of people with type 2 diabetes has been increasing worldwide, with an estimated prevalence of 2.8% in 2000 and 4.4% in 2030 [1]. According to community-based studies, the prevalence of diabetes in Japan has rapidly increased during the past two decades [2]. Insight into the role of dietary factors in the development of diabetes may contribute to its prevention.

In experimental studies, calcium and vitamin D have been shown to improve pancreatic beta cell function and peripheral insulin sensitivity [3–5]. In humans, evidence on this issue so far is mainly derived from cross-sectional studies as reviewed [6], while findings from prospective studies are limited and inconsistent. Two cohort studies found a moderate, but not statistically significant association between dietary calcium intake and the risk of diabetes after adjustments for other dietary factors [7, 8], although the association with supplemental intake was statistically significant. A high intake of dairy foods, a major food source of calcium, has also been shown to be associated with a lower risk of type 2 diabetes [7–10]. Similarly, vitamin D intake from supplement [7] or supplement plus diet [11], but not from diet alone was associated with a lower incidence of diabetes. As regards blood vitamin D, a prospective study in Finland showed an inverse association between serum 25-hydroxyvitamin D (25-OHD) concentrations and the risk of type 2 diabetes [12]. However, in a large-scale randomised controlled trial in US American women [13], calcium plus vitamin D_3 supplementation did not reduce the risk of developing diabetes over 7 years of follow-ups. Given the scarcity and inconsistency of prospective evidence [6], it is unclear whether these nutrients prevent type 2 diabetes.

To the best of our knowledge, there are no reports on the relation between both calcium and vitamin D intake, and the incidence of type 2 diabetes in the Japanese population, which consumes, on average, a relatively low amount of calcium [14]. We therefore examined the associations of calcium, vitamin D and dairy foods intake with the risk of type 2 diabetes in a large-scale cohort of the Japanese population. Since calcium and vitamin D have been hypothesised to act jointly, rather than independently, in reducing the risk of diabetes [7], we also explored their combined effect on the risk of type 2 diabetes.

Methods

Study cohort The Japan Public Health Center-based Prospective Study (JPHC) was established in 1990 for cohort I and in 1993 for cohort II. Details of the study design have been described elsewhere [15]. The participants of cohort I included residents, aged 40 to 59 years, in five Japanese Public Health Center areas (Iwate, Akita, Nagano, Okinawa and Tokyo); the participants of cohort II included residents, aged 40 to 69 years, in six Public Health Center areas (Ibaraki, Niigata, Kouchi, Nagasaki, Okinawa and Osaka). Study participants were informed about the objectives of the study and those who responded to the survey questionnaire were regarded as consenting to participate in the study. This study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Questionnaire surveys A questionnaire survey was conducted at baseline and at the 5- and 10-year follow-ups. Information on medical history and health-related lifestyles, including smoking, drinking and dietary habits, was obtained in each survey. In the present analysis, we used data from the 5-year survey, which was carried out in 1995 for cohort I and in 1998 for cohort II, as baseline. We did this because the questionnaire used for that survey contained more comprehensive information on food intake than that used for the first survey.

Participants Within the study population at baseline (n=140,420), we excluded residents of two areas (Tokyo and Osaka) because of the differences in recruitment criteria. Of the remaining 116,672 individuals, 95,373 (82%) responded to the baseline survey. Of these, 80,128 (84%) completed a questionnaire at the 5-year survey, which provided the baseline of the present analysis. Of these, 71,075 (89%) responded to a questionnaire at the 10-year follow-up. We excluded individuals with a history of stroke, cardiovascular disease, cancer, chronic liver disease or kidney disease (n=10,694) at the first and 5-year follow-up surveys. We also excluded those with >3 and <3 standard deviations of energy intake (n=585). As a result, 59,796 individuals (25,877 men, 33,919 women) were analysed.

