Brief Report

Relationship Between Dietary Vitamin D and Deaths From Stroke and Coronary Heart Disease

The Japan Collaborative Cohort Study

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Background and Purpose—There is growing evidence about the importance of vitamin D for cardiovascular health. Therefore, we examined the relationship between dietary vitamin D intake and risk of mortality from stroke and coronary heart disease in Japanese population.

Methods—A prospective study encompassing 58 646 healthy Japanese adults (23 099 men and 35 547 women) aged of 40 to 79 years in whom dietary vitamin D intake was determined via a self-administered food frequency questionnaire. The median follow-up period was 19.3 years (1989–2009). The hazard ratios and 95% confidence intervals of mortality were calculated using categories of vitamin D intake.

Results—During 965 970 person-years of follow-up, 1514 stroke and 702 coronary heart disease deaths were documented. Vitamin D intake was inversely associated with risk of mortality from total stroke especially intraparenchymal hemorrhage but not from coronary heart disease; the multivariable hazard ratios (95% confidence intervals) for the highest (≥440 IU/d) versus lowest (<110 IU/D) categories of vitamin D intake were 0.70 (0.54–0.91; *P* for trend=0.04) for total stroke and 0.66 (0.46–0.96; *P* for trend=0.04) for intraparenchymal hemorrhage.

Conclusions—Dietary vitamin D intake seems to be inversely associated with mortality from stroke. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.019417.)**

Key Words: coronary disease ■ diet ■ stroke ■ surveys and questionnaires ■ vitamin D

A growing body of evidence indicates that vitamin D targets the cardiovascular system, exerting potential protection against neurovascular injury.[1] Specifically, low serum levels of vitamin D have been associated with an increased risk for stroke.[2,3] Although the major source of vitamin D for humans is exposure to sunlight, dietary and supplemental vitamin D are also essential for maintaining optimal vitamin D concentrations in the body.[1] Despite the evident association between serum vitamin D levels and risk of cardiovascular disease (CVD),[2,3] studies investigating the relationship between dietary vitamin D intake and risk of CVD are scarce and shown inconsistent results; no association in both sexes,[4] inverse associations in both sexes,[5,6] and inverse association in men but not women.[7] In particular, these relationships have not been examined for the Japanese population; therefore, we examined the relationship between dietary vitamin D intake and risk of mortality from stroke, stroke types, and coronary heart disease (CHD) in a large population-based Japanese study: The JACC (Japan Collaborative Cohort) Study.

Subjects and Methods

To investigate factors related to cancer and CVD, 24 institutions participated in a multicenter collaborative study; the JACC Study that was launched at 1988 to 1990. The sampling methods and protocols of the JACC Study have been described in detail elsewhere.[8] In brief, recruitment of 110 585 inhabitants of 45 communities across Japan and aged 40 to 79 years was done by investigators who were responsible for conducting the cohort in that community. Informed consent was obtained from participants or community leaders, and the ethical committees of Hokkaido University and Osaka University approved the protocol of this study. Data, analytic methods, and study materials are available to other researchers at http://publichealth.med.hokudai.ac.jp/jacc/. Because the calculation of dietary nutrients was not conducted for participants with missing information for >4 food items, including rice or miso soup, a total of 58 646 individuals were eligible for the current analysis (Figure I in the online-only Data Supplement). At baseline, participants completed a self-administered questionnaire about their demographic characteristics and lifestyles and included a food frequency questionnaire inquiring about their usual frequency of food intake for the past year.[8] Dietary (not supplementary) vitamin D intake was calculated by multiplying the participants' frequency scores by the vitamin D content of each food

Received June 28, 2017; final revision received November 12, 2017; accepted December 6, 2017.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.019417/-/DC1.

