Original Article

Polymorphisms of the Vitamin D Receptor Gene and Sex-Differential Associations with Lipid Profiles in Chinese Han Adults*

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Abstract

Objective To explore the association of single nucleotide polymorphisms (SNPs) of the vitamin D receptor gene (*VDR*) with circulating lipids considering gender differences.

Methods Of the Han Chinese adults recruited from a health examination center for inclusion in the study, the circulating lipids, 25-hydroxyvitamin D (25OHD), and other parameters were measured. The *VDR* SNPs of *Cdx2* (rs11568820), *Fok1* (rs2228570), *Apa1* (rs7975232), and *Taq1* (rs731236) were genotyped with a qPCR test using blood DNA samples, and their associations with lipids were analyzed using logistic regression.

Results In the female participants (n = 236 with dyslipidemia and 888 without dyslipidemia), multiple genotype models of *Fok1* indicated a positive correlation of B (not A) alleles with LDLC level ($P < 0.05$). In the male participants (n = 299 with dyslipidemia and 564 without dyslipidemia), the recessive model of *Cdx2* and the additive and recessive models of *Fok1* differed ($P < 0.05$) between the HDLC-classified subgroups, respectively, and *Fok1* BB and *Cdx2* TT presented interactions with 25OHD in the negative associations with HDLC ($P < 0.05$).

Conclusion In the Chinese Han adults included in the study, the *Fok1* B-allele of *VDR* was associated with higher LDLC in females, and the *Fok1* B-allele and the *Cdx2* T-allele of *VDR* were associated with lower HDLC in males. The interaction of VD and *Fok1* BB or *Cdx2* TT in males synergistically decreased HDLC levels.

Key words: Vitamin D; Vitamin D receptor; Gene polymorphism; Lipid; Dyslipidemia

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INTRODUCTION

Vitamin D (VD) is a micronutrient for human health, which is predominantly derived from 7-dehydrocholesterol in the skin under sunlight exposure and is also absorbed from food as a secondary source. Through two steps of hydroxylation, VD is converted to 25-hydroxyvitamin D (25OHD) and then 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. The circulating

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concentration of 25OHD is generally used as a biomarker of VD status, and 1,25$(OH)_2$D is the functional metabolite working in the manner of a hormone in the osseous and extra-osseous metabolisms[1]. Previous studies suggested that VD deficiency was associated with abdominal obesity and/or dyslipidemia[2], and many studies supported the opinion that VD supplementation was beneficial for ameliorating lipid profiles[3]. However, confounders in various populations led to inconsistency for each of the lipid parameters, namely triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDLC), and high-density lipoprotein cholesterol (HDLC), as suggested by human studies and meta-analyses[3,4]. Researchers have to conduct a close examination of those potential confounders and pay special attention to the functioning of the VD receptor (VDR), which is the most important mediator of the VD function[5].

VDR gene variants have the potential to influence biological outcomes[5,6]. It has been reported that VDR has an effect on skeletal muscles independent of VD, and the decreased expression of VDR protein is related to various disease states and aging[7]. In the VDR knockout animal model, a decreased size and muscle fiber strength were observed, and VDR expression is also required in myoblasts[8,9]. Aside from skeletal health status, it was also reported that the single nucleotide polymorphisms (SNPs) of *VDR* were associated with risks to non-skeletal health[6], such as myocardial infarction, cancer, and death[10]. Moreover, these kinds of associations aroused concerns about dyslipidemia since expressions of some lipid metabolism-related genes are regulated by calcitriol-stimulation[11], and some may even have VD-responsive elements (VDREs) to bind the 1,25$(OH)_2$D-activated VDR[12]. Thus, both the VD status and the VDR function have the potential to affect the expressions of lipid metabolic genes, ultimately affecting the physiological activities of cells[1]. Moreover, by involving biological (in terms of reproductive function, sexual hormones, expressions of heterosome-located genes, etc.) and lifestyle (e.g., smoking, drinking, physical activity, etc.) factors[13], sexual dimorphism should be taken into careful consideration when conducting medical research[14].

