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SERUM 25-HYDROXYVITAMIN D LEVEL AND RISK FOR INCIDENT STROKE IN CHINESE COMMUNITY-DWELLING OLDER MEN

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Abstract: *Objective:* This study examined the association of serum vitamin D level and stroke incidence in older Chinese men. *Design:* Prospective cohort study. *Setting:* Hong Kong, China. *Participants:* 939 community-dwelling Chinese men aged 65 and older. *Measurements:* Baseline serum 25-hydroxyvitamin D (25OHD) level was measured using a competitive radioimmunoassay kit. Data on stroke incidence between 2001 and 2008 were retrieved from territory-wide hospital database. Cox regression analyses were performed with adjustments for age, body mass index, serum parathyroid hormone level, education, season of blood sampling, self-reported history of stroke and diabetes, hypertension status, and lifestyle factors. *Results:* Seventy nine (8.4%) men had incident stroke. In either crude or adjusted models, serum 25OHD level was not associated with stroke incidence. Results remained unchanged when serum 25OHD level was divided into quartiles or dichotomized into low (<50 nmol/L) and adequate (>=50 nmol/L) levels for analyses. Subjects with increasing age [adjusted HR (95% CI), 1.08 (1.03-1.13)], higher serum PTH level [2.58 (1.49-4.45)] and self-reported history of stroke [5.40 (3.01-9.71)] were associated with higher stroke incidence (p<0.001). *Conclusions:* The findings show no association between serum 25OHD level and risk of stroke in older Chinese men. The lack of association may possibly be due to the relatively high serum 25OHD level of the study ample. The implication of the positive association of serum PTH level with stroke incidence was limited by the lack of renal function measurements in this study.

Key words: 25-hydroxyvitamin D, parathyroid hormone, stroke, Chinese.

Introduction

Stroke is an important public health challenge worldwide because of its enormous burden on morbidity and mortality (1, 2). There is a large variation in stroke mortality and burden worldwide (3). A recent review of large population- based studies showed that the overall stroke incidence rates in low to middle income countries had exceeded the level of stroke incidence seen in high-income countries over the past four decades. A 42% decrease in stroke incidence was noted in high-income countries whereas over 100% increase in stroke incidence was observed in low to middle income countries (4).

Vitamin D deficiency is a public health problem worldwide (5, 6). Previous studies also showed that vitamin D deficiency was common in Hong Kong. Over 90% of women in Hong Kong had serum 25-hyroxyvitamin D (25OHD) level < 50 nmol/L (7). Another study showed that 22.5% community dwelling Chinese adults over 50 years in Hong Kong had serum 25OHD level < 50 nmol/L, and male sex, instead of female sex was associated with low serum 25OHD levels in this community sample (8).

Several lifestyle factors, such as smoking status, diet with low intake of fish and fruit, physical inactivity and excessive alcohol intake have been identified as modifiable risk factors of stroke (1, 9). In recent years, the role of vitamin D status in prevention and treatment of stroke has received research interest (9-11). However, most studies were conducted on Western populations and the findings were inconclusive (10-13). As little is known of Chinese populations whose dietary habits and lifestyle differ from those of Western populations, this prospective study examined the association between serum 25OHD level and stroke incidence in older Chinese men in Hong Kong. Data on serum 25OHD level in older Chinese women were not measured in this study due to resource limitation.

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Materials and Methods

Study Population

Two thousand Chinese men aged 65 years or over living in the community were recruited in a health survey between 2001 and 2003 by placing recruitment notices in community centers for the older people and housing estates. Participants were volunteers and were able to walk or take public transport to the study site. Subjects who had bilateral hip replacements and who could not walk independently were excluded. They were recruited using a stratified sampling method so that approximately 33% would be in each of these age groups: 65-69, 70-74, 75+. Compared with the general population in this age group, participants had higher educational level (12–18% v. 3–9% with tertiary education in the age groups 80+, 75–79,70–74, and 65–69 years) (14). This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. Written informed consent was obtained from all subjects. Due to limited resources, only a random subpopulation consisting of 988 men had fasting venous sampling for assay of serum 25OHD and PTH. Among these 988 men, 49 men were excluded as they were taking vitamin D supplement or the values of serum 25OHD and PTH level were outliers. The final sample included data from 939 men (47% of the original cohort) for analysis (Figure 1).