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item (based on the Japan Food Composition Tables, Fifth Edition), followed by summing the content of all the food items. The portion size for each food item was estimated in a validation study[8] in which the food frequency questionnaire was validated by using four 3-day weighed dietary records during a 1-year period as a reference standard, with a Spearman rank correlation coefficient for vitamin D intake of 0.39 for 85 individuals.[8] The main food contributors of vitamin D intake were fresh fish (75%), fried vegetables (15%), and dry fish (5%).

The underlying causes of death registered in death certificates were coded in accordance with the *International Classification for Diseases* (*10th Revision*). Subjects who died after moving out of their original communities were treated as censored cases.

The vitamin D dietary reference intake (DRI) for Japanese aged 40 to 79 years is 220 IU/d, and accordingly calorie-adjusted vitamin D intake was modeled as 4 categorical variables <110 (less than half the DRI), 110 to 219 (half DRI up to less than DRI), 220 to 439 (DRI up to less than double the DRI), and ≥440 IU/d (double the DRI or more). Because there was no interaction with sex for all end points, the differences between means and proportions of participants' characteristics across the increasing categories of vitamin D intake among the whole sample were tested via the ANCOVA and χ^2 tests. Person-years of follow-up were defined as the period from submission of the initial baseline questionnaire to either death, departure of a participant from his/her original community, or termination of follow-up at the end of 2009, whichever came first.

Kaplan–Meier curves were constructed for cumulative mortality according to categories of vitamin D intake, and multivariable-adjusted hazard ratios (HRs; 95% confidence intervals [CIs]) were calculated by Cox proportional hazard model using the lowest category of intake as a reference. Adjustment were made for age, sex, medical history of hypertension, and diabetes mellitus; smoking status; quintiles of body mass index; hours of exercise; hours of walking; ethanol intake; use of multivitamin supplementation; calorie-adjusted quintiles of carbohydrate, meat, calcium, sodium, potassium, and saturated fatty acid intakes; and total calorie intake. Probability values for statistical tests were 2 tailed, and $P<0.05$ was regarded as statistically significant. Analyses were performed using the SAS statistical package (version 9.4, SAS).

Results

During 965 970 person-years (median, 19.3 years) of follow-up, we documented 702 deaths from CHD and 1514 deaths from strokes, including 503 ischemic strokes, 208 subarachnoid hemorrhages, and 346 intraparenchymal hemorrhages.

Differences in participants' characteristics are given in Table I in the online-only Data Supplement, and Kaplan–Meier curves for cumulative mortality according to categories of vitamin D intake are shown in Figure II in the online-only Data Supplement. The multivariable HRs (95% CIs) for the highest versus the lowest categories of vitamin D intake were 0.82 (0.68–0.98; *P* for trend=0.07) for total stroke, 0.70 (0.52–0.94; *P* for trend=0.04) for hemorrhagic stroke, and 0.66 (0.46–0.96; *P* for trend=0.04) for intraparenchymal hemorrhages (Table). No significant associations were observed for CHD mortalities.

Discussion

Our findings are consistent with previous studies that reported that both vitamin D status and vitamin D intake affect physiological and pathophysiological processes in the circulatory system.[2–7] Several studies have indicated that low serum levels of vitamin D are associated with increased risk for incident stroke and stroke death.[2–4] The multivariable HR (95% CIs) for cerebrovascular death in the highest versus lowest quintiles of 25(OH)D concentration in a Finnish cohort study was 0.48 (0.31–0.75).[3]

Although the relationship between serum vitamin D levels and risk of CVD has been extensively studied, the evidence on the associations with dietary vitamin D intake is scarce and inconsistent.[4–7] Dietary vitamin D intake was not associated with CVD events in a British study: the HR (95% CIs) for a 1-SD increment in dietary vitamin D intake was 0.94 (0.83–1.08).[4] In Japanese Americans, the multivariable HR (95% CIs) for incident stroke in the lowest versus highest quartiles of dietary vitamin D intake was 1.22 (1.01–1.47).[5] A Finnish study showed that the multivariable HR (95% CIs) for stroke in the highest versus lowest tertiles of total vitamin D intake (dietary and supplementary) was 0.46 (0.23–0.90).[6] Relative to a total dietary vitamin D intake (dietary and supplementary) of <100 IU/d, an intake of ≥600 IU/d was associated with a decreased risk of stroke in men of the Health Professionals Follow-Up Study; 0.77 (0.57–1.03), but not in women of the Nurses' Health Study; 0.96 (0.79–1.18).[7] However, this relationship for the men was evident only for supplementary, and not dietary, vitamin D intake.