Located on chromosome 12, the *VDR* gene spans at least 75 kb in length. From the 5'–3' direction of its sense (forward) strand, *Cdx2* (rs11568820, C > T), *Fok1* [rs2228570, A > B (degenerate base standing for C, G, and T, i.e., not A)], *Apa1* (rs7975232, C > A), and *Taq1* (rs731236, A > G) are the generally the relevant SNPs in various ethnicity groups[15-17]. These SNPs may affect mRNA expression, amino acid sequence, and protein activity. Particularly, *VDR* SNPs have been reported to have effects on 25OHD levels in circulation[18,19]. For example, Santos et al.[20] studied a group of Brazilian girls aged 7–18 years and found that the *VDR* wild-types of *Bsm1*, *Apa1*, and *Taq1* were associated with lower 25OHD levels. Therefore, it is necessary to further explore the relationship between *VDR* SNPs and specific lipid parameters, as well as VD status in both females and males. In the present study, we focused on the *VDR* SNPs of *Apa1*, *Cdx2*, *Fok1*, and *Taq1* in this regard, which have been studied in genotype-phenotype associations, in order to avoid weak evidence or unknown biological significance for less studied or new SNPs regarding their associations with lipids.

METHODS

Subjects and Sample Collection

The sample size (N) was estimated with the formula $N \geq (Z_{1-\alpha/2}/\delta)^2 \times p \times (1 - p)$, wherein Z was 1.96 for the two-sided 95% confidential intervals (*CI*s), P was the dyslipidemia prevalence of 34.64% in Shenzhen adults as known in 2012 but unpublished at the design stage of our study[21], δ was 2.2%, representing tolerable error, and the calculated N was 1,798.

After signing written consent forms to be subjects in the study, adult volunteers visiting a health examination center in Shenzhen City in Guangdong Province, China, were recruited between July 2013 and January 2014. A questionnaire survey administered *via* face-to-face interview was conducted to collect the basic health information of each participant. The inclusion criteria were: 1) Han Chinese aged ≥ 20 years old; 2) living in Shenzhen for > 2 years; 3) free of liver diseases, renal diseases, and any cancers in the past six months; and 4) not pregnant (for women). The excluded subjects were those who 1) had severe organic diseases, 2) had acute infection symptoms, allergic diseases, and malignant tumors, 3) had a family history of genetic diseases including familial dyslipidemia, 4) had taken VD supplements in the past six months, 5) had taken medicines to control lipid levels within the past 12 hours, or 6) had taken diuretics, engaged in strenuous exercise, or had overeaten within the 24 hours before the test.

From ulnar veins of the subjects, who had fasted overnight, blood samples were collected with vacuum tubes, and within two hours post-collection,

supernatant and blood cells were separated by centrifugation of 3,000 ×*g* at 4 °C for 10 min. The body mass index (BMI) was calculated as body weight (kg)/ height $(m)^2$. The above protocol for the cross-sectional study was approved by the Ethics Committee of the Shenzhen Center for Chronic Disease Control and was in accordance with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (registration ID number NCT04707612).

Index Measurement

Parameters of lipids, glucose, hemogram, etc., were assayed right on the day, and the rest of the samples were aliquoted with EP tubes and stored at -80 °C for later use. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the subjects were measured by a standard mercury sphygmomanometer. Glycated hemoglobin (HbA1c) was detected with a Japan Arkray Instruments analyzer (ion chromatography method). The serum levels of TG, TC, LDLC, HDLC, and fasting plasma glucose (FPG) were tested by the Beckman-LX20 automatic biochemical analyzer. The plasma 25OHD concentration was detected with a commercial ELISA kit (Cat. #: AC-57F1, IDS Ltd., UK). According to the Chinese guidelines for dyslipidemia management[22], TG ≥ 2.3 mmol/L, TC ≥ 6.2 mmol/L, LDLC ≥ 4.1 mmol/L, HDLC < 1.0 mmol/L, or previously diagnosed dyslipidemia, were the criteria used to define the dyslipidemia group (DL), and those subjects who did not match the DL criteria were assigned to the non-dyslipidemia group (ND).

In the logistic analyses, from the viewpoint of preventive medicine, as well as to avoid the small subject numbers for the genotypes of low minor allele frequency (MAF)[23], the available marginally-elevated cut-off values for TG (≥ 1.7 mmol/L), TC (≥ 5.2 mmol/L), and LDLC (≥ 3.4 mmol/L), as well as the only available cut-off value for HDLC (< 1.0 mmol/L), were used to define the abnormal subgroups for the corresponding lipid parameters.

