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

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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	13 180	31 735	11 414	
Person-years	37 995	212 860	521 461	193 652	
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.

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Disclosures

None.

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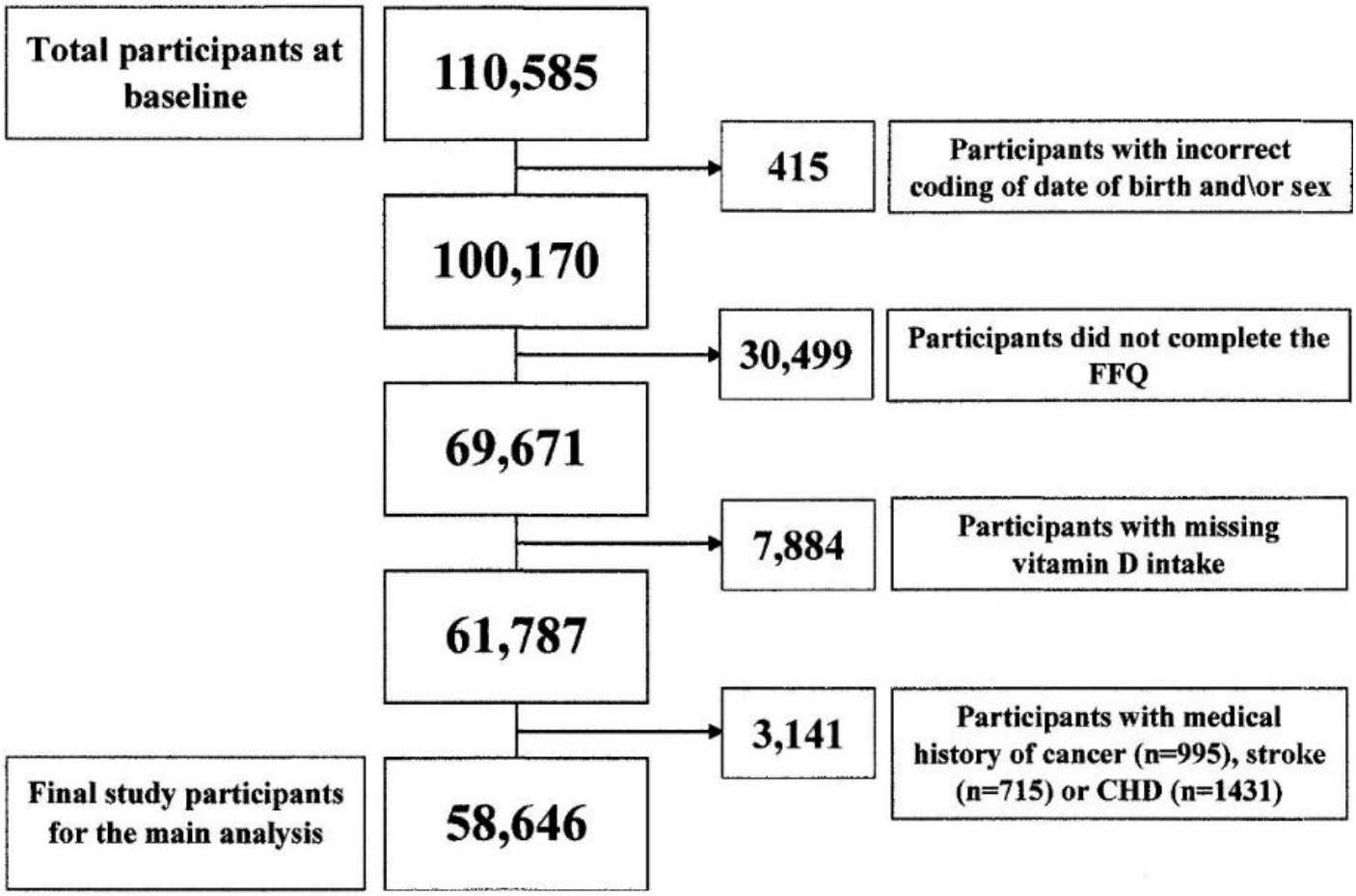
SUPPLEMENTAL MATERIAL

