

Plasma 25-hydroxyvitamin D Concentration and Metabolic Syndrome among Middle-aged and Elderly Chinese

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Objective: To evaluate the association between 25-hydroxyvitamin D [25(OH)D] and metabolic syndrome (MetS) in Chinese population.

Research design and methods: Plasma 25(OH)D was measured in a cross-sectional sample of 1443 men and 1819 women aged 50-70 years from Beijing and Shanghai. MetS was defined according to the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans. Fasting plasma glucose, insulin, lipid profile, HbA1c and inflammatory markers were measured.

Results: The geometric mean of plasma 25(OH)D was 40.4 nmol/l and percentages of vitamin D deficiency [25(OH)D <50 nmol/l] and insufficiency ($50 \leq 25(\text{OH})\text{D} < 75$ nmol/l) were 69.2% and 24.4%, respectively. Compared with the highest 25(OH)D quintile (≥ 57.7 nmol/l), the odds ratio for MetS in the lowest quintile (≤ 28.7 nmol/l) was 1.52 (95% CI 1.17-1.98, P for trend = 0.0002), after multiple adjustment. Significant inverse associations existed also between 25(OH)D and individual MetS components, plus HbA1c. Moreover, we observed significant inverse associations of 25(OH)D with fasting insulin and insulin resistance index (homeostasis model assessment of insulin resistance, HOMA-IR) in overweight and obese individuals ($\text{BMI} \geq 24$ kg/m²), but not in their normal weight counterparts (test for interaction: $P = 0.0363$ and 0.0187 for insulin and HOMA-IR, respectively).

Conclusions: Vitamin D deficiency is common in the middle-aged and elderly Chinese and low 25(OH)D level is significantly associated with increased risk of having MetS and insulin resistance. Prospective studies and randomized clinical trials are warranted to determine the role of 25(OH)D in the development of MetS and related metabolic diseases.

Vitamin D deficiency is now recognized as a worldwide concern (1). A growing body of evidence suggests that 25-hydroxyvitamin D [25(OH)D], generally accepted indicator of vitamin D status, is inversely associated with adiposity, glucose homeostasis, lipid profiles and blood pressure along with its classical role in calcium homeostasis and bone metabolism (1-6). Even though the underlying mechanism has not been well understood, vitamin D appears to exert effects through directly modulating gene expression via vitamin D receptors (VDRs) (1) as well as through regulating extra- and intracellular calcium (1, 7).

Metabolic syndrome (MetS), a constellation of cardio-metabolic disease risk factors, has become a global epidemic (8). Several epidemiologic studies (5, 6, 9, 10) have suggested that 25(OH)D status is inversely associated with MetS in western populations, although data from morbid obesity is inconsistent (11,12). Nevertheless, evidence from Asian population is limited. Due to the ethnic differences on vitamin D metabolism and its nutritional status indicated by previous studies (3, 13), it is unclear whether the findings from western populations could be extrapolated directly to Asian people. With rapid nutrition and lifestyle transition in last 20 years, MetS has become one of the most widespread health problems in Asian countries (8). However, little is known whether vitamin D deficiency plays an important role in the heightened prevalence of MetS and other metabolic disorders among Asian people. Therefore, the aim of our study was to evaluate plasma 25(OH)D concentration and its association with MetS among Chinese people aged 50-70 years.

RESEARCH DESIGN AND METHODS

The present study is a part of the Nutrition and Health of Aging Population in China (NHAPC) project, which is a

population-based cross-sectional study among non-institutionalized Chinese people aged 50-70 years in Beijing (latitude 40° north) and Shanghai (latitude 31° north), China. The details of the study design have been described previously (14). In brief, the study was conducted simultaneously in both geographic locations from April to June 2005. In each city, one rural and two urban districts were selected. A total of 3289 eligible participants (1458 men and 1831 women) were recruited. After excluding those who did not have adequate blood samples for 25(OH)D measurement (n = 27), 3262 individuals were eligible for the present analysis. The study was approved by the Institutional Review Board of the Institute for Nutritional Sciences and all participants provided informed consents.