DNA Preparation and SNP Genotyping

The protocols for DNA preparation and SNP genotyping described in our previous studies[23,24] were also adopted in the present study. Briefly, an asymmetric amplification with molecular beacon-based real-time quantitative PCR (MB-qPCR) followed by a melting step was performed to determine the variation of the SNP loci. Before its application to the large sample size analysis, the method was verified with the gold standard of Sanger sequencing (ThermoFisher, Shanghai, China). The information of primers and molecular beacons for the genotyping experiment with qPCR (Roche 480II, Singapore) is presented in Supplementary Table S1, available in www.besjournal.com.

The nucleotide bases used in our study were consistent with those in dbSNP of NCBI, i.e., C > T for rs11568820 (*Cdx2*), A > B (not A) for rs2228570 (*Fok1*), C > A for rs7975232 (*Apa1*), and A > G for rs731236 (*Taq1*). If the complementary bases [G > A for *Cdx2*, T > V (standing for A, C, and G) for *Fok1*, G > T for *Apa1*, and T > C for *Taq1*], or the letter standing for the DNA-digestibility with the corresponding restriction enzyme (*f* > *F* for *Fok1*, *a* > *A* for *Apa1*, and *T* > *t* for *Taq1*), were used in the references, the original usages were provided as bracketed annotations in our article.

Data Analysis

The statistical analyses were performed using SPSS for Windows version 25 (IBM Corp., Armonk, NY, USA). Clinical data were presented as medians and interquartile ranges (25% to 75%) and compared with rank-sum tests (Wilcoxon rank test or Kruskal-Wallis rank test). The genotypes of the four SNPs were tested with Hardy-Weinberg equilibrium (HWE) analyses for sampling representation. For genotypic comparisons, differences in allele and genotype frequencies were evaluated using the chi-square (χ^2) test. The homozygous genotypes of CC for *Cdx2*, AA for *Fok1*, CC for *Apa1*, and AA for *Taq1* were used as reference genotypes, respectively. For both genders, the additive, dominant, recessive, homozygous, and allelic models for each of the SNPs were entered into the logistic regression analyses for odds ratios (*OR*s) and 95% *CI*s with adjustment for age, BMI, FPG, HbA1c, 25OHD, SBP, and DBP. In order to analyze the interaction between VD nutritional levels and *VDR* SNPs, the interaction factor calculated by 25OHD concentrations and *VDR* SNPs were entered into the logistic regression with adjustment for those confounders mentioned above. A simple linear regression was used to assess the association between circulating 25OHD and lipid profiles. A *P*-value of less than 0.05 was considered to be statistically significant.

RESULTS

Clinical Profiles of the Participants

A total of 1,987 adults were included in the analysis, aged from 20 to 81 years old. Among them,

there were 1,124 females aged 39 (31–49) (median and interquartile range) years old and 863 males aged 36 (30–44) years old. The clinical profiles of the participants were divided into DL and ND for each gender, as summarized in Table 1. It was indicated that several metabolic or metabolism-related parameters were statistically different between DL and ND adults ($P < 0.05$), such as age, BMI, FPG, HbA1c, SBP, DBP, TG, TC, LDLC, HDLC, etc. In particular, 25OHD concentrations were statistically different between DL and ND groups in men but not in women.

Genotypic Frequencies of VDR

The results of the genotyping experiment on the SNPs with MB-qPCR are shown in Supplementary Figure S1, available in www.besjournal.com. The HWE test showed that the population sampled from the Health Examination Center was representative of the population at large (Supplementary Table S2, available in www.besjournal.com). The genotypic and allelic frequencies of *VDR* SNPs between DL and ND groups are summarized in Supplementary Table S3, available in www.besjournal.com. In the female participants, both genotypic and allelic frequencies of *Fok1* showed differences between DL and ND groups ($P < 0.05$); while in the male participants, these differences were not observed. The genotypic and allelic frequencies of the other three SNPs, namely *Cdx2*, *Apa1*, and *Taq1*, did not display significant differences between the DL and ND groups for either gender ($P \geq 0.05$), and neither did their different genetic models (Supplementary Tables S4–S6, available in www.besjournal.com).