Demographic and Overall Health Characteristics

Information was collected regarding age, education, self-reported history of stroke and diabetes, smoking habit and alcohol use. Self-reported medical history including stroke and diabetes was obtained at baseline based on subjects' report of their physician's diagnoses, supplemented by the identification of drugs brought to the interviewers. Information on the duration and level of past and current use of cigarettes, cigars and pipes was obtained. Smoking history was classified in terms of former smoking (at least 100 cigarettes smoked in a lifetime), current smoking and never smoking. For alcohol consumption, subjects were asked to report their daily frequency of intake of alcohol and other beverages in portion sizes specified on the semi-quantitative food frequency questionnaire (FFQ). They were also asked to report on how many days of the week they consumed alcohol. Drinking status was defined as never, former or current drinker. Current drinkers were defined as those who drank at least 12 drinks of beer, wine (including Chinese wine) or liquor over the previous 12 months.

Physical Activity Assessment

Physical activity level was assessed using the Physical Activity Scale of the Elderly (PASE) (15). This is a 12-item scale measuring the average number of hours per day spent in leisure, household and occupational physical activities over the previous 7 days. Frequencies of different activities are counted as different weights. Each activity is multiplied by according weight. These weighted values are summed to yield a composite PASE score. A higher score indicates higher physical activity level.

Dietary Assessment

Dietary intake was assessed at baseline using a validated FFQ, and mean nutrient quantitation per day was calculated using food tables derived from McCance and Widdowson (16) and the Chinese Medical Sciences Institute (17). The FFQ had been validated (18) and consisted of 280 food items. Each subject was asked to complete the questionnaire – the food item, the size of each portion, the number of times of consumption each day and each week in the past year. Portion size was explained to subjects using a catalogue of pictures of individual food portions. Details of dietary assessment have been described elsewhere (19).

Data on Stroke Incidence

Data on incident stroke were retrieved from the Clinical Management System (CMS) database of the Hong Kong Hospital Authority (HA), which covers over 95% of all hospital admissions in Hong Kong. The CMS is a computerized system for all aspects of clinical management implemented by the HA in 1995; and by 1999, it has been adopted by all hospitals run by the HA. It is a usual practice for stroke patients admitted to HA acute hospitals to have a CT scan within 24 hours of admission. The diagnoses for hospital admission were coded by the ICD-9-CM and verified by experts in the HA. Patients with severe stroke who died before arrival at HA hospitals were also included. Over 90% of all hospital admissions for stroke were to hospitals run by the HA rather than to private hospitals (20); the HA admission data provide a good reflection of the stroke cases in Hong Kong.

Blood Pressure Measurement

Blood pressure was measured after 5 minutes rest in the sitting position using a standard mercury sphygmomanometer (WA Baum Co. Inc., Copiague, NY, USA) by trained staff. The first and fifth Korotkoff phases were recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP). The average of two readings was taken. Hypertension was defined as SBP >140 mmHg and/or DBP >90 mmHg and/or use of anti-hypertensive medication (21). Anti-hypertension medication included in the present study were diuretics, beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor antagonist, calcium channel blockers and alpha blockers.

Anthropometry

Body weight was measured, with subjects wearing a light gown, using the Physician Balance Beam Scale (Healthometer, Illinois, USA). Height was measured using the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, UK). Body mass index (BMI) was calculated as [body weight in kg / (height in m)^2].

Laboratory Assay of Serum 25OHD and PTH

Fasting venous samples were collected at baseline for assay of serum 25OHD and PTH. Serum was stored at -80°C and levels of 25OHD were measured by a competitive RIA (DiaSorin, Stillwater, MN). This assay measures both 25OHD3 and 25OHD2. Intra-assay and inter-assay CVs were 6% and 18%, respectively. Serum levels of intact PTH were measured by an immunoluminometric assay (Diagnostic Products Corp., Los Angeles, CA). Intra-assay and inter-assay CVs were 5% and 9%, respectively.

Statistical Analyses

Statistical analyses were performed using the statistical package SPSS version 16.0 (SPSS Inc., Illinois, US). Data was checked for normality by descriptive analysis and data transformation was applied for skewed data. Student's t test and chi square test were used to examine the differences in mean age, BMI, PASE, dietary intake of sodium, potassium, calcium, magnesium, and also the differences in the distribution of education level, smoking habit, alcohol use, hypertension status, and self-reported history of diabetes and stroke between participants with and without blood sampling.

