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SEX, RESIDENCE AND FISH INTAKE PREDICT VITAMIN D STATUS IN CHINESE CENTENARIANS

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Abstract: *Objectives:* This study aims to investigate the prevalence of vitamin D deficiency in Chinese centenarians and to identify the factors associated with vitamin D deficiency. *Design:* Cross-sectional population-based study. *Setting:* Hainan province in the south of China. *Participants:* 943 subjects aged 100 years old and older. *Methods:* Details on sociodemographics and lifestyle characteristics were collected using a structured questionnaire. Anthropometrics and blood samples were obtained. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D concentration < 20ng/mL (50nmol/L). *Results:* The overall prevalence of vitamin D deficiency among these 943 centenarians was 39.9% (376 subjects) and the mean serum vitamin D concentrations were 22.7±9.5 (ng/mL). Female centenarians had higher prevalence of vitamin D deficiency than male (44.0% vs. 21.7%, P < 0.001). Multivariate logistic regression analyses showed that being female, urban residency, lower body mass index, higher serum parathyroid hormone levels, no fish consumption, and less sun exposure time were all significant and independent determinants of vitamin D deficiency. No significant associations of vitamin D deficiency with ethnic, education, geographic location, tea drinking, alcohol use, or smoking were found in this study. *Conclusion:* Vitamin D deficiency was common in Chinese centenarians, especially in women. Given that vitamin D deficiency is linked to numerous adverse health outcomes, dietary, outdoor activities and other intervention measures are needed to correct vitamin D deficiency in this population.

Key words: Vitamin D, prevalence, determinants, centenarians, China.

Introduction

Despite the growing numbers of centenarians, little is known about their vitamin D status and correlates of this condition. Previous studies observed high prevalence of vitamin D deficiency in centenarians from United States and Italy (1, 2), but to our knowledge there was no reported study of vitamin D deficiency and its determinants in centenarians in China.

Vitamin D has been traditionally considered as critical in musculoskeletal health and mineral homeostasis. In addition, recent findings revealed that vitamin D plays beneficial role on extra-skeletal tissues as well (3-6). A plethora of epidemiological and observational studies have demonstrated the correlations between poor vitamin D status and falls, sarcopenia, depression, cognitive impairment and numerous age-related conditions (7-13). Older adults are at particularly risk for vitamin D deficiency for a number of reasons. Despite the similar sun exposure, older people have a reduced capacity to produce vitamin D precursors in the skin after exposure to ultraviolet B irradiation (14). Other factors including less outdoor activities, sun exposures, few dietary vitamin D intake and poor renal function also negatively affect serum 25-hydroxyvitamin D status (15). The contribution of these and other biological, lifestyle and dietary factors may vary significantly with age and culture.

Information on determinants of vitamin D status may be of help to identify those at risk of vitamin D deficiency and to indicate interventions to correct this deficiency. Given that vitamin D deficiency increased as people age and was linked to several major health problems, it is necessary to investigate how prevalent this condition is and what factors are associated with this condition in Chinese centenarians (11).

The aim of the study was to investigate the prevalence of vitamin D deficiency in a population-based sample of Chinese centenarians and to identify the factors associated with vitamin D deficiency in this population.

Material Methods

Study population

Participants were from the China Hainan Centenarian Cohort Study (CHCCS), one of the largest centenarians health studies conducted in China from 2014 to 2016. The CHCCS is located in Hainan province which situated in the southernmost of China. Details of this study have been described elsewhere (16). A total of 1002 centenarians (180 men and 822 women aged 100 and over) were surveyed and blood samples were collected. Fifty-nine participants were excluded from the data analyses because of missing information on the vitamin D levels and relevant variables. The final analyses included 943 centenarians, 175 men and 768 women. Written informed consent was obtained from all men and women who participated in the CHCCS study. The Ethics Committee of the Hainan branch of the Chinese People's Liberation Army General Hospital (Sanya, Hainan) approved the study protocol (No. 301hn11201601).