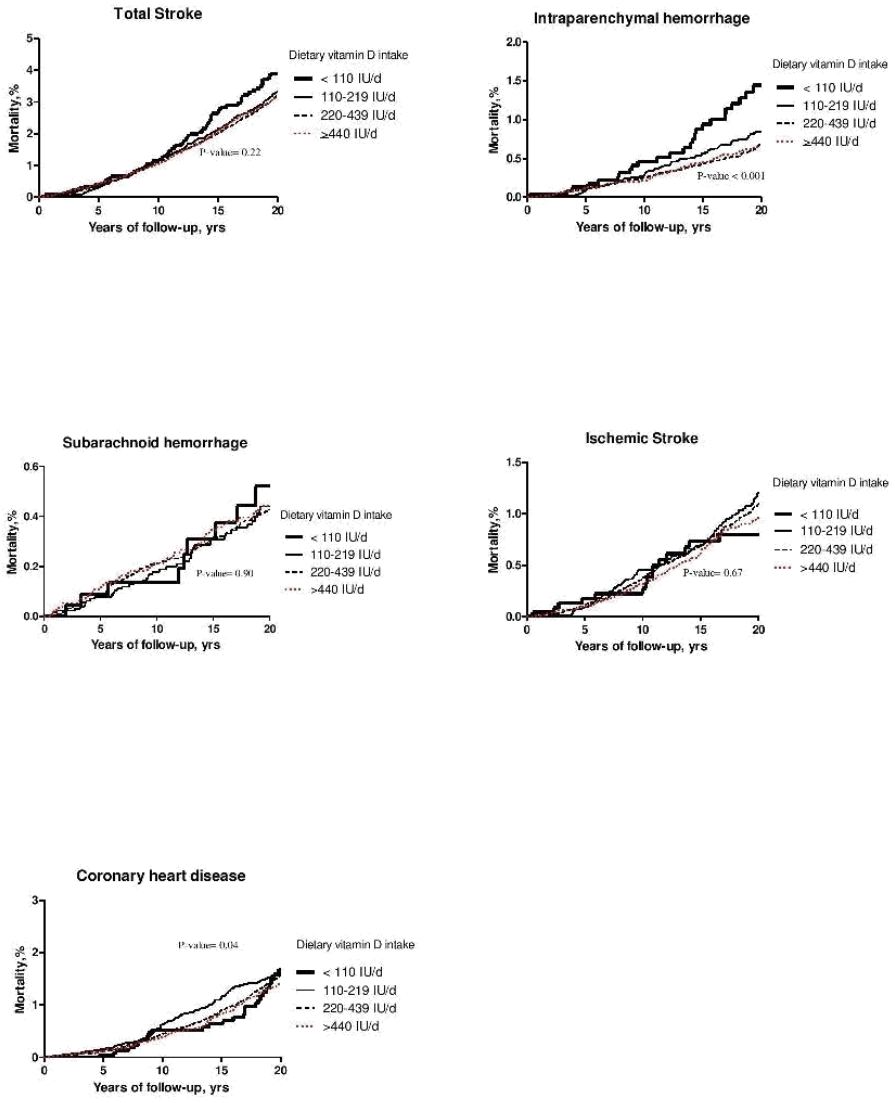
Supplemental Figure I. Participants' flow chart



Supplemental Table I. Participant's characteristics according to categories of dietary vitamin D intake

	Categories of dietary vitamin D intake *				
	<=110 IU/day	111-220 IU/day	221-440 IU/day	>440 IU/day	P-trend
Median intake, IU/day	79.5	181.2	307.9	508.4	
No. at risk	2317	13180	31735	11414	
Age, year	54.8±9.4	55.5 ± 10.2	56.1 ± 10.0	57.2 ± 9.4	<0.0001
Percentage of males	77.6	50.0	35.9	29.2	<0.0001
Body mass index, kg/m^2	22.9 ± 2.8	22.8 ± 3.0	22.8 ± 3.0	22.9 ± 3.0	0.01
History of hypertension, %	17.4	19.6	20.1	20.3	0.01
History of diabetes, %	4.0	4.4	4.5	4.8	0.10
Ethanol intake, g/day	39.5 ± 27.1	30.1 ± 22.8	26.7 ± 22.2	25.6 ± 21.5	<0.0001
Current smoker, %	46.1	31.4	22.4	18.8	<0.0001
College or higher education, %	11.0	13.1	12.6	12.4	0.69
Manual worker, %	54.4	67.5	71.6	73.6	<0.0001
Sports and/or walking 5 hours or more/week, %	55.6	51.1	51.0	54.1	0.001
Daily multivitamin supplementation, %	2.7	3.2	3.3	3.6	0.25
Calorie-adjusted carbohydrate intake, g/day	267 ± 49	251 ± 34	236 ± 30	220 ± 30	<0.0001
Calorie-adjusted meat intake, g/day	18.8 ± 9.0	26.1 ± 18.1	30.1 ± 19.3	31.1 ± 23.3	<0.0001
Calorie-adjusted fish intake, g/day	8.1 ± 3.0	25.8 ± 8.2	49.3 ± 14.3	86.4 ± 13.8	<0.0001
Calorie-adjusted saturated fatty acids intake, g/day	6.3 ± 3.1	8.5 ± 3.0	10.0 ± 3.0	11.3 ± 3.2	<0.0001
Calorie-adjusted sodium intake, mg/day	1370 ± 814	1765 ± 660	2138 ± 630	2600 ± 639	<0.0001
Calorie-adjusted calcium intake, mg/day	353 ± 152	150 ± 144	518 ± 143	588 ± 148	<0.0001
Calorie-adjusted potassium intake, mg/day	1624 ± 545	2054 ± 499	2404 ± 502	2799 ± 539	<0.0001
Total calorie intake, kcal/day	2009 ± 445	1547 ± 442	1503 ± 440	1628 ± 400	<0.0001