Food frequency questionnaire The food frequency questionnaire used for the 5-year follow-up survey included questions about 147 food and beverage items with standard portions/units and eating frequency. Nine response options were available for eating frequency: rarely, one to two times/month, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, once a day, two to three times/day, four to six times/day and ≥7 times/day. Slightly different options were used for beverage intake: rarely, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, once a day, two to three times/day, four to six times/day, seven to nine times/day and ≥10 times/day. A standard portion size was specified for each food item and the respondents were asked to choose their usual portion from among three categories: less than half, same and more than 1.5 times the standard portion. We calculated the average daily intake of nutrients, including calcium and vitamin D, by multiplying the frequency of the consumption of each food by its nutrient content per serving and totalling the nutrient intake for all food items. In Japan, vitamin D fortification of dairy products was not a common practice at the time of survey. The validity of the dietary calcium and vitamin D intake was assessed in a sub-sample of the cohort by comparing the estimated intake according to the questionnaire with that based on dietary records [16]. The Spearman's correlation coefficients of the energy-adjusted intake of calcium and vitamin D between the questionnaire and the dietary records were 0.54 and 0.77 for the men in cohort I, 0.68 and 0.56 for the men in cohort II, 0.45 and 0.43 for the women in cohort I and 0.68 and 0.52 for the women in cohort II, respectively [16].

Ascertainment of diabetes mellitus In the 10-year follow-up questionnaire, study participants were asked if they had ever been diagnosed as having diabetes and, if so, when the initial diagnosis had been made. Because the 5-year survey was used as baseline in the present study, only participants who were subsequently diagnosed (i.e. after 1995 for cohort I and after 1998 for cohort II) were regarded as incident cases during the follow-up. We did not obtain information on the type of diabetes; however, considering the minimum age of the study population (45 years old at baseline [5-year survey]), we reasonably assumed that most reported cases were type 2 diabetes. To assess the validity of self-reported diabetes, we examined a series of medical records of some study participants in three districts of the study areas, finding that 94% of the self-reported cases of diabetes were confirmed by medical records [17]. We also examined the sensitivity of self-reported diabetes among JPHC cohort I participants for whom data on plasma glucose were available from the 1990 health check-up. Of the 6,118 participants with plasma glucose data, 248 had self-reported diabetes. Of the 5,870 participants who did not have self-reported diabetes, 49 participants (0.83%) had diabetes based on a single measurement and according to the diagnostic standards commonly used in Japan at that time (1990), i.e.: (1) fasting plasma glucose ≥7.8 mmol/l; and (2) casual plasma glucose ≥11 mmol/l [18]. Taking into account the above-mentioned positive predictive value, the sensitivity and specificity of self-reported diabetes were 82.9% and 99.7%, respectively.

Statistical analysis Analyses were performed on men and women, separately. Dietary intakes of calcium and vitamin D were adjusted for total energy intake using the residual method [19]. Baseline characteristics were presented according to quartiles of dietary calcium and vitamin D intake, and their trend associations assessed using a linear regression analysis for continuous variables or a logistic regression for categorical variables, with the median value of calcium or vitamin D intake in each category assigned to the corresponding category. A logistic regression analysis was used to assess the associations of the dietary intake of calcium, vitamin D and dairy food with the incidence of type 2 diabetes. The odds ratios and 95% CIs were calculated for each quartile of intake using the lowest consumption category as a reference. All logistic regression analyses were adjusted for age (year; continuous) and study area (nine Public Health Centers). The multivariate analyses were additionally adjusted for the following nine factors: (1) BMI (<21, 21–22.9, 23–24.9, 25–26.9 or ≥27 kg/m^2); (2) family history of diabetes mellitus (yes or no); (3) smoking status (none, past, current smoking <20 cigarettes/day or current smoking ≥20 cigarettes/day); (4) alcohol intake (men: none, <150, 150–299, 300–449 or ≥450 g ethanol per week; women: none, <150, 150–299 or ≥300 g ethanol per week); (5) history of hypertension (yes or no); (6) exercise frequency (less than once/week or once or more times per week); (7) coffee consumption (none, less than daily, 1 cup/day, ≥2–3 cups/day); (8) energy-adjusted magnesium intake (mg; continuous); and (9) total energy intake (kJ; continuous). The above analyses were also performed for selected foods containing high amounts of calcium: total dairy products, milk, cheese and yogurt. The analysis for calcium was stratified according to vitamin D intake (less than median or median or greater) to assess whether vitamin D had a modifying effect on the association between calcium and diabetes risk. Similarly, we examined the above associations according to BMI (<25 or ≥25 kg/m^2), smoking status (non-smokers or current smokers) and drinking status (non-drinkers or current drinkers), since these variables are known to be associated with the risk of type 2 diabetes and might modify nutrient–diabetes associations. An interaction term of two exposure variables was created and added in the model to assess a statistical interaction. Tests for trends were assessed by assigning the median intake value of each quartile of nutrients or food intake in each category. All p values were two sided; statistical significance was determined at $p<0.05$.