Logistic Regression Analyses of the Relationship between VDR SNPs and Dyslipidemia

Logistic regression analyses were performed with adjustment for age and BMI since the adjustment for 25OHD did not change the overall correlations (see Supplementary Tables S7–S8). For female participants (see Table 2), between the subgroups of LDLC (≥ 3.4 *vs*. < 3.4 mmol/L), *VDR Fok1* presented significance ($P < 0.05$) in its additive (BB *vs*. AB *vs*. AA, $P = 0.03$, $OR = 1.28$, 95% *CI*: 1.03–1.59), recessive (BB *vs.* AB + AA, $P = 0.03$, $OR = 1.44$, 95% *CI*: 1.04–2.00), homozygous (BB *vs*. AA, $P = 0.02$, $OR = 2.89$, 95% *CI*: 1.18–7.05), and allelic (B *vs.* A, $P = 0.04$, $OR = 1.26$, 95% *CI*: 1.01–1.59) models, but between the subgroups of TC (≥ 5.2 *vs*. < 5.2 mmol/L) and HDLC (< 1.0 *vs.* ≥ 1.0 mmol/L), no significance ($P \geq 0.05$) was found in all models of the four SNPs.

Table 3 displays the logistic regression analyses of the relationships between the lipids and the SNPs of *VDR* in the male participants. Between the subgroups of HDLC (< 1.0 *vs*. ≥ 1.0 mmol/L), the data presented significance ($P < 0.05$) in the recessive model of *Cdx2* (TT *vs*. CT + CC, $P = 0.04$, $OR = 2.70$, 95% *CI*: 1.08–6.80)

Table 1. Clinical profiles of study subjects (medians and interquartile ranges)

Variables	Female			Male		
	DL (n = 236)	ND (n = 888)	P-value	DL (n = 299)	ND (n = 564)	P-value
Age, y	50 (38.3–57)	36 (30–46)	< 0.001	39 (33–47)	33 (29–42)	< 0.001
BMI, kg/m^2	23.1 (21.1–24.9)	21.6 (20.0–23.2)	< 0.001	25.3 (24.0–27.0)	23.9 (22.0–25.6)	< 0.001
25OHD, nmol/L	59.3 (49.6–71.3)	58.4 (49.2–68.3)	0.245	60.8 (50.8–71.1)	63.4 (54.3–73.6)	0.005
Sun exposure time, min/w	23.0 (10.0–39.0)	20.0 (10.0–39.0)	0.680	24.0 (10.0–41.0)	24.0 (13.0–50.0)	0.135
FPG, mmol/L	5.6 (5.3–6.0)	5.3 (5.0–5.6)	< 0.001	5.5 (5.2–5.9)	5.3 (5.0–5.6)	< 0.001
HbA1c, %	5.8 (5.5–6.1)	5.5 (5.4–5.7)	< 0.001	5.7 (5.5–6.0)	5.6 (5.4–5.8)	< 0.001
SBP, mmHg	118 (108–133.8)	111.5 (104–121)	< 0.001	126 (118–136)	121.5 (112–131)	< 0.001
DBP, mmHg	71 (64–79)	67 (61–73)	< 0.001	77 (71–85)	73 (67–80)	< 0.001
TG, mmol/L	1.7 (1.0–2.8)	0.8 (0.6–1.1)	< 0.001	2.7 (2.1–3.6)	1.2 (0.9–1.6)	< 0.001
TC, mmol/L	6.4 (5.4–6.9)	4.9 (4.4–5.4)	< 0.001	5.7 (4.7–6.4)	5.0 (4.4–5.5)	< 0.001
LDLC, mmol/L	3.7 (3.0–3.9)	2.7 (2.4–3.1)	< 0.001	3.2 (2.7–3.7)	2.8 (2.5–3.1)	< 0.001
HDLC, mmol/L	1.6 (1.4–1.8)	1.4 (1.3–1.6)	< 0.001	1.5 (1.3–1.6)	1.3 (1.2–1.5)	< 0.001

Note. BMI: body mass index; DBP: diastolic blood pressure; DL: dyslipidemia; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; ND: non-dyslipidemia; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride.

and the additive (BB *vs.* AB *vs.* AA, $P = 0.02$, $OR = 2.25$, 95% *CI*: 1.12–4.52) and recessive (BB *vs.* AB + AA, $P = 0.02$, $OR = 2.73$, 95% *CI*: 1.11–6.70) models of *Fok1*, while other models of the genotype showed no significance ($P \geq 0.05$). Differences were not found for *Apa1* and *Taq1* between the subgroups defined by any of the lipid profiles ($P \geq 0.05$).