*The dietary reference intake (DRI) for Japanese population aged 40-79 years is 5.5μg (220 IU) and the categories of intake are less than half the DRI, between half to DRI, up to double the DRI and more than double the DRI.



***Supplementary Figure*II:** Kaplan-Meier analysis of cumulative mortality for total stroke, sub-stroke type, and coronary heart disease according to categories of vitamin D intake.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) We indicated the study's design with a commonly used term in the title or the abstract
		(*b*) We provided in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	We explained the scientific background and rationale for the investigation being reported in page 3 lines 2-11.
Objectives	3	We stated specific objectives, including any prespecified hypotheses in page 3 lines 10-14.
Methods		
Study design	4	We presented key elements of study design early in the paper in page 4 lines 4-7 and page 4 lines 13-15.
Setting	5	We described the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection in page 3 line 16 to page 4 line 12.
Participants	6	(*a*) *Cohort study*— we Gave the eligibility criteria, and the sources and methods of selection of participants in page 3 line 16 to page 4 line 1. We described methods of follow-up in page 4 lines 22-25.
Variables	7	We clearly defined all outcomes, exposures, predictors, potential confounders, and effect modifiers in page 4 line 4 to page 5 line 7 .
Data sources/ measurement	8*	For each variable of interest, we gave sources of data and details of methods of assessment (measurement)and described comparability of assessment methods between FFQ and WDR in page 4 lines 4-12.
Bias	9	We described efforts to address potential sources of bias in page 7 lines 19-22 and page 8 lines 3-13.
Study size	10	We explained how the study size was arrived at 58,646 in page 3 line 24 to page 4 line 1.
Quantitative variables	11	We explained how quantitative variables were handled in the analyses and described which groupings were chosen and why in page 4 line 16-19.
Statistical methods	12	(*a*) We describe all statistical methods, including those used to control for confounding in page 4 line 19 to page 5 line 9.
		(*b*) We described methods used to examine subgroups and interactions in page 4 line 19-22.
		(*d*) *Cohort study*— we explained how loss to follow-up was addressed in page 4 line 24.
		(*e*) We described sensitivity analyses in page 7 line 21,22.

Continued on next page

Results		
Participants	13*	(a) We reported numbers of individuals at each stage of study in page 5 line 11 and added a participant's flow chart.
		(c) We added a flow diagram
Descriptive data	14*	(a) We gave characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders in page 5 line 15 and supplemental table I.
		(c) *Cohort study*—We summarised follow-up time in page 5 line 11.
Outcome data	15*	*Cohort study*—We reported numbers of outcome events or summary measures over time in page 5 lines 11-13.
Main results	16	(a) We gave u confounder-adjusted estimates and their precision (eg, 95% confidence interval) in page 5 lines 16-20.
Other analyses	17	We reported other analyses done—eg analyses of subgroups and interactions in page 4 line 19-21, and sensitivity analyses in page 7 line 21,22.
Discussion		
Key results	18	We summarised key results with reference to study objectives in page 5 lines 22-24.
Limitations	19	We discussed limitations of the study, taking into account sources of potential bias or imprecision and discussed both direction and magnitude of any potential bias in page 7 line 13 to page 8 line 11.
Interpretation	20	We gave a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence in page 8 line 12,13.
Other information		
Funding	22	We gave the source of funding in page 9 lines 4-11.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.