Data collection: In a home interview, a standardized questionnaire was used by trained health workers to collect information such as age, sex, geographic location (Beijing/Shanghai), residential region (urban/rural), visit date (April, or May/June), education level (≤ 6 , 7-9, or ≥ 10 years in school), smoking (current, former, or never), alcohol drinking (yes/no) and self-reported diabetes, hypertension, dyslipidemia, coronary heart disease (CHD), stroke and medication use. Physical activity level was classified as low, moderate, or high according to the International Physical Activity Questionnaire (short last 7-day format) scoring protocol with minor modification (14). According to participants' responses to the corresponding questions, family history of cardiovascular disease (CVD) or diabetes was classified as yes or no.

After the home interview, all participants were invited to attend a physical examination after an overnight fast. Measurements of weight, height, waist circumference, and blood pressure have been described previously (14). BMI was calculated as $\text{weight (kg)/height}^2 \text{ (m}^2\text{)}$ and categorized as normal weight ($< 24.0 \text{ kg/m}^2$), overweight or

obesity ($\geq 24.0 \text{ kg/m}^2$) according to the criteria for Chinese people (15).

Laboratory methods: Peripheral venous blood samples were collected in tubes containing liquid EDTA and centrifuged at 4°C . After being frozen, the samples were shipped on dry ice to the Institute for Nutritional Sciences and stored at -80°C until analysis. The plasma glucose, triglycerides and HDL cholesterol (HDL-C) were measured enzymatically on an automatic analyzer (Hitachi 7080, Japan) with reagents purchased from Wako Pure Chemical Industries (Osaka, Japan). HbA1c was quantified from resolved red blood cell with an automated immunoassay (Tina-quant Hemoglobin A1c II, Roche Diagnostics, Indianapolis, IN, USA) which was standardized according to DCCT/NGSP. Plasma high-sensitive C-reactive protein (CRP) was measured by a particle-enhanced immunoturbidimetric assay (Ultrasensitive CRP kit, Orion Diagnostica, Espoo, Finland). Interleukin-6 (IL-6) was measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) (Quantikine HS IL-6 Immunoassay, R&D Systems, Inc, Minneapolis, MN). Fasting insulin was determined by radioimmunoassay (Linco Research, MO). Insulin resistance index (homeostasis model assessment of insulin resistance, HOMA-IR) was calculated using updated homeostasis model assessment methods (<http://www.dtu.ox.ac.uk/>). Plasma 25(OH)D concentration was assayed with a radioimmunoassay kit (DiaSorin, Stillwater, MN). Vitamin D nutritional status was assessed as “sufficiency” ($\geq 75 \text{ nmol/l}$), “insufficiency” ($50 \leq 25(\text{OH})\text{D} < 75 \text{ nmol/l}$), or “deficiency” ($< 50 \text{ nmol/l}$) (1). All the intra- and inter-assay coefficients of variation were $< 13\%$.

Definition of the MetS: MetS was defined using the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans (16) as presenting 3 or more of the

following components: 1) waist circumference $\geq 90 \text{ cm}$ for men or $\geq 80 \text{ cm}$ for women; 2) triglycerides $\geq 1.7 \text{ mmol/l}$; 3) HDL-C $< 1.03 \text{ mmol/l}$ for men or $< 1.30 \text{ mmol/l}$ for women; 4) blood pressure $\geq 130/85 \text{ mmHg}$ or current use of antihypertensive medications; and 5) fasting glucose $\geq 5.6 \text{ mmol/l}$ or previously diagnosed type 2 diabetes or on oral hypoglycemic agents or insulin.