Serum 25OHD level was stratified into quartiles or dichotomized according to vitamin D status for analyses. Differences across serum 25OHD quartiles were calculated by chi square test for categorical variables and by analysis of variance (ANOVA) or non-parametric Krusal-Wallis test for continuous variables. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for stroke incidence during the follow-up period according to continuous serum 25OHD level or quartiles of serum 25OHD level or different vitamin D status. The follow-up period was defined as the time from the baseline examination to the date of first hospitalization due to stroke, the date of death of any other causes or the date to the latest database update (i.e. September 2008), whichever came first. The models were adjusted for baseline age (years), BMI (kg/m2), PASE, education level (primary or below, secondary or matriculation, University or above), smoking habit (never smoker vs ex- or current smoker), alcohol use (yes vs no), dietary intake of calcium, sodium, potassium, magnesium, serum PTH (natural log-transformed; pmol/L), self-reported history of diabetes (yes vs no) and stroke (yes vs no), hypertension status (yes vs no), and season of blood sampling (spring and winter vs summer and autumn). Cubic spline cox proportional hazard model was also used to examine whether the relationship between serum 25OHD level and incident stroke was nonlinear. Stroke threshold concentrations were calculated using log likelihood cut point analysis. The cut point of serum 25OHD level dichotomized to produce the highest log likelihood value was considered the best value (22). An α level of 5% was used as the level of significance.

Results

There were no significant differences in education level, smoking habit, alcohol use, daily intake of calcium, sodium, magnesium and potassium from diet, self-reported history of diabetes and stroke, hypertension status, and incident stroke between men with (n=988) and without (n=1 012) blood sampling. However, men with blood sampling were older, more likely to exercise, and had lower BMI ($p<0.05$) than men without blood sampling (data not shown).

Characteristics of 939 men in the final sample are shown in Table 1. Seventy nine (8.4%) men were identified with incident stroke. Mean(SD) age of the sample was 72.8(5.1) years. Mean(SD) serum 25OHD level and median(interquartile range) serum PTH level was 77.9(20.5) nmol/L and 4.1(3.1-5.5) pmol/L respectively. 55(5.9%), 390(41.5%) and 494(52.6%) men had serum 25OHD level below 50 nmol/L, between 50 and 74.9 nmol/L, and at or above 75 nmol/L respectively. Men in the highest quartile of serum 25OHD level were likely to have lower serum PTH level, lower BMI, lower dietary sodium intake and blood sampling in summer and autumn (Table 1).

Serum 25OHD level was not significantly associated with stroke incidence in either crude or adjusted models. The results remained unchanged when serum 25OHD level was divided into quartiles or dichotomized into low (<50 nmol/L) and adequate (>=50 nmol/L) levels for analyses (Table 2). Subjects with increasing age, higher serum PTH level and self-reported history of stroke were statistically associated with higher stroke incidence in adjusted models. The adjusted HR (95% CI) was 1.08