Results

During the 5-year follow-up period, 1,114 participants were newly diagnosed with diabetes (634 men [2.4%], 480 women [1.4%]). Table 1 shows the potential confounders according to dietary calcium and vitamin D intake at baseline. The dietary intake of calcium was positively associated with age and sports participation in both sexes, but was inversely associated with current smoking and heavy alcohol drinking in both sexes, and with BMI and

Table 1 Baseline characteristics according to quartiles of energy-adjusted dietary intakes of calcium and vitamin D

Characteristic	Men (quartiles of intake)					Women (quartiles of intake)				
	Lowest	Second	Third	Highest	*p* value, trend	Lowest	Second	Third	Highest	*p* value, trend
Calcium										
Age, years	55 (8)	56 (8)	57 (8)	58 (8)	<0.001	57 (8)	57 (8)	57 (8)	58 (8)	<0.001
BMI (kg/m^2)	23.6 (2.9)	23.6 (2.8)	23.5 (2.8)	23.6 (2.8)	0.33	23.7 (3.2)	23.5 (3.1)	23.5 (3.0)	23.4 (3.0)	<0.001
Family history of diabetes (%)	5.6	6.6	5.9	6.1	0.03	5.5	5.8	6.1	6.1	0.003
Current smokers (%)	53.8	50.5	45.2	37.9	<0.001	7.0	4.5	3.5	3.5	<0.001
Alcohol intake ≥150 g/week (%)	67.6	55.8	47.8	34.0	<0.001	4.6	2.4	1.4	1.0	<0.001
Sports ≥1 time/week (%)	16.3	19.2	22.2	26.6	<0.001	14.7	19.0	21.3	25.7	<0.001
Antihypertensive medication (%)	21.9	21.7	22.3	23.0	0.005	22.1	22.1	23.3	23.3	0.197
Coffee ≥1 cup/day (%)	31.4	34.1	32.0	30.4	0.97	38.9	35.8	33.5	31.5	<0.001
Dietary intake (median)										
Calcium (mg/day)	254	356	457	629	<0.001	356	487	608	810	<0.001
Vitamin D (μg/day)	7.7	9.7	10.3	10.9	<0.001	8.3	9.7	10.4	10.1	<0.001
Magnesium (mg/day)	245	286	307	331	<0.001	248	281	298	314	<0.001
Dairy products (median) (g)	21	68	180	260	<0.001	39	124	214	304	<0.001
Calcium supplement use (%)	0.1	0.2	0.2	0.1	0.34	0.5	0.4	0.6	0.7	0.07
Vitamin D										
Age (years)	56 (8)	56 (8)	57 (8)	58 (8)	<0.001	58 (8)	56 (8)	57 (8)	58 (7)	<0.001
BMI (kg/m^2)	23.7 (2.9)	23.6 (2.8)	23.5 (2.8)	23.4 (2.8)	<0.001	23.7 (3.2)	23.5 (3.1)	23.4 (3.0)	23.5 (3.1)	<0.001
Family history of diabetes (%)	5.7	5.8	6.3	6.5	<0.001	4.9	6.5	6.5	5.6	0.046
Current smokers (%)	46.8	47.2	46.8	46.6	<0.001	4.7	4.5	4.6	4.6	<0.001
Alcohol intake ≥150 g/week (%)	57.4	52.9	50.6	44.5	<0.001	2.8	2.4	2.5	1.8	<0.001
Sports ≥1 time/week (%)	21.0	22.2	21.1	19.9	0.01	20.7	21.0	20.4	18.8	<0.001
Antihypertensive medication (%)	20.5	21.5	22.8	24.1	0.02	23.4	20.9	21.9	24.7	0.01
Coffee ≥1 cup/day (%)	37.6	34.4	30.5	25.6	<0.001	41.9	38.7	33.0	26.2	<0.001
Dietary intake (median)										
Calcium (mg/day)	348	403	423	439	<0.001	495	548	565	568	<0.001
Vitamin D (μg/day)	4.7	8.1	11.5	18.0	<0.001	4.8	8.1	11.4	17.4	<0.001
Magnesium (mg/day)	265	284	298	315	<0.001	264	278	289	301	<0.001
Dairy products (median) (g)	70	121	130	114	0.54	123	195	200	164	<0.001
Calcium supplement use (%)	0.2	0.2	0.1	0.1	0.10	0.6	0.7	0.4	0.4	0.02