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Table 1

Unadjusted mean serum 25(OH)D levels, and prevalence of vitamin D deficiency (< 20ng/mL) by sociodemographics, BMI, PTH, lifestyle characteristics, and season

	n	25(0H)D levels		Vitamin D deficiency, % (95% CI)	P
Overall	943	22.75±9.46		39.9 (36.7-43.0)	
Age, yr			0.274		0.313
100-104	738	22.64±9.55		40.9 (37.4-44.5)	
105-109	175	23.52±9.04		34.9 (27.7-42.0)	
≥ 110	30	20.75±9.46		43.3 (24.5-62.2)	
Gender			<0.001		<0.001
Female	768	21.59±8.70		44.0 (40.5-47.5)	
Male	175	27.81±10.91		21.7 (15.6-27.9)	
Ethnic			0.252		0.308
Han	829	22.62±9.47		40.5 (37.12-43.9)	
Non-Han	114	23.70±9.39		35.1 (26.2-44.0)	
Education			0.919		0.534
Illiterate	858	22.74±9.36		39.9 (36.6-43.1)	
Primary school or above	85	22.85±10.42		40.0 (29.4-50.6)	
Residency			0.008		0.006
Urban	221	20.83±8.28		48.0 (41.4-54.6)	
Rural	722	23.33±9.72		37.4 (33.9-40.9)	
Geographic location			0.354		0.645
Coastal	857	22.66±9.47		40.1 (36.9-43.4)	
Inland	86	23.65±9.36		37.2 (27.0-47.4)	
Work before retirement			0.389		0.268
Mental and moderate manual work	26	20.27±7.90		53.8 (33.3-74.4)	
Heavy manual work	418	22.74±9.94		40.7 (35.9-45.4)	
BMI, kg/m2			0.134		0.013
< 18.5	496	22.31±9.44		43.3 (39.0-47.7)	
≥ 18.5	447	23.23±9.46		36.0 (31.6-40.5)	
WC, cm			0.869		0.791
< 75	464	22.70±9.70		39.4 (35.0-43.9)	
≥ 75	479	22.80±9.24		40.3 (35.9-44.7)	
PTH, pg/mL			<0.001		<0.001
< 45	486	24.44±9.57		32.9 (28.4-37.4)	
≥ 45	457	20.94±9.00		47.3 (42.1-52.5)	
Tea			0.019		0.186
Never	829	23.02±9.68		39.1 (35.7-42.5)	
Former or current	114	20.79±7.45		45.6 (30.8-60.4)	
Smoking			0.161		0.221
Never	829	22.59±9.38		40.7 (37.3-44.0)	
Former or current	114	23.91±9.98		34.2 (23.9-44.5)	
Alcohol drinking			<0.001		0.004
Never	781	22.13±9.06		42.0 (38.5-45.5)	
Former or current	162	25.73±10.72		29.6 (24.2-35.0)	
Milk consumption			<0.001		0.002
Never	212	20.33±7.69		49.5 (42.7-56.3)	
< 1 serve/day	542	23.59±9.73		35.6 (31.6-39.7)	
≥ 1 serve/day	189	23.05±10.05		41.3 (34.2-48.4)	
Fish intake			0.001		0.001
Never	63	18.55±8.21		60.3 (47.9-72.7)	
< 1 serve/day	395	22.82±10.21		40.5 (35.6-45.4)	
≥ 1 serve/day	485	23.23±8.83		36.7 (32.4-41.1)	
Sun exposure			<0.001		<0.001
≥ 1 h/day	562	24.20±9.34		32.7 (28.9-36.6)	
< 1 h/day	381	20.59±9.23		50.4 (45.4-55.4)	
Season of blood collection			0.007		0.030
Winter	326	21.61±9.01		44.2 (38.8-49.6)	
Summer	617	23.35±9.64		37.6 (33.8-41.4)	

Abbreviations: BMI: body mass index; WC: waist circumference; PTH: parathyroid hormone.

Sociodemographic, lifestyle and anthropometric variables

Sociodemographic details including age, gender, ethnicity, education, residence, geographic location, and type of work before retirement were asked. Ethnicities were categorized into Han and non-Han (ethnic minorities). Given that majority of centenarians received no education, participants were categorized into illiterate and primary school or above. Residence were dichotomized into urban versus rural. Geographical locations were dichotomized into coastal versus inland. Work types before retirement were classified as mental, moderate manual and heavy manual work.