Statistical methods: Difference in plasma 25(OH)D concentrations between participants with and without MetS was tested by the general linear model with controlling for age, sex, geographic location, residential region and visit date. A logistic regression model was employed to evaluate the odds ratios (ORs) and 95% confidence intervals (CIs) of having MetS for each quintile of 25(OH)D compared with the highest quintile with adjusting for potential confounders that suggested in previous studies (3,5,6,9,17). In addition, effects of inflammatory factors on the association between 25(OH)D and MetS were tested by models adjusted for CRP and IL-6. Tests of linear trend across increasing quintiles of 25(OH)D were performed by assigning the median value to each quintile and treating it as a continuous variable. Multiple linear regression model was used to assess the association of 25(OH)D (continuous) with fasting glucose, HbA1c, waist circumference, triglycerides, HDL-C, blood pressure, fasting insulin and HOMA-IR. Likelihood ratio test was used to test the potential modifying effect of sex and obesity status ($<$ or $\geq 24 \text{ kg/m}^2$). When appropriate, natural log-transformed values were used for the analyses. Statistical inference was made when P value < 0.05 (two sided). The statistical analyses were performed using Stata 9.2 (Stata Corp, College Station, Texas).

RESULTS

The geometric mean of 25(OH)D was 40.4 nmol/l in our study participants. The percentages of vitamin D deficiency,

insufficiency and sufficiency were 69.2%, 24.4% and 6.4%, respectively. Across 25(OH)D quintiles, subjects in lower 25(OH)D quintiles were more likely to be north (Beijing) and urban residents, to have a physical examination in April, higher educational levels, and family history of CVD and diabetes. They also tended to have an adverse cardio-metabolic profile. In addition, these subjects were less physically active and less likely to be male and alcohol drinkers than those in higher 25(OH)D quintiles (Table 1).

Plasma 25(OH)D concentrations were lower in participants with MetS than those without MetS (39.3 vs. 41.6 nmol/l, $P < 0.0001$). The risk of having MetS increased progressively across the highest to the lowest quintiles of 25(OH)D with the ORs of 1.31 (95% CI, 1.03-1.66), 1.36 (95% CI, 1.07-1.73), 1.67 (95% CI, 1.31-2.13), and 1.62 (95% CI, 1.26-2.08), respectively (P for trend < 0.0001) (Table 2) after adjustment for age, sex, geographic location, residential region and visit date (model 1). Further controlling for education, behavioral factors, self-reported CHD and stroke and family history of CVD and diabetes (model 2) did not materially change the inverse associations. After additionally adjusting for CRP and IL-6 (model 3), the ORs slightly attenuated, but remained significant (P for trend = 0.0002). The association appeared to be stronger in men than in women (data not shown), although the interaction for genders was not statistically significant ($P = 0.1745$). When study participants were dichotomized with the cutoff point of 50 nmol/l, the risk of having MetS was 27% higher in those 25(OH)D concentration < 50 nmol/l (OR, 1.27; 95% CI, 1.06-1.53) than those ≥ 50 nmol/l after controlling for all the covariates in model 3.

In both simple and multiple adjusted linear regression analyses, 25(OH)D was inversely associated with fasting glucose, HbA1c, triglycerides, waist circumference and diastolic blood pressure, and positively

associated with HDL-C (Table 3). Further adjustment for BMI (not for waist circumference) did not substantially alter the associations. Gender specific interactions were observed in the associations of 25(OH)D with triglycerides and HDL-C (test for interaction: $P = 0.0034$ and 0.0027 for triglycerides and HDL-C, respectively) and both associations were only significant in men, but not in women.

There were negative associations of 25(OH)D with fasting insulin and HOMA-IR in the total population ($P = 0.0114$ and 0.0044 for insulin and HOMA-IR, respectively), after controlling for potential confounding factors (Table 3). We further observed a modifying effect of obesity status on these associations (test for interaction: $P = 0.0363$ and 0.0187 for insulin and HOMA-IR, respectively). In stratified analyses, 25(OH)D was negatively associated with fasting insulin and HOMA-IR only in participants with $\text{BMI} \geq 24 \text{ kg/m}^2$ ($P = 0.0001$ and $P < 0.0001$ for insulin and HOMA-IR, respectively), but not in those with $\text{BMI} < 24 \text{ kg/m}^2$ ($P = 0.5948$ and 0.5874 for insulin and HOMA-IR, respectively). When overweight and obese participants were divided into 25(OH)D quintiles, the multivariate-adjusted geometric mean of fasting insulin was 13.86 pmol/L lower ($P = 0.0003$) and HOMA-IR was 0.26 lower ($P = 0.0002$) for the participants in the highest quintile compared with the lowest.