In our study, the inverse relationship between vitamin D intake and risk of stroke was evident especially for intraparenchymal hemorrhage but not for ischemic stroke. However, several previous studies have shown that such a relationship does exist for ischemic stroke in Western populations.[2,5] In a meta-analysis of 10 longitudinal studies, comparing individuals with severe vitamin D deficiency (<10.0 ng/mL) with those with optimal vitamin D status (≥30.0 ng/mL), the multivariable HR (95% confidence interval) for ischemic stroke was 1.36 (1.09–1.70) while that for hemorrhagic stroke was 1.44 (0.76–2.73).[2] However, the authors attributed the lack of association with hemorrhagic stroke to the lower statistical power of that test (164 hemorrhagic versus 1256 ischemic events).

The incidence of hemorrhagic stroke in the Japanese population is twice that in Western population; this discrepancy may be attributable to both genetic and environmental factors. Higher blood pressure and lower total cholesterol levels are critical risk factors for hemorrhagic stroke in the Japanese.[9] Specifically, the risk of incident hypertension is higher in subjects with low serum concentrations of vitamin D,[10] and low cholesterol levels are accompanied by low vitamin D levels because cholesterol is an important precursor to vitamin D synthesis.[11] Also, low serum vitamin D levels are associated with microbleeding from small deep cerebral vessels in patients with acute or transient ischemic stroke.[12] Thus, a higher risk of intraparenchymal hemorrhage associated with poor vitamin D status is plausible in the Japanese population.

To the best of our knowledge, this is the first study to show an association between dietary vitamin D intake and the risk of CVD mortality in Japanese population. Study limitations include the lack of repeated measurements of vitamin D intake because this variable might have changed during the long follow-up period. The lack of information on sunlight exposure and vitamin D supplement use is additional weaknesses in this study. The primary source of vitamin D for humans is cutaneous synthesis, and only a small amount is contributed by the

Table. Mortality From Coronary Heart Disease and Stroke According to Dietary Vitamin D Intake, JACC Study

	Categories of Dietary Vitamin D Intake, IU/d				
	<110	110–219	220–439	≥440	*P* Trend
No. of participants	2317	13180	31735	11414	
Person-years	37995	212860	521461	193652	
Total stroke, n	72	335	807	300	
Model 1	1.00	0.77 (0.59–0.99)	0.73 (0.57–0.94)	0.68 (0.52–0.88)	0.02
Model 2	1.00	0.78 (0.60–1.01)	0.74 (0.57–0.96)	0.66 (0.49–0.89)	0.02
Intraparenchymal hemorrhage, n	27	85	172	62	
Model 1	1.00	0.57 (0.37–0.88)	0.47 (0.31–0.70)	0.42 (0.27–0.67)	0.004
Model 2	1.00	0.57 (0.36–0.90)	0.47 (0.29–0.74)	0.44 (0.26–0.77)	0.04
Subarachnoid hemorrhage, n	9	44	112	43	
Model 1	1.00	0.75 (0.37–1.55)	0.72 (0.36–1.44)	0.68 (0.33–1.42)	0.46
Model 2	1.00	0.74 (0.35–1.56)	0.68 (0.32–1.43)	0.62 (0.26–1.39)	0.31
Ischemic stroke, n	16	120	271	96	
Model 1	1.00	1.18 (0.70–1.99)	1.07 (0.64–1.78)	0.94 (0.55–1.61)	0.16
Model 2	1.00	1.24 (0.72–2.12)	1.10 (0.64–1.90)	0.88 (0.49–1.60)	0.07
Coronary heart disease, n	30	171	376	125	
Model 1	1.00	1.03 (0.69–1.51)	0.92 (0.63–1.34)	0.78 (0.52–1.16)	0.04
Model 2	1.00	1.00 (0.67–1.49)	0.92 (0.61–1.37)	0.75 (0.48–1.18)	0.06