Comparison of 25OHD Concentration

No differences were found in the comparison of

Table 2. Logistic regression analyses of lipids with SNPs of *VDR* in adult females with adjustment for age and body mass index

Gene models	TG ≥ 1.7 *vs*. < 1.7 mmol/L		TC ≥ 5.2 *vs*. < 5.2 mmol/L		LDLC ≥ 3.4 *vs*. < 3.4 mmol/L		HDLC < 1.0 *vs*. ≥ 1.0 mmol/L	
	P	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)
Apa1 (rs7975232)								
Add.: AA *vs*. AC *vs*. CC	0.45	1.11 (0.84–1.48)	0.47	0.93 (0.75–1.14)	0.39	1.11 (0.87–1.42)	0.93	1.03 (0.52–2.02)
Dom.: AA + AC *vs*. CC	0.59	1.11 (0.77–1.59)	0.34	0.88 (0.67–1.15)	0.59	1.09 (0.79–1.50)	0.84	1.10 (0.45–2.69)
Rec.: AA *vs*. AC + CC	0.76	1.10 (0.61–1.98)	0.86	0.96 (0.62–1.48)	0.35	1.27 (0.77–2.09)	0.95	0.96 (0.22–4.22)
Hom.: AA *vs*. CC	0.20	0.25 (0.03–2.05)	0.56	1.31 (0.53–3.22)	0.17	2.01 (0.74–5.50)	0.84	1.29 (0.12–13.92)
Alle.: A *vs*. C	0.44	1.12 (0.84–1.51)	0.36	0.90 (0.73–1.12)	0.61	1.07 (0.83–1.38)	0.87	1.06 (0.52–2.19)
Cdx2 (rs11568820)								
Add.: TT *vs*. CT *vs*. CC	0.13	0.82 (0.64–1.06)	0.77	0.97 (0.81–1.17)	0.76	1.04 (0.83–1.29)	0.35	0.74 (0.40–1.38)
Dom.: TT + CT *vs*. CC	0.09	0.72 (0.50–1.05)	0.30	0.86 (0.65–1.14)	0.70	1.07 (0.77–1.49)	0.74	0.85 (0.34–2.14)
Rec.: TT *vs*. CT + CC	0.57	0.88 (0.56–1.37)	0.48	1.12 (0.82–1.55)	0.99	1.00 (0.68–1.48)	0.20	0.38 (0.09–1.65)
Hom.: TT *vs*. CC	0.33	0.61 (0.23–1.64)	0.23	1.49 (0.77–2.88)	0.58	1.26 (0.56–2.84)	0.34	0.33 (0.04–3.16)
Alle.: T *vs*. C	0.10	0.80 (0.62–1.04)	0.81	0.98 (0.81–1.18)	0.70	0.96 (0.76–1.20)	0.27	0.70 (0.37–1.33)
Fok1 (rs2228570)								
Add.: BB *vs*. AB *vs*. AA	0.54	1.08 (0.84–1.39)	0.36	1.09 (0.91–1.30)	**0.03**	1.28 (1.03–1.59)	0.63	1.16 (0.64–2.13)
Dom.: BB + AB *vs*. AA	0.49	1.17 (0.75–1.81)	0.67	1.07 (0.78–1.46)	0.20	1.29 (0.88–1.90)	0.59	0.77 (0.29–2.01)
Rec.: BB *vs*. AB + AA	0.69	1.08 (0.74–1.59)	0.28	1.17 (0.88–1.54)	**0.03**	1.44 (1.04–2.00)	0.19	1.80 (0.75–4.30)
Hom.: BB *vs*. AA	0.27	0.60 (0.24–1.48)	0.76	1.11 (0.58–2.11)	**0.02**	2.89 (1.18–7.05)	0.95	1.06 (0.16–7.25)
Alle.: B *vs*. A	0.30	1.15 (0.89–1.49)	0.20	1.13 (0.94–1.36)	**0.04**	1.27 (1.01–1.59)	0.46	1.27 (0.67–2.40)
Taq1 (rs731236)								
Add.: GG *vs*. AG *vs*. AA	0.10	0.57 (0.29–1.11)	0.36	0.81 (0.53–1.24)	0.81	0.94 (0.57–1.55)	0.86	0.87 (0.20–3.83)
Dom.: GG + AG *vs*. AA	0.13	0.59 (0.30–1.17)	0.38	0.82 (0.53–1.28)	0.88	0.96 (0.57–1.62)	0.94	0.95 (0.20–4.48)
Rec.: GG *vs*. AG + AA	1.00	0.00 (0.00–NA)	0.47	0.43 (0.05–4.10)	0.93	1.11 (0.12–10.47)	1.00	0.00 (0.00–NA)
Hom.: GG *vs*. AA	NA	NA (NA–NA)	NA	NA (NA–NA)	NA	NA (NA–NA)	NA	NA (NA–NA)
Alle.: G *vs*. A	0.11	0.58 (0.30–1.14)	0.31	0.80 (0.52–1.23)	0.72	0.91 (0.55–1.51)	0.88	0.89 (0.19–4.07)