Information on lifestyle characteristics such as smoking, alcohol use, tea drinking, milk consumption, and fish intake were collected. Current use of vitamin D supplements, sun exposure time and season of blood drawing were also recorded. Smoking, alcohol use and tea drinking were categorized as never, former and current. Milk and fish consumption were divided into three categories: never, occasional (<1 serve/day) and daily consumption (≥1 serve/day). Milk refers to cow's milk. Vitamin D supplements were defined as prescribed and over the counter vitamin D. Sun exposure time was dichotomized into insufficient (<1 h/day) and abundant (≥1 h/day). Season of blood drawing was dichotomized in winter (October to March) and summer (April to September).

Anthropometrics were measured, namely weight, height, body mass index (BMI) and waist circumference (WC). BMI was calculated as the weight in kilograms divided by square height in meters and dichotomized into two groups (<18.5 kg/m2 and ≥18.5 kg/m2) according to the median. WC was measured in the middle of the lower limit of the rib cage and the iliac crest, WC was dichotomized into two groups (<75 and ≥75, cm) according to the median.

Laboratory assessment

Blood samples were obtained from each participant by a group of experienced nurses and transported to the Clinical Laboratory in chilled biotransport container within 4 hours. Serum 25-hydroxyvitamin (25(OH)D) concentrations were measured by automated radioimmunoassay analyzers (DiaSorin, Stillwater, MN, USA) using a standard procedure. This method detects both D2 and D3 forms of vitamin D metabolites and thus reflects body vitamin D derived from the diet, supplements as well as that formed in vivo by ultraviolet exposure(17). The inter-assay and intra-assay coefficients of variation for 25(OH)D in the present study were 8.3% and 6.7%, respectively. Vitamin D deficiency was defined as 25(OH)D < 20 ng/mL or 50 nmol/L according to the Endocrine Society Clinical Practice Guidelines (18). Serum intact parathyroid hormone (PTH) levels were measured using automated electrochemiluminescence immunoassay (ECLIA) analyzers (Roche Co., Cobas e602, Germany). Serum PTH levels were divided into two groups according to the median of concentrations (45 pg/mL).

Statistical analysis

Data were reported as mean and standard deviation (SD) for normally distributed variables or as median and corresponding 25th and 75th percentiles for non-normally distributed variables. Counts and percentages were reported for categorical variables. Differences in continuous variables were explored with the unpaired t test, Mann-Whitney U-test and one-way analysis of variance (ANOVA). Chi-square test or Fisher's exact test were used to compare categorical variables. Logistic regression analyses were used to determine the prevalence ratio (PR) for factors correlated to vitamin D deficiency. Crude and adjusted PRs and 95% confidence interval (CI) were calculated for sociodemographics, anthropometrics, PTH, lifestyle characteristics, and season of blood drawing. The multivariable models included age, gender, ethnic, education, residence, geographic location, work type, BMI, WC, PTH, tea, smoking, alcohol, milk, fish consumption, sun exposure time and season of blood collection. All analyses were carried out using SPSS software (version 19.0 for windows; IBM co., NY, USA; No. of serial: 5087722). A P value <0.05 was considered statistically significant.

Results

A total of 943 individuals aged 100 years or elder were included in this study. Mean age of the participants was 102.8±2.8 years. The majority participants were female (768, 84.4%), Han ethnic (829, 87.9%), illiterate (858, 91.0%), residing in rural areas (722, 76.6%), living in coastal regions (857, 90.9%), and doing manual work before retirements (917, 97.2%). The mean BMI was (18.2±3.2, kg/m2) and the average WC was (75.3±8.9, cm). Around half of the participants were underweight. Table 1 showed the characteristics of the study population. About three percent of participants were current smoker and nine percent were former smoker. The proportions of current tea and alcohol drinker were ten percent and eight percent, respectively. Nearly twenty percent of participants consume milk and fifty-one percent consume fish every day. Sixty percent of participants went outdoors and had daily sun exposure more than one hour. About two thirds of the study participants were surveyed and had their blood collected during summer. None of them reported vitamin D supplements intake currently.