Table 1
Baseline subject characteristics by quartiles of serum 25OHD level

Variable	Serum 25OHD level (nmol/L)								P*
	1st <63 n=239		2nd >63 to <76 n=252		3rd >76 to <91 n=221		4th >91 n=227		
	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%	
Serum 25OHD concentration (nmol/L)	54.4	7.0	69.9	4.1	83.5	4.4	106.1	13.1	---
Serum PTH concentration (pmol/L)†	4.7	(3.6-6.1)	4.1	(3.1-5.6)	4.1	(2.9-5.0)	3.7	(2.7-4.9)	<0.001
Age (years)	72.5	5.2	73.1	5.3	72.6	4.6	72.9	5.1	0.628
BMI (kg/m2)	23.5	3.3	23.0	2.9	23.3	3.2	22.7	3.0	0.022
PASE score	101.7	60.8	94.6	46.5	99.0	50.3	102.8	55.3	0.623
Dietary intake									
Calcium (mg/d)	626.9	306.6	611.2	283.4	622.4	280.2	610.1	273.3	0.639
Potassium (mg/d)	3212.5	1165.6	3202.6	1173.0	3171.1	1289.4	3294.0	1218.1	0.548
Sodium (mg/d)	1800.7	846.2	1678.3	903.6	1662.9	869.4	1622.1	758.1	0.027
Magnesium (mg/d)	376.8	166.6	373.7	164.9	396.6	208.1	380.5	181.4	0.519
Education level									
Primary or below	126	52.7	148	58.7	127	57.5	147	64.8	0.080
Secondary / Matriculation	70	29.3	76	30.2	60	27.1	57	25.1	
University or above	43	25.4	28	11.1	34	15.4	23	10.1	
Smoking habit									
Never smoke	206	86.2	219	86.9	197	89.1	200	88.1	0.783
Ex- or current Smoker	33	13.8	33	13.1	24	10.9	27	11.9	
Alcohol use									
No	176	73.6	189	75.0	175	79.2	177	78.0	0.468
Yes	63	26.4	63	25.0	46	20.8	50	22.0	
Season of blood sampling									
Winter and Spring (low vitamin D season)	133	55.6	116	46.0	98	44.3	82	36.1	<0.001
Summer and Autumn (high vitamin D season)	106	44.4	136	54.0	123	55.7	145	63.9	
Self-reported history									
Diabetes	32	13.4	36	14.3	40	18.1	38	16.7	0.476
Stroke	9	3.8	11	4.4	17	7.7	18	7.9	0.110
Hypertension‡	155	64.9	172	68.3	143	64.7	162	71.4	0.371
Stroke incidence	18	7.5	16	6.3	21	9.5	24	10.6	0.341

*Differences between groups were assessed by chi square test and ANOVA; †Median(interquartile range), group difference was assessed by Krusal Wallis test; ‡Defined as average systolic or diastolic blood pressure>140 or 90 mmHg respectively, or use of anti-hypertensive medications

Table 2
HRs (95%CIs) of risk of stroke by serum 25OHD levels (n=939)

Serum 25OHD level (nmol/L)	Case/Control	Crude HR (95% CI)	P value or Ptrend*	Adjusted† HR (95% CI)	P value or Ptrend*
Continuous	---	1.01 (0.99-1.02)	0.388	1.01 (0.10-1.02)	0.252
By quartiles					
Q1 (<63)	18/221	1	0.106	1	0.097
Q2 (>63 to <76)	16/236	0.85 (0.43-1.66)		0.80 (0.40-1.59)	
Q3 (>76 to <91)	21/200	1.31 (0.70-2.46)		1.36 (0.71-2.58)	
Q4 (>91)	24/203	1.47 (0.80-2.72)		1.50 (0.77-2.90)	
By vitamin D status					
Adequate (>=50)	72/812	1	0.263	1	0.514
Low (<50)	7/48	1.56 (0.72-3.39)		1.31 (0.58-2.98)	

*P for trend was performed for quartiles of serum 25OHD in the Cox regression model; †Adjusted for age, BMI, education, PASE, dietary intakes of potassium, sodium, magnesium and calcium, serum PTH level (ln), smoking habit, alcohol use, self-reported history of diabetes and stroke, hypertension status, and season of blood sampling

(1.03-1.13) for age, 2.58 (1.49-4.45) for serum PTH level (ln) and 5.40 (3.01-9.71) for self-reported history of stroke (all p<0.001). There was a tendency to a nonlinear relationship between serum 25OHD and stroke risk (Figure 2). The threshold values for stroke risk using log likelihood cut point analysis for serum 25OHD level was 80 nmol/L.

Figure 1
Number of subjects included in data analysis

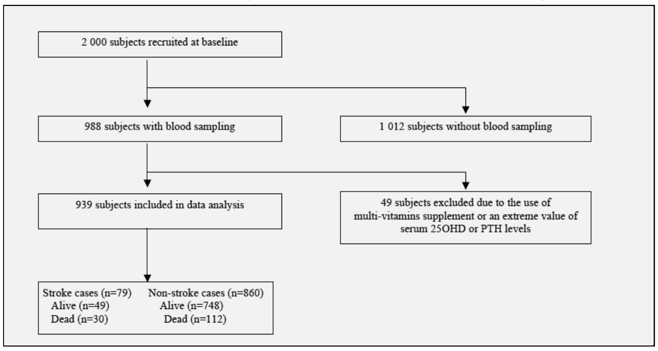
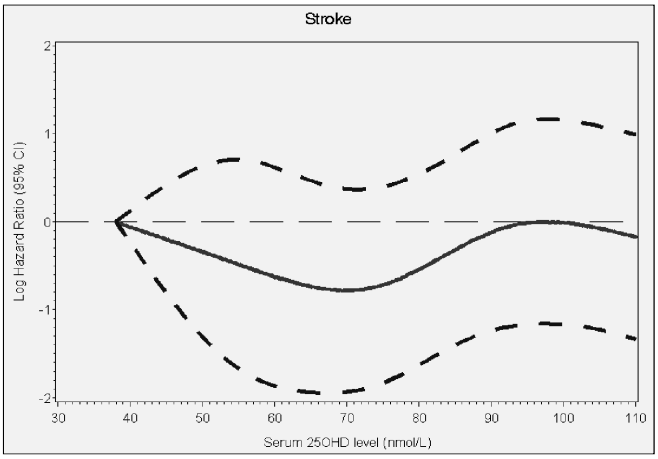