The vitamin D dietary reference intake (DRI) for Japanese aged 40–79 years is 220 IU/d. Model 1: Age and sex-adjusted hazard ratio and 95% confidence interval. Model 2: Adjusted further for body mass index, past histories of diabetes mellitus and hypertension, hours of sports and walking, smoking, alcohol intake, multivitamin supplementation, and calorie-adjusted intakes of carbohydrate, meat, calcium, sodium, potassium, and saturated fatty acids. JACC indicates Japan Collaborative Cohort.

diet. However, there has been a positive correlation between dietary vitamin D intake and serum vitamin D levels.[13] Also, in the 1980s to 1990s, vitamin D supplementation was unpopular among the Japanese, and only 3.3% of the participants of the current study reported the daily use of multivitamin supplementation (we adjusted for this in the multivariate analyses). The sensitivity analysis excluding participants with multivitamin supplementation, however, did not affect the results materially (data not shown). Another limitation is that only ≈53% of potential participants completed the food frequency questionnaire. Respondents were 3 years younger, more educated, and had more perceived mental stress than nonrespondents; however, we adjusted these variables in our analysis. Third, based on a validation study for this cohort,[8] the food frequency questionnaire–based intake of vitamin D was underestimated by 25%; however, this systematic underestimation would not have materially affected the relationship. Finally, mortality rather than incidence data formed the used end points, which known to be biased to severe types of stroke and also might be liable to misclassification. However, as for stroke mortality, the widespread use of computed tomographic scans in Japanese hospitals since the 1980s has potentially made the death certificate diagnosis of stroke and its types sufficiently accurate.[14] However, 25% to 33% of the CHD deaths appearing on the death certificates were contaminated[15]; therefore, the lack of associations between dietary vitamin D intake and mortality from CHD might be in part because of the contamination of diagnosis.

In conclusion, a higher dietary intake of vitamin D is suggested to help reducing risk of stroke mortality—particularly intraparenchymal hemorrhage—in Japanese men and women.

Acknowledgments

We thank all staff members involved in this study for their valuable help in conducting the baseline survey and follow-up.

Sources of Funding

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (Monbusho) and Grants-in-Aid for Scientific Research on Priority Areas of Cancer, as well as Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from the Japanese Ministry of Education, Culture, Sports, Science, and Technology (Monbu-Kagaku-sho; nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, 20390156, and 26293138). Grant-in-Aid from the Ministry of Health, Labour and Welfare, Health and Labor Sciences research grants, Japan (Research on Health Services: H17–Kenkou–007; Comprehensive Research on Cardiovascular Disease and Life–Related Disease: H18–Junkankitou [Seishuu]–Ippan–012; Comprehensive Research on Cardiovascular Disease and Life–Related Disease: H19–Junkankitou [Seishuu]–Ippan–012; Comprehensive Research on Cardiovascular and Life–Style Related Diseases: H20–Junkankitou [Seishuu]–Ippan–013; Comprehensive Research on Cardiovascular and Life–Style Related Diseases: H23–Junkankitou [Seishuu]–Ippan–005), and an Intramural Research Fund (22-4-5) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center; and Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H26-Junkankitou

[Seisaku]-Ippan-001. This study was also supported by the National Cancer Center Research and Development Fund (27-A-4) and JSPS KAKENHI Grant Number JP 16H06277.

Disclosures

None.

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Stroke
Journal of the American Heart Association

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Stroke. published online January 8, 2018;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628