Data are means (SD) unless otherwise indicated

Intake of calcium, vitamin D and magnesium were adjusted for total energy intake coffee consumption among women. The dietary intake of vitamin D was positively associated with age in both sexes, but was inversely associated with BMI, heavy alcohol intake, sports participation and coffee consumption in both sexes, and with calcium supplement use among women.

In the analysis with adjustments for age and area only, we observed a statistically significant inverse association between dietary calcium intake and the risk of type 2 diabetes in women (Table 2). The odds ratio comparing the highest vs lowest quartile group of calcium intake was 0.74 (95% CI 0.57–0.96; p=0.039 for trend) among women. The association was slightly attenuated and no longer statistically significant after further adjustment for other potential confounders. The multivariable odds ratio for the highest vs lowest quartiles of calcium intake was 0.76 (95% CI 0.56–1.03; p=0.095 for trend) among women. The exclusion of calcium supplement users from the analysis (n=25,836 for men, n=33,735 for women) did not notably alter the results; the odds ratio was 0.77 (95% CI 0.56–1.04; p=0.116 for trend) among women. There was no association between calcium intake and the risk of diabetes in men. Vitamin D intake alone was not appreciably associated with the risk of type 2 diabetes either in men or in women. Additional adjustment of saturated fat intake did not appreciably alter these results (data not shown).

In women, the intake of dairy foods was significantly inversely associated with the risk of type 2 diabetes. In models with adjustment of age and area only, the odds ratios for the highest vs lowest intake category were 0.65 (95% CI 0.49–0.88; p=0.007 for trend), 0.79 (95% CI 0.64–0.97; p=0.02 for trend), 0.94 (95% CI 0.68–1.30; p= 0.71 for trend) and 0.72 (95% CI 0.55–0.93; p=0.04 for

Table 2 ORs of type 2 diabetes according to quartiles of energy-adjusted dietary intake of calcium and vitamin D

Intake per quartile and sex	At risk (n)	Cases (n)	Age- and area-adjusted OR (95% CI)	Multivariable OR (95% CI)*
Calcium				
Men				
Lowest	6,469	174	1.00	1.00
Second	6,469	143	0.82 (0.66–1.03)	0.83 (0.66–1.05)
Third	6,470	162	0.93 (0.75–1.16)	0.97 (0.76–1.24)
Highest	6,469	155	0.89 (0.71–1.11)	0.93 (0.71–1.22)
p value for trend			0.52	0.95
Women				
Lowest	8,479	134	1.00	1.00
Second	8,480	118	0.88 (0.69–1.14)	0.90 (0.70–1.18)
Third	8,480	126	0.94 (0.73–1.20)	0.95 (0.73–1.25)
Highest	8,480	102	0.74 (0.57–0.96)	0.76 (0.56–1.03)
p value for trend			0.039	0.095
Vitamin D				
Men				
Lowest	6,469	156	1.00	1.00
Second	6,469	182	1.20 (0.96–1.49)	1.17 (0.93–1.46)
Third	6,470	145	0.96 (0.76–1.21)	0.93 (0.73–1.18)
Highest	6,469	151	1.01 (0.79–1.28)	0.96 (0.74–1.23)
p value for trend			0.58	0.35
Women				
Lowest	8,479	139	1.00	1.00
Second	8,480	104	0.76 (0.58–0.98)	0.77 (0.59–1.00)
Third	8,480	105	0.76 (0.58–0.99)	0.76 (0.57–1.00)
Highest	8,480	132	0.94 (0.72–1.23)	0.88 (0.67–1.16)
p value for trend			0.94	0.67