Figure 2
Spline model for the detection of any nonlinear relationship between risk of stroke and serum 25OHD. There was a tendency to a nonlinear relationship between serum 25OHD level and stroke risk. The threshold values for stroke risk using log likelihood cut point analysis for serum 25OHD level was 80 nmol/L



Discussion

In recent years, there is growing evidence to show that vitamin D plays an important role in a broad range of body functions beyond bone health, including cardiovascular health. However few epidemiological studies focused on the association between vitamin D status and risk of stroke, and these studies seldom included serum PTH level as one of the measures (10-12, 23-25). Results of these studies were inconclusive. Most studies showed that vitamin D deficiency was independently associated with increased risk of stroke (10, 11, 23-25) and only one recent study reported no association (12). Differences in the study design, study populations and covariates adjusted for may account for the inconclusive findings among these studies. Anderson and colleagues prospectively analyzed 41 504 patient records to determine the relation of vitamin D levels to the prevalent and incident cardiovascular risk factors and diseases, including mortality (10). 63.6% of the studied population had vitamin D deficiency (<75 nmol/L) and vitamin D deficiency was associated with significant increase in the prevalent and incident cardiovascular risk factors and outcomes. Among subjects aged 50 years or above, those with very low vitamin D level (<37.5 nmol/L) had an increased risk of incident stroke (HR=1.78, P=0.004) as compared to those with normal vitamin D level (>75 nmol/L) after adjustment for potential confounders. The results were consistent with those of the LUdwigshafen RIsk and Cardiovascular Health study which included 3 316 patients who were referred to coronary angiography at baseline between 1997 and 2000. When compared with survivors in binary logistic-regression analyses, the odds ratios for fatal stroke were 0.67 (95% CI: 0.46 to 0.97; P=0.032) per z value of 25OHD after adjustment for possible confounders (11).

There are several potential mechanisms to explain for the association between vitamin D status and stroke or other cardiovascular risks. Vitamin D could suppress the renin–angiotensin–aldosterone system (RAAS) by inactivating renin gene expression and inhibiting renin synthesis (26). Recent findings from an animal study also suggest that 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter (27). Other effects of vitamin D include renoprotective effects, vasodilatatory and antiatherosclerotic properties, and effects on calcium homeostasis including prevention of secondary hyperparathyroidism (26, 28, 29). Moreover, a paracrine effect of 25OHD in the arterial wall is proposed in view of the fact that 25OHD-1-α-hydroxylase is not only expressed in the kidney but also in a variety of other tissues, including vascular smooth muscle cell and endothelial cells (30).

In this study, no association between vitamin D status and incident stroke was observed. The results were supported by a recent prospective study of 1 471 healthy community-dwelling older women (12). Although men with blood sampling were more likely to exercise and have lower BMI compared to men without blood sampling, this would have an inference in the incidence of stroke and therefore making it less likely to yield a significant difference between high and low 25OHD level in the present study. Our data however showed that there was no significant difference in the stroke incidence between the two groups and thus excluded this possibility. In contrast, we speculated that high mean 25OHD levels and low prevalence of vitamin D deficiency of our sample may explain for the absence of associations between vitamin D status and incident stroke. About 6% of our participants had serum 25OHD level below 50 nmol/L. The prevalence of vitamin D deficiency was low, compared with other published studies among Caucasians (10, 11, 24). Lifestyle differences may account for the variations of vitamin D status among different populations. For example, older people in the Netherlands spent an average of about 2.3 hours per week on physical activity (31), while older people in Hong Kong were more likely to go into the sun and performed more outdoor activities (32, 33). Due to the crowded home environment, it is also common for the elderly in Hong Kong to go to the nearby park or riverside to perform physical activities. Moreover, the seasonal variation in the quantity of sunlight in Hong Kong is not as great compared with Western countries. Compared with temperate regions lying between 40-60°N/S, including the greater parts of northern and western Europe, and North America, where the seasonal (winter to summer) difference in sunshine hours tends to be as great as 6 hours and more, this seasonal effect tends to be slight in subtropical region where Hong Kong is situated (22.25°N) (34). Therefore, the elderly in Hong Kong are likely to have greater sunlight exposure. Although there appears to be a statistically significant impact of season on the assessment of 25OHD levels in our study (Table 1), season of blood sampling has been controlled for multivariate analyses and the absence of association between serum 25OHD level and the risk of stroke is still observed in the present study.