Serum 25(OH)D levels in the study showed a relatively normal distribution (Figure 1). The mean vitamin D concentrations were (22.7 ± 9.5, ng/mL) in the total study participants, and were (27.8 ± 10.9, ng/mL) in men and (21.6 ± 8.7, ng/mL) in women. The overall prevalence of vitamin D deficiency was 39.9% (95%CI, 36.7% - 43.0%). Among this sample of participants, women were significantly more likely to have vitamin D deficiency than man (44.0% vs. 21.7%, P < 0.001). When examining other factors (Table 1), the prevalence rate of vitamin D deficiency was significantly more common among those who were living in urban areas, had

lower BMI(<18.5 kg/m2), had higher PTH levels (>45 pg/mL), never drank alcohol, never consumed milk, never ate fish, had less sun exposure (< 1 h/day), and had blood sample collected in winter or spring (all P <0.05).

Figure 1

Frequency distribution of serum 25(OH)D levels in centenarians (n=943). The Gaussian curve was created by nonlinear regression of the frequency distribution. Abbreviation: 25(OH) D, 25-Hydroxyviatamin D

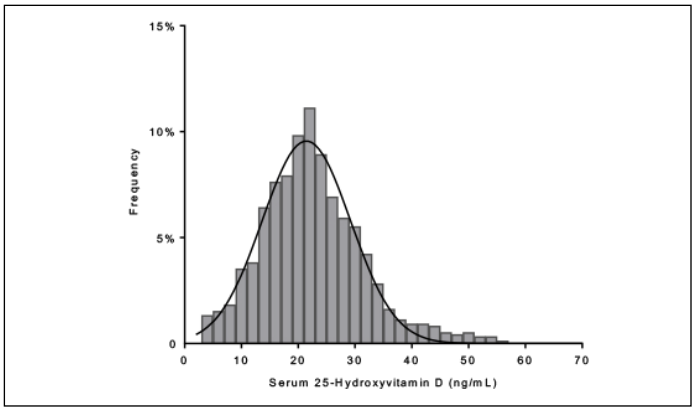

Table 2 showed the results from multivariate analyses. After adjusting for all potential related factors, the model revealed that participants who were female, living in urban areas, had lower BMI, had high PTH levels, never ate fish, had less sun exposure were all significant and independent correlates of vitamin D deficiency. Among these independent correlates, being female was the strongest indicator for vitamin D deficiency; women had more than two times of odds for vitamin D deficiency compared with men (PR: 2.57, 95% CI: 1.55-4.27). Participants with high PTH levels also demonstrated higher PRs compared to low PTH levels. By contrast, a 33% lower PR for vitamin D deficiency was estimated in subjects who reported living in rural areas than in urban areas. Approximately 56% and 48% lower PRs were found for daily fish intake and occasional fish intake, compared to group that never consume fish. Lower PRs were also significantly related to BMI and sun exposure in the results. The difference of association between season of blood collection and vitamin D deficiency showed a possible trend toward statistical significance (P = 0.052). No significant correlations between vitamin D deficiency and age, ethnic, education, geographic location, work type, WC, tea drinking or smoking were found in this study.

Discussions

This study reports a high prevalence of vitamin D deficiency among a representative sample of Chinese centenarians. The prevalence rates of this condition were 39.9% overall, ranging from 21.7% in men and 44.0% in women. The concentrations of 25(OH)D observed in the China Hainan Centenarian Cohort Study were similar to those observed in Georgia Centenarian Study (GCS) (1). These findings add to the growing literature, including findings from the GCS and Italian Multicentric Study on Centenarians (IMUSCE), which suggest that this nutritional deficiency is a common condition among the exceptional long-lived population across the cultures and races, particularly among women and those without abundant sun exposure (1, 2, 19, 20).

This study was conducted in Hainan, where shares almost same latitude as Hawaii (20° North) and has sufficient sunshine throughout the years. Despite this, a high proportion of vitamin D deficiency among this group of centenarians was observed. The high prevalence of vitamin D deficiency in centenarians in Hainan was not unexpected based on the exceptional age (1). Advanced age is associated with decreased concentrations of the precursor 7-dehydrocholesterol in the skin and thus reduced epidermal capacity to synthesis vitamin D (14). However, the concentrations of 25(OH)D in Hainan centenarians are higher than those observed for elderly men and women in Chinese Longitudinal Healthy Longevity Survey (CLHLS) and Risk Evaluation of Cancers in Chinese Diabetic Individuals (REACTION) study (21, 22). As there was no habit of consuming vitamin D supplement among the centenarians in this study, the higher serum levels of vitamin D in this population may possibly be explained by the sufficient sun exposure and dietary patterns (ie., fish intake).