Excluding those with diagnosed diabetes mellitus and CVD yielded similar results patterns (data not shown).

CONCLUSIONS

We observed approximately 94% of our study participants having 25(OH)D deficiency or insufficiency. Lower 25(OH)D was associated with increased risk of having MetS and its individual components. In addition, poor 25(OH)D status was also significantly associated with increased insulin resistance, especially among those who were

overweight or obese.

Although two studies reported that the VDR gene polymorphism was not associated with MetS (18, 19), the inverse association between 25(OH)D and MetS found in our study is consistent with that from three previous cross-sectional reports in American (9,10) and British adults (6). These three studies (6, 9, 10) were also conducted in the general populations with large sample sizes; two American studies (9,10) included subjects aged >20 years and the other one (6) was consisted of participants 45 years old. In these studies (6, 9, 10), 25(OH)D concentrations were relatively higher than in ours. A cohort study by Forouhi et al. (5) found that baseline concentration of 25(OH)D was inversely associated with an increased MetS risk z score. However, a study in southern California residents (17) did not observe a significant association between 25(OH)D and MetS, which may be attributed to extraordinary high levels of 25(OH)D (mean concentration was 108.9 nmol/l in men and 101.6 nmol/l in women). Whether there is a threshold or a specific range for the association between 25(OH)D and metabolic abnormalities merits further investigation.

Elevated CRP and IL-6 levels have been found to be positively associated with MetS (8) and inversely correlated with 25(OH)D in our and other studies (20). Thus we further explored whether the observed inverse association between 25(OH)D and MetS was mediated by CRP and/or IL-6. In our study, the association was slightly attenuated, but remained significant after controlling for CRP and IL-6. Our result was in accordance with the data from the Third National Health and Nutrition Examination Survey (NHANES III) (9) in which 25(OH)D was inversely associated with MetS independent of CRP levels.

Poor 25(OH)D status in our study was shown to be inversely associated with HbA1c and individual MetS features such as

fasting glucose, waist circumference, diastolic pressure and triglycerides, and positively associated with HDL-C. However, unlike some of the previous studies (6, 9, 10), we have noticed that plasma 25(OH)D was associated with triglycerides and HDL-C only in men but not in women. These gender specific associations may partly explain the stronger 25(OH)D-MetS association of men than women in our study. Although the mechanistic role of vitamin D deficiency in the pathogenesis of dyslipidemia is not well understood, vitamin D supplement was reported to attenuate the beneficial effect of hormone replacement therapy on serum lipid levels (21). Thus, the potential sex-specific effects of vitamin D on metabolic disorders need to be elucidated further.

Insulin resistance is a major underlying mechanism for the MetS. Experimental studies have suggested that vitamin D may exert its beneficial effects by stimulating the expression of insulin receptor to improve insulin responsiveness for glucose transport, or by controlling calcium influx which is essential for insulin-mediated intracellular process in insulin-responsive tissues (7). Most epidemiologic studies (3, 5, 19), but not all (18), suggested that serum 25(OH)D or the VDR polymorphism were associated with insulin sensitivity. Moreover, data from the NHANES III documented an ethnic difference in the association between 25(OH)D and insulin resistance (4), with a stronger association in Caucasians than African Americans, who have much lower levels of 25(OH)D concentrations. Interestingly, in our population, with similar 25(OH)D levels as African Americans, the 25(OH)D was also negatively associated with fasting insulin and HOMA-IR, and the associations were stronger among overweight and obese subjects.