Furhtermore, the low number of incident stroke (n=79) in the present study may have limited the power to detect an association between serum 25OHD levels and stroke incidence. Repeated analyses were therefore performed with data on myocardial infarction (MI) incidence added to data on stroke incidence (n=100). A significant association between serum 25OHD level and risk of incident stroke and MI was observed when serum 25OHD level was divided into quartiles for analyses. An evaluated risk of incident stroke and MI was noted when serum 25OHD level exceeded 76 nmol/L. The adjusted HR (95% CI) of incident stroke and MI compared to the lowest quartile (<63 nmol/L) of serum 25OHD was 0.97 (0.53-1.79), 1.63 (0.91-2.91) and 1.62 (0.89-2.96) for the 2nd quartile (>63 to <76 nmol/L), the 3rd quartile (>76 to <91 nmol/L) and the highest quartile (>91 nmol/L) of serum 25OHD level respectively (ptrend=0.040). There was also a tendency to a nonlinear relationship between serum 25OHD and stroke and MI risk. The threshold values for stroke and MI risk using log likelihood cut point analysis for serum 25OHD level was 80 nmol/L (data not shown). These findings are consistent with recent evidence that both too high (>100 nmol/L) and too low (<37.5 nmol/L) level of serum 25OHD is associated with increased risk of cardiovascular events and some cancers (35).

Our study showed an increased risk of stroke incidence with increasing serum PTH level, independent of the influence of vitamin D levels. There is evidence to show that PTH may affect stroke through its cardiovascular properties (36). An elevated level of plasma or serum PTH is linked with higher cardiovascular mortality, increased risk of hypertension and elevated blood pressure (19, 37-40). The PTH results observed in the present study suggest that there may be a vitamin D effect plus an effect of renal dysfunction. However, the lack of serum calcium data and renal indices in the present study makes this difficult to interpret and we cannot exclude the possibility that the positive association between serum PTH level and stroke incidence could be due to reduced renal function.

The strengths of our study included prospective study design, stroke incident data retrieved from representative hospital database, and adjustment for several potential confounders. However, our study had several limitations. First, serum 25OHD and PTH levels measured at a single point in time may only reflect recent exposure rather than long-term exposure. Second, we did not collect information on medical history of chronic kidney disease, which may be an important confounding factor (41). In addition, increasing PTH level with age is partly due to decreasing kidney function. However data on serum calcium and kidney function were not available in this study. Third, although the majority of patients with stroke are admitted to public hospitals, a small number may have been treated in private hospitals. However this number is likely to be small since over 90% of people needing hospital treatment go to public hospitals. Moreover there is no community stroke clinic where patients are treated without being admitted to hospitals. Finally, our sample as a whole was of a higher educational standard compared with the general Hong Kong population, and there were slight differences in some demographic and lifestyle characteristics between those with and without blood sampling. Therefore, the results may not be generalized to the general population.

In conclusion, this study showed that vitamin D status was not associated with stroke incidence in a sample of community-dwelling Chinese older men who are vitamin D replete. The positive association between serum PTH level and stroke incidence observed could be entirely due to reduced renal function with ageing, and the interpretation of this association was limited by the lack of renal function measurements in the present study. Future studies are warranted to evaluate the role of serum 25OHD and PTH as determinants of risk of stroke in populations with higher prevalence of vitamin D deficiency, and to investigate the underlying mechanisms of serum 25OHD and PTH in stroke and other cardiovascular diseases.

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Conflict of interest: The authors declare no conflict of interest.

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