*Adjusted further for age (continuous), area (nine Public Health Center areas), BMI (<21, 21–22.9, 23–24.9, 25–26.9 or ≥27 kg/m^2), family history of diabetes mellitus (yes or no), smoking status (none, past, current smoking <20 or ≥20 cigarettes/day), alcohol intake (men: none, <150, 150–299, 300–449 or ≥450 g ethanol/week; women: none, <150, 150–299 or ≥300 g ethanol/week), history of hypertension (yes or no), exercise frequency (less than once/week or ≥once/week), consumption of coffee (less than daily, 1–3 cups/day or ≥4 cups/day), energy-adjusted magnesium (continuous) and total energy (continuous) trend) for total dairy products, milk, cheese and yogurt, respectively. In multivariable analyses, these associations were attenuated. No significant association between dairy product intake and the risk of diabetes was observed in men (Table 3). We repeated the above analyses without adjustment for intake of magnesium, a component of dairy foods, but the results were not materially changed (data not shown).

In a stratified analysis according to vitamin D intake, the inverse association between calcium intake and the risk of diabetes was more pronounced among participants who consumed a median or greater amount of vitamin D; the odds ratios (95% CI) for the highest vs lowest quartiles of calcium intake were 0.62 (0.41–0.94; p=0.050 for trend) in men and 0.59 (0.38–0.91; p=0.043 for trend) in women (Table 4). In contrast, calcium intake was not associated with the risk of diabetes in either sex in the lower vitamin D intake group. p for interaction between calcium (continuous) and vitamin D (dichotomous) was 0.02 and 0.06 for men and women, respectively. In stratified analyses according to BMI, smoking status or alcohol intake, the associations with calcium or vitamin D were not notably different between the stratified subgroups (data not shown).

Discussion

In this large-scale cohort of Japanese adults, intake of calcium and vitamin D was not associated with a significantly lower risk of type 2 diabetes. However, both in men and women there was a clear decreasing trend of type 2 diabetes risk with increasing dietary intake of calcium among persons with a higher vitamin D intake. Dairy food intake was inversely associated with the risk of type 2 diabetes in women, but not in men. To our knowledge, this is the first prospective study in a Japanese population to show an association between both calcium and vitamin D intake and the risk of type 2 diabetes.

Although calcium intake was not clearly associated with risk of type 2 diabetes, there was a suggestion of an inverse association in women. This finding appears to be consistent with results from studies in US American women showing a marginally significant inverse association with dietary calcium intake in multivariable analyses [7, 8]. A notable finding in our study is that a distinct inverse association between calcium and the risk of diabetes was observed in the higher, but not in the lower vitamin D intake subgroup.

Table 3 ORs of type 2 diabetes according to the intake of dairy products, milk, cheese and yogurt

	Men			Women		
Intake (g/day) per product group	At risk (*n*)	Cases (*n*)	Multivariable OR (95% CI)*	At risk (*n*)	Cases (*n*)	Multivariable OR (95% CI)*
Dairy products						
<50	8,776	217	1.00	7,674	136	1.00
50–<150	6,016	141	0.99 (0.79–1.23)	8,154	113	0.82 (0.64–1.07)
150–<300	7,772	189	1.04 (0.85–1.28)	11,958	160	0.82 (0.64–1.04)
≥300	3,313	87	1.18 (0.90–1.56)	6,133	71	0.71 (0.51–0.98)
p value for trend			0.21			0.054
Milk						
<50	12,102	304	1.00	12,485	191	1.00
50–<100	732	19	1.07 (0.66–1.72)	1,282	23	1.29 (0.83–2.01)
100–<200	4,463	98	0.90 (0.71–1.13)	6,349	98	1.08 (0.84–1.39)
≥200	8,580	213	1.02 (0.85–1.24)	13,803	168	0.87 (0.70–1.09)
p value for trend			0.88			0.16
Cheese						
0	13,085	326	1.00	16,939	253	1.00
0.1–<5	10,390	261	1.08 (0.91–1.29)	13,570	182	1.08 (0.88–1.33)
≥5	2,402	47	0.88 (0.64–1.21)	3,410	45	1.12 (0.80–1.57)
p value for trend			0.39			0.56
Yogurt						
0	15,820	386	1.00	12,551	209	1.00
0.1– <60	7,528	193	1.14 (0.95–1.37)	14,100	186	0.85 (0.69–1.05)
≥60	2,529	55	1.01 (0.75–1.36)	7,268	85	0.77 (0.58–1.01)
p value for trend			0.94			0.13