Obesity is known to be associated with decreased bioavailability of vitamin D, which is sequestered in body fat (2). In fact,

Forouhi et al. (5) reported a significant interaction between 25(OH)D and BMI on the risk for 10-year increase in HOMA-IR. In addition, the release of free fatty acid from adipose tissue can induce insulin resistance, while 1,25-dihydroxyvitamin D [1,25-(OH)₂D] has been shown to counteract the free fatty-acid-induced insulin resistance (22). The stronger association of vitamin D with insulin resistance among the participants of overweight and obesity suggests that adequate vitamin D status is more important for the prevention of insulin resistance and MetS in these individuals.

Our data suggested that vitamin D deficiency was common in middle-aged and elderly Chinese (i.e., 69.2% participants with 25(OH)D \leq 50 nmol/L). Indeed, poor vitamin D status in middle and older Chinese were also reported previously from 2 small bone-related studies conducted in Beijing (23) and Shenyang (24), respectively. Although little is known to what extent the high prevalence of vitamin D deficiency in our population could be explained by certain environmental and/or genetic factors, plausible explanations include: 1) the skin of elderly is less efficient to form vitamin D₃, major precursor of 25(OH)D (25); 2) use of vitamin D supplement is rare among older Chinese (24); 3) unlike in the United State and other western countries, few vitamin D fortified foods are available in China and 4) our study participants were from a relatively high latitude, especially those in Beijing (latitude 40° north), who had lower 25(OH)D levels than their Shanghai counterparts (median 35.6 nmol/l in Beijing vs. 47.6 nmol/l in Shanghai). Hence, much attention should be paid to improve vitamin D nutritional status in Chinese, particularly for those who are older, female, obese, less physically active, and living in high latitudes and urban areas.

To our knowledge, this is the first study to investigate the distribution and association of 25(OH)D levels with MetS in Chinese people. The major strength of this

study is that we used the data from a large representative sample of middle-aged and older men and women living in the two largest municipalities in China. Our analyses took into account many potential covariates that might confound the observed associations. Furthermore, we completed the field study within a relatively short period, which minimized the seasonal variation in the biomarkers. Nevertheless, several limitations should be acknowledged. A cause-effect relationship between 25(OH)D and MetS cannot be inferred due to the cross-sectional nature of the study design. Although data on sun exposure and vitamin D supplement was not available, we used a direct measure of vitamin D status, which reflects cumulative sun exposure and dietary vitamin D intake. In addition, because we did not measure serum calcium and parathyroid hormone, we could not determine whether the association of 25(OH)D with MetS was partly mediated by calcium or secondary hyperparathyroidism. However, data from NHANES 2003-2004 (10) and the Medical Research Council Ely Prospective Study (5) suggested that the associations between 25(OH)D and insulin resistance and MetS were independent of calcium and parathyroid hormone.

In conclusion, our findings suggest that reduced 25(OH)D is associated with an increased risk of having MetS and adverse levels of MetS components. The association of 25(OH)D with insulin resistance is stronger in overweight and obese individuals than normal weight participants. Since there is evidence of ethnic variation of 25(OH)D effect and limited data on the association of 25(OH)D with MetS in Asians, our data provides novel insights into the nature of this association among Asians. Moreover, because of the high prevalence of MetS and vitamin D deficiency in the middle-aged and elderly Chinese population, our results may have important public health implications. Increased sun exposure or use of vitamin D supplement or fortified foods are

simple and inexpensive means to prevent vitamin D deficiency and related health problems. Nevertheless, the benefits of vitamin D on MetS and related diseases such as type 2 diabetes need to be confirmed in future prospective studies and clinical trials.