This study also shows that gender was a significant factor associated with vitamin D deficiency. Females had a significantly higher prevalence rate than males. This finding confirmed the results from several previous reports (22-24). However, the Georgia Centenarian Study reported a higher prevalence of vitamin D deficiency in male centenarians than females (1). This discrepancy could be explained by the use of vitamin D supplement in American old adults. Female centenarians would have more intake of vitamin D supplement as they were more likely to suffer from osteoporosis and fractures (25). In addition, the Framingham Heart Study found that the regular use of vitamin D supplements was strongly associated with 25(OH)D concentrations in women but not in men (26).

Besides gender difference, multiple regression analysis revealed that residence was another predictor of vitamin D deficiency in the centenarians. As expected, the vitamin D deficiency was more prevalent in the participants from urban areas than those from rural districts. Urbanization is regarded as a predictor of hypovitaminosis D as people were more likely to stay indoors compared to those in rural areas (27). Lack of outdoor activities was associated with less sunlight exposure and further reduces the cutaneous vitamin D synthesis (28).

The negative correlation between higher serum PTH and vitamin D was expected and has been documented elsewhere in old adults (29). Interestingly, BMI, another well-established negative indicator, was positively correlated with vitamin D

Table 2
Crude and adjusted prevalence ratio and 95% CI for vitamin D deficiency (<20ng/mL)

	Crude PR	95% CI	P	Adjusted PR	95% CI	P
Age, yr						
100-104	1.00	Referent		1.00	Referent	
105-109	0.77	0.55-1.09	0.141	0.71	0.49-1.03	0.072
≥ 110	1.10	0.53-2.31	0.792	1.01	0.46-2.22	0.986
Gender						
Male	1.00	Referent		1.00	Referent	
Female	2.83	1.93-4.17	<0.001	2.57	1.55-4.27	<0.001
Ethnic						
Han	1.00	Referent		1.00	Referent	
Non-Han	0.79	0.53-1.19	0.267	0.89	0.55-1.45	0.649
Education						
Illiterate	1.00	Referent		1.00	Referent	
Primary school or above	1.01	0.64-1.59	0.980	1.59	0.90-2.83	0.111
Residence						
Urban	1.00	Referent		1.00	Referent	
Rural	0.65	0.48-0.88	0.005	0.67	0.48-0.94	0.019
Geographic location						
Coastal	1.00	Referent		1.00	Referent	
Inland	0.88	0.56-1.40	0.597	1.10	0.66-1.85	0.715
Work before retirement						
Mental or moderate manual work	1.00	Referent		1.00	Referent	
Heavy manual work	1.02	0.92-1.14	0.688	1.06	0.79-1.42	0.712
BMI, kg/m2						
< 18.5	1.00	Referent		1.00	Referent	
≥ 18.5	0.74	0.57-0.96	0.022	0.75	0.56-1.00	0.044
WC, cm						
< 75	1.00	Referent		1.00	Referent	
≥ 75	1.04	0.80-1.35	0.789	1.28	0.95-1.73	0.101
PTH, pg/mL						
<45	1.00	Referent		1.00	Referent	
≥ 45	1.27	1.14-1.42	<0.001	1.71	1.29-2.26	<0.001
Tea drinking						
Never	1.00	Referent		1.00	Referent	
Former and Current	1.12	0.94-1.34	0.186	0.74	0.47-1.16	0.185
Smoking						
Never	1.00	Referent		1.00	Referent	
Former and Current	0.90	0.78-1.04	0.221	0.75	0.0.42-1.32	0.314
Alcohol drinking						
Never	1.00	Referent		1.00	Referent	
Former and Current	0.82	0.73-0.93	0.004	0.78	0.51-1.20	0.260
Milk consumption						
Never	1.00	Referent		1.00	Referent	
< 1 serve/day	0.78	0.56-1.10	0.161	0.74	0.48-1.15	0.185
≥ 1 serve/day	1.35	0.91-2.00	0.140	1.09	0.75-1.60	0.646
Fish consumption						
Never	1.00	Referent		1.00	Referent	
< 1 serve/day	0.45	0.26-0.77	0.004	0.52	0.28-0.95	0.032
≥ 1 serve/day	0.38	0.22-0.65	<0.001	0.44	0.24-0.80	0.007
Sun exposure						
≥ 1 h/day	1.00	Referent		1.00	Referent	
< 1 h/day	2.09	1.60-2.73	<0.001	1.87	1.40-2.49	<0.001
Season of blood collection						
Winter	1.00	Referent		1.00	Referent	
Summer	0.76	0.58-1.00	0.050	0.73	0.53-1.00	0.052