*Adjusted variables as in Table 2 (footnote)

Table 4 Multivariable odds ratios of type 2 diabetes according to quartiles of calcium intake, stratified by median intake of vitamin D

Quartiles of calcium intake per vitamin D intake	Men			Women		
	At risk (*n*)	Cases (*n*)	Multivariable OR (95% CI)*	At risk (*n*)	Cases (*n*)	Multivariable OR (95% CI)*
Low vitamin D (<median)						
Lowest	4,166	107	1.00	5,053	73	1.00
Second	3,218	71	0.86 (0.63–1.19)	4,195	63	1.14 (0.79–1.63)
Third	2,870	73	1.01 (0.72–1.41)	3,762	56	1.12 (0.76–1.66)
Highest	2,684	87	1.31 (0.92–1.89)	3,949	51	0.94 (1.62–1.43)
p value for trend			0.08			0.70
High vitamin D (≥median)						
Lowest	2,303	67	1.00	3,426	61	1.00
Second	3,251	72	0.76 (0.53–1.08)	4,285	55	0.70 (0.48–1.02)
Third	3,600	89	0.87 (0.61–1.25)	4,718	70	0.79 (0.54–1.15)
Highest	3,785	68	0.62 (0.41–0.94)	4,531	51	0.59 (0.38–0.91)
p value for trend			0.050			0.043

*Adjustment variables, see Table 2 (footnote)

p=0.02 and p=0.06 for interaction of calcium (continuous) and vitamin D (dichotomous), men and women respectively

This is in line with the hypothesis that calcium and vitamin D act jointly to protect against type 2 diabetes. In a prospective study among US American nurses [7], a combined daily intake of >1,200 mg of calcium and >800 IU of vitamin D was associated a 33% lower risk of type 2 diabetes compared with a daily intake of ≤600 mg and ≤400 IU respectively. Although the lowest risk was observed in persons with a combined high intake of calcium and vitamin D, the benefit of the two nutrients appears to be additive in the US study.

We found a marginally significant risk reduction associated with the highest intake of calcium and dairy products in women, but not in men. This sex-related difference in association could be ascribed to chance, but another explanation is possible. Thus in the present cohort, women consumed greater amounts of calcium and dairy products than men, with median daily calcium intake at 404 mg for men and 546 mg for women and that for dairy products at 111 g for men and 171 g for women. If apparent risk reduction is observed only above a certain intake level, comparatively lower intake of calcium and dairy products in men than in women could explain the observed discrepancy in association.

A few intervention studies have examined the effects of the combined intake of calcium and vitamin D on type 2 diabetes, but their results have been inconsistent. Specifically, supplementation with 400 IU of vitamin D and 1,000 mg of calcium did not reduce the risk of type 2 diabetes over a 7-year follow-up among participants with normal and impaired fasting glucose levels [13]. In another trial of 221 elderly persons with normal glucose tolerance, combined supplementation with 700 IU of vitamin D and 500 mg of calcium citrate malate had no effect on glycaemia or insulin resistance during a 3-year follow-up, compared with the placebo group [20]. In that study, however, the administration of calcium and vitamin D supplements significantly attenuated the increase in fasting glycaemia and insulin resistance among participants with impaired fasting glucose, compared with control participants [20].

Regarding the intake of dairy foods, we found statistically significant inverse associations with the risk of type 2 diabetes in age- and area-adjusted analyses in women, but the association was attenuated after multivariable adjustments. An inverse association with type 2 diabetes has been reported for the intake of dairy foods in men [9] and women [7], for the intake of low-fat dairy foods in women [8, 10] and for yogurt intake in men [9] and women [10]. Our study did not find a risk reduction associated with milk intake, a finding consistent with the results of American studies [9, 10], although one study [9] reported a lower risk of type 2 diabetes with low-fat milk intake.