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Table 1. Characteristics of study participants according to 25-hydroxyvitamin D quintiles

Characteristics	Quintiles of 25-hydroxyvitamin D (nmol/l)				
	Q1 ≤28.7	Q2 28.8-36.8	Q3 36.9-45.5	Q4 45.6-57.6	Q5 ≥57.7
n	652	653	652	653	652
Age (yrs)	58.8 (6.3)	58.1 (6.0)	58.8 (5.9)	58.2 (5.9)	59.1 (5.9)
Male, n (%)	233 (35.7)	252 (38.6)	279 (42.8)	311 (47.6)	368 (56.4)
Urban residents, n (%)	423 (64.9)	384 (58.8)	367 (56.3)	260 (39.8)	189 (29.0)
Residents of Beijing, n (%)	466 (71.5)	419 (64.2)	331 (50.8)	238 (36.5)	168 (25.8)
Visit date (April), n (%)	433 (66.4)	389 (59.6)	334 (51.2)	245 (37.5)	183 (28.1)
Smoking, n (%)					
Never	395 (60.6)	422 (64.6)	423 (64.9)	409 (62.6)	376 (57.7)
Former	67 (10.3)	51 (7.8)	63 (9.7)	59 (9.0)	87 (13.3)
Current	190 (29.1)	180 (27.6)	166 (25.5)	185 (28.3)	189 (29.0)
Alcohol drinking, yes, n (%)	167 (25.6)	183 (28.0)	189 (29.0)	193 (29.6)	196 (30.1)
Physical activity, n (%)					
Low	63 (9.7)	40 (6.1)	47 (7.2)	50 (7.7)	43 (6.6)
Moderate	310 (47.6)	307 (47.0)	294 (45.1)	228 (34.9)	230 (35.3)
High	279 (42.8)	306 (46.9)	311 (47.7)	375 (57.4)	379 (58.1)
Education (yrs), n (%)					
0-6	201 (30.8)	223 (34.2)	240 (36.8)	317 (48.6)	371 (56.9)
7-9	278 (42.6)	254 (38.9)	249 (38.2)	201 (30.8)	177 (27.2)
≥10	173 (26.5)	176 (27.0)	163 (25.0)	135 (20.7)	104 (16.0)
Hypertension, yes, n (%)*	373 (57.2)	372 (57.0)	367 (56.3)	329 (50.4)	344 (52.8)
Self-reported CHD, yes, n (%)†	67 (10.6)	54 (8.4)	48 (7.6)	29 (4.6)	28 (4.4)
Self-reported stroke, yes, n (%)‡	33 (5.1)	32 (4.9)	23 (3.5)	24 (3.7)	19 (2.9)
Family history of diabetes, yes, n (%)	105 (16.1)	89 (13.6)	86 (13.2)	93 (14.2)	74 (11.4)
Family history of CVD, yes, n (%)	179 (27.5)	154 (23.6)	152 (23.3)	149 (22.8)	97 (14.9)
BMI (kg/m ²)	24.9 (3.8)	24.9 (3.8)	24.6 (3.6)	24.3 (3.2)	23.5 (3.3)
Waist circumference (cm)	85.2 (10.5)	84.7 (10.7)	84.2 (10.8)	83.2 (10.1)	81.3 (10.2)
Fasting glucose (mmol/l)	5.52 (5.08-6.09)	5.46 (5.09-6.00)	5.46 (5.09-5.98)	5.42 (4.99-5.88)	5.28 (4.96-5.72)