Abbreviations: BMI: body mass index; WC: waist circumference; PTH: parathyroid hormone.

in this study (although the adjusted P value of 0.054 slightly missed the margin of statistical significance). Previous studies indicated that being obese or overweight were the independent predictors of vitamin D deficiency, yet few of them compared the prevalence rates between normal and underweight individuals (30). This study showed that participants with lower BMI (< 18.5 kg/m2) had a higher prevalence than those with BMI ≥ 18.5 kg/m2. One plausible explanation is the participants with higher BMI (≥ 18.5 kg/m2) had better nutritional status than their underweighted counterparts. The data from this study provided new hypothesis that the relationship between BMI and vitamin D deficiency could be inverted U-shape in the oldest-old, and this hypothesis warrants examinations among old adults from different cultures, races and latitudes with considerable sample sizes.

Similar to other studies, sun exposure time and season of blood collection were independent correlates to vitamin D deficiency in this population (1, 31). During exposure to sunlight, 7-dehydrocholesterol in the skin absorbs ultraviolet radiation and is converted to pre-vitamin which in turn isomerizes into vitamin D (31). Sufficient amount of sun exposure time was considered to promote adequate cutaneous vitamin D synthesis (32). Season had a large impact on serum vitamin D levels even after controlling for other factors. This finding suggests that controlling for the seasons of blood sample collecting is imperative at all ages, even in centenarians (1). Prevalence of vitamin D deficiency was higher in winter and lower in summer, this finding was similar to previous studies (1, 15). Difference in the level of UV lights exposure may explain the seasonal variation (33).

Traditional sources of vitamin D are fatty fish and their oils and fortified milk (33). This study found that fish but not milk consumption was a significant indicator negatively associated with vitamin D deficiency. Given that the study sample had no habitual intake of vitamin D supplements, this result implied that fish consumption may be essential for the dietary intake of vitamin D in the exceptional-aged individuals, especially in females. The lack of a benefit of milk consumption on vitamin D status was expected. Milk only has 2.5 μg vitamin D (100 IU) per cup, thus consuming one or two cups of milk everyday will only contribute a very small proportion of the 25 μg vitamin D (1000 IU) daily recommendation (1, 34).

The strength of the study was providing the basic information and comparable results on vitamin D status and deficiency condition using a population-based data of Chinese centenarians with a considerable sample size. In addition, all participants reported no vitamin D supplements intake history, allowing us to consider a large number of varied correlates of vitamin D deficiency without this confounder. There are some limitations that should be acknowledged. First, this study was cross-sectional designed, and thus causality could not be inferred. Second, information on lifestyle factors, nutritional diet intake and sun exposure time were obtained by self-reported in centenarians, thus recall bias possible occurred during data collection. Third, the study population all resided in Hainan province (at latitude 20°, North), where sunlight is abundant and fish consumption is high, and this may limit the generalizability of the findings.

In summary, Vitamin D deficiency was common in the Chinese centenarian population, especially among females. This study suggested that the significant and independent correlates of this deficiency were gender, residence, serum PTH concentrations, fish intake, and sun exposure. Given that vitamin D deficiency is linked to numerous adverse health outcomes, interventions on dietary intake, outdoor activities and other modifiable lifestyle factors are needed to correct vitamin D deficiency in this population.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical standard: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Written informed consent was obtained from all men and women who participated in the CHCCS study. The Ethics Committee of the Hainan branch of the Chinese People's Liberation Army General Hospital (Sanya, Hainan) approved the study protocol (No. 301hn11201601).

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