Vitamin D intake was not independently associated with the risk of type 2 diabetes in our study. Two prospective studies have shown an inverse association with supplemental [7] and total [11] vitamin D intake, but not with dietary vitamin D intake. A possible explanation for the lack of association with dietary vitamin D in our study and in others is the fact that sunlight-induced cutaneous synthesis of vitamin D also contributes to systemic vitamin D levels [4]. Consequently, dietary vitamin D intake alone may not explain the overall vitamin D status. Data from the present study population do not enable us to examine the contribution of dietary vitamin D intake to circulating 25-OHD concentrations, an indicator of systemic vitamin D status. However, a study of Japanese women, which was conducted in winter [21], showed that persons who frequently consumed fish, a rich source of vitamin D, had higher mean blood 25-OHD concentrations than those who consumed fish infrequently. Thus, dietary vitamin D intake could be used in ranking systemic vitamin D status at least when the amount of sunlight-induced cutaneous synthesis of vitamin D is low.

The precise mechanisms whereby calcium and vitamin D exert glucose-lowering effects are not clear. Calcium is essential for insulin-mediated intracellular processes. Intracellular calcium levels are tightly controlled within a narrow range to maintain insulin signalling [22]. Calcium deficiency leads to the secretion of parathyroid hormone and increases calcium inflow from the extracellular fluid into intracellular regions, resulting in cellular calcium overload and impaired insulin sensitivity [5, 23]. In epidemiological studies, calcium intake was positively associated with insulin sensitivity [24–26]. Vitamin D is also involved in insulin regulation [3, 4]. 1,25-Dihydroxyvitamin D_3, an active form of circulating vitamin D, binds to the vitamin D receptor on pancreas beta cells and enhances insulin receptor expression, resulting in improved insulin sensitivity [27, 28]. Vitamin D deficiency has also been shown to impair insulin secretion in experimental studies [3, 4]. Moreover, because vitamin D facilitates calcium absorption in the intestines [29], vitamin D and calcium may act synergistically to reduce the risk of type 2 diabetes. Dairy foods rich in calcium may decrease the risk of diabetes through calcium-related mechanisms. In addition, milk protein induces the release of insulinogenic amino acids and the peptide hormone incretin, both of which augment insulin secretion [30].

Japanese patients with type 2 diabetes are on average leaner than white counterparts, which might reflect differences in insulin secretion and sensitivity between the two ethnic groups [31]. A multi-ethnic study of US American women [32] found that Japanese-Americans had lower beta cell function than non-Hispanic whites, suggesting a need to improve beta cell function as well as insulin sensitivity in order to prevent type 2 diabetes in the Japanese. If calcium and vitamin D have beneficial effects on beta cell function and insulin sensitivity, sufficient intake of these nutrients may have a large impact on reducing the risk of type 2 diabetes among Japanese.

The major strengths of our study include its prospective design, large sample size and the use of a validated food frequency questionnaire. However, several study limitations should also be mentioned. First, the incidence of diabetes was ascertained on the basis of self-reported information obtained from the participants. According to a validation study, self-reported diabetes exhibited a fairly good agreement with documented diabetes on the basis of medical records (94%), while sensitivity (82.6%) and specificity (99.7%) of self-reported diabetes were also high. Second, the dietary intake of calcium and vitamin D was only measured at one time-point and thus may not reflect long-term exposure. Third, we were unable to distinguish regular from low-fat dairy foods, two categories that may have different effects on the risk of diabetes. Fourth, we did not consider sunlight-induced cutaneous synthesis of vitamin D. Studies involving the measurement of blood 25-OHD, a marker of systemic vitamin D exposure, could reveal the association between vitamin D and the risk of type 2 diabetes more precisely. Finally, significant results obtained in subgroup analysis may be due to chance and thus should be interpreted with caution.

In conclusion, the present study provided no clear evidence to support an independent role of calcium and vitamin D in the development of type 2 diabetes. An inverse association between calcium intake and type 2 diabetes risk in persons with a higher vitamin D intake suggests that these nutrients may act jointly, rather than independently, in lowering risk of type 2 diabetes. This possibility warrants further investigation.

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