HbA1c (%)	5.76 (5.46-6.22)	5.75 (5.48-6.14)	5.73 (5.46-6.10)	5.78 (5.47-6.11)	5.68 (5.39-6.02)
Insulin (pmol/l)§	87.0 (61.2-123.0)	87.0 (60.0-120.6)	82.2 (61.2-113.4)	80.7 (59.4-106.8)	73.8 (55.2-99.3)
HOMA-IR	1.67 (1.18-2.30)	1.66 (1.17-2.26)	1.59 (1.18-2.12)	1.52 (1.14-2.02)	1.40 (1.07-1.88)
Triglycerides (mmol/l)	1.15 (0.83-1.82)	1.17 (0.82-1.80)	1.15 (0.80-1.71)	1.06 (0.73-1.61)	0.92 (0.65-1.38)
HDL cholesterol (mmol/l)	1.25 (0.34)	1.27 (0.33)	1.27 (0.33)	1.27 (0.33)	1.32 (0.33)
C-reactive protein (mg/l)	0.79 (0.36-1.92)	0.74 (0.35-1.68)	0.67 (0.33-1.49)	0.60 (0.32-1.37)	0.59 (0.29-1.25)
Interleukin-6 (pg/ml)¶	1.13 (0.73-1.86)	1.07 (0.73-1.65)	1.00 (0.62-1.49)	1.06 (0.69-1.57)	0.94 (0.61-1.49)

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance.

Data are n (%), mean (SD) or median (interquartile of rang).

*Blood pressure \geq 140/90 mm Hg, or current use of anti-hypertensive medications.

†77 participants were excluded with a missing value of self-reported CHD.

‡10 participants were excluded with a missing value of self-reported stroke.

§4 participants were excluded with a missing value of fasting insulin.

||23 participants were excluded with a missing value of HOMA-IR.

¶89 participants were excluded with a missing value of IL-6.

Table 2. Adjusted odds ratios and 95% confidence intervals of having metabolic syndrome according to quintiles of plasma 25-hydroxyvitamin D concentrations

	Quintiles of 25-hydroxyvitamin D (nmol/l)					<i>P</i> for trend
	Q5 ≥57.7	Q4 45.6-57.6	Q3 36.9-45.5	Q2 28.8-36.8	Q1 ≤28.7	
cases/participants	193/652	248/653	279/652	326/653	335/652	
Model 1*	1.00 (reference)	1.31 (1.03-1.66)	1.36 (1.07-1.73)	1.67 (1.31-2.13)	1.62 (1.26-2.08)	<0.0001
Model 2†	1.00 (reference)	1.31 (1.02-1.66)	1.38 (1.08-1.77)	1.76 (1.37-2.26)	1.64 (1.27-2.13)	<0.0001
Model 3‡	1.00 (reference)	1.28 (1.00-1.64)	1.33 (1.03-1.71)	1.71 (1.32-2.21)	1.52 (1.17-1.98)	0.0002

*Model 1: adjusted for age, sex, geographic location (Beijing/Shanghai), residential region (urban/rural) and visit date (April, or May/June).

†Model 2: further adjusted for education (≤6, 7-9, or ≥10 years in school), physical activity (low, moderate, or high), smoking (current, former, or never), alcohol drinking (yes/no), family history of cardiovascular disease (yes/no) and diabetes (yes/no), and self-reported coronary heart disease (yes/no) and stroke (yes/no).

‡Model 3: further adjusted for inflammatory factors (C-reactive protein and interleukin-6).

Table 3. Adjusted regression coefficients of 25-hydroxyvitamin D (nmol/l) with components of metabolic syndrome, HbA1c, fasting insulin and HOMA-IR*

	Model 1 †		Model 2 ‡		Model 3 §		Model 4	
	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
All (n = 3262)								
Fasting glucose (mmol/l)	-0.17 (0.08)	0.0277	-0.17 (0.08)	0.0337	-0.18 (0.08)	0.0262	-0.17 (0.08)	0.0281
HbA1c (%)	-0.21 (0.05)	<0.0001	-0.20 (0.05)	<0.0001	-0.21 (0.05)	<0.0001	-0.21 (0.05)	<0.0001
Fasting insulin (pmol/l)	-0.08 (0.02)	0.0004	-0.07 (0.02)	0.0036	-0.06 (0.02)	0.0088	-0.06 (0.02)	0.0114
HOMA-IR#	-0.09 (0.02)	0.0002	-0.07 (0.02)	0.0014	-0.07 (0.02)	0.0035	-0.06 (0.02)	0.0044
Waist circumference (cm)	-1.61 (0.46)	0.0005	-1.64 (0.47)	0.0005	-1.46 (0.48)	0.0023	-	-
Triglycerides (mmol/l)**	-0.13 (0.03)	<0.0001	-0.12 (0.03)	<0.0001	-0.11 (0.03)	<0.0001	-0.10 (0.03)	<0.0001
HDL cholesterol (mmol/l)††	0.07 (0.01)	<0.0001	0.07 (0.02)	<0.0001	0.06 (0.02)	<0.0001	0.06 (0.01)	<0.0001
Diastolic pressure (mmHg)	-1.29 (0.48)	0.0072	-1.32 (0.49)	0.0074	-1.25 (0.50)	0.0122	-1.15 (0.48)	0.0169
Systolic pressure (mmHg)	-1.37 (0.95)	0.1486	-1.52 (0.98)	0.1185	-1.28 (0.99)	0.1964	-1.08 (0.95)	0.2577
Gender								
Men (n = 1443)								
Triglycerides (mmol/l)	-0.19 (0.04)	<0.0001	-0.19 (0.04)	<0.0001	-0.19 (0.04)	<0.0001	-0.19 (0.04)	<0.0001
HDL cholesterol (mmol/l)	0.10 (0.02)	<0.0001	0.10 (0.02)	<0.0001	0.10 (0.02)	<0.0001	0.10 (0.02)	<0.0001
Women (n = 1819)								
Triglycerides (mmol/l)	-0.07 (0.04)	0.0574	-0.04 (0.04)	0.2554	-0.03 (0.04)	0.4546	-0.02 (0.03)	0.5907
HDL cholesterol (mmol/l)	0.03 (0.02)	0.0841	0.03 (0.02)	0.1182	0.02 (0.02)	0.3121	0.02 (0.02)	0.4327
Obesity status								
BMI <24 kg/m ² (n = 1526)								
Fasting insulin (pmol/l)	-0.04 (0.03)	0.2653	-0.03 (0.03)	0.4596	-0.02 (0.04)	0.5948	-	-
HOMA-IR	-0.03 (0.03)	0.2977	-0.02 (0.03)	0.4530	-0.02 (0.03)	0.5874	-	-
BMI ≥24 kg/m ² (n = 1736)								
Fasting insulin (pmol/l)	-0.14 (0.03)	<0.0001	-0.13 (0.03)	<0.0001	-0.12 (0.03)	0.0001	-	-
HOMA-IR	-0.15 (0.03)	<0.0001	-0.13 (0.03)	<0.0001	-0.13 (0.03)	<0.0001	-	-

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance.

*25-hydroxyvitamin D, fasting insulin, HOMA-IR and triglycerides were log transformed before analysis.

†Model 1: adjusted for age, sex (not for sex-stratified analysis), geographic location (Beijing/Shanghai), residential region (urban/rural) and visit date (April, or May/June).

‡Model 2: further adjusted for education (≤ 6 , 7-9, or ≥ 10 years in school), physical activity (low, moderate, or high), smoking (current, former, or never), alcohol drinking (yes/no), family history of cardiovascular disease (yes/no) and diabetes (yes/no), and self-reported coronary heart disease (yes/no) and stroke (yes/no). For fasting glucose, HbA1c, fasting insulin and HOMA-IR, hypertension (yes/no) was included in the model.

§Model 3: further adjusted for inflammatory factors (C-reactive protein and interleukin-6, continuous variables).

||Model 4: further adjusted for BMI (not for waist circumference and obesity status-stratified analysis).

¶4 participants were excluded with a missing value of fasting insulin; *P* for interaction between 25-hydroxyvitamin D and obesity status: 0.0363.

#23 participants were excluded with a missing value of HOMA-IR; *P* for interaction between 25-hydroxyvitamin D and obesity status: 0.0187.

***P* for interaction between 25-hydroxyvitamin D and sex: 0.0034.

††*P* for interaction between 25-hydroxyvitamin D and sex: 0.0027.