Note. Abbreviations: Add.: additive model; Alle.: allelic model; B: degenerate base standing for C, G, and T; *CI*: confidence interval; Dom.: dominant model; HDLC: high-density lipoprotein cholesterol; Hom.: homozygous model; LDLC: low-density lipoprotein cholesterol; NA: not available; *OR*: odds ratio; Rec.: recessive model; SNPs: single nucleotide polymorphisms; TC: total cholesterol; TG: triglyceride; *VDR*: vitamin D receptor gene.

25OHD concentrations across genotype models of *VDR* gene polymorphisms in both genders (see Supplementary Table S9, available in www.besjournal.com). When the plasma 25OHD concentrations in subjects with abnormal and normal lipid profiles were compared, it was shown that women with low HDLC had higher 25OHD while men with high TG had lower 25OHD than the subjects with normal lipid parameters ($P < 0.05$, Supplementary Table S10, available in www.besjournal.com).

Table 3. Logistic regression analyses of lipids with SNPs of *VDR* in adult males with adjustment for age and body mass index

Gene models	TG ≥ 1.7 *vs.* < 1.7 mmol/L		TC ≥ 5.2 *vs.* < 5.2 mmol/L		LDLC ≥ 3.4 *vs.* < 3.4 mmol/L		HDLC < 1.0 *vs.* ≥ 1.0 mmol/L	
	P	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)
Apa1 (rs7975232)								
Add.: AA *vs.* AC *vs.* CC	0.65	1.06 (0.83–1.34)	0.89	0.98 (0.79–1.23)	0.86	0.98 (0.74–1.29)	0.12	1.71 (0.88–3.31)
Dom.: AA + AC *vs.* CC	0.54	1.10 (0.81–1.49)	0.43	0.89 (0.67–1.18)	0.71	0.94 (0.66–1.33)	0.13	2.10 (0.80–5.48)
Rec.: AA *vs.* AC + CC	0.90	1.04 (0.62–1.74)	0.27	1.32 (0.81–2.15)	0.88	1.05 (0.57–1.92)	0.50	1.55 (0.43–5.53)
Hom.: AA *vs.* CC	0.85	1.09 (0.44–2.72)	0.26	1.67 (0.68–4.09)	0.55	1.36 (0.50–3.73)	0.28	3.17 (0.40–25.19)
Alle.: A *vs.* C	0.49	1.09 (0.85–1.40)	0.66	1.05 (0.84–1.33)	0.86	0.98 (0.73–1.30)	0.34	1.40 (0.70–2.78)
Cdx2 (rs11568820)								
Add.: TT *vs.* CT *vs.* CC	0.66	0.96 (0.78–1.17)	0.09	0.85 (0.71–1.03)	0.46	0.92 (0.73–1.16)	0.10	1.65 (0.91–3.00)
Dom.: TT + CT *vs.* CC	0.90	0.98 (0.72–1.33)	0.14	0.81 (0.61–1.07)	0.65	0.92 (0.65–1.31)	0.54	1.36 (0.51–3.59)
Rec.: TT *vs.* CT + CC	0.56	0.90 (0.62–1.29)	0.20	0.80 (0.57–1.13)	0.40	0.83 (0.54–1.28)	**0.04**	2.70 (1.08–6.80)
Hom.: TT *vs.* CC	0.12	1.87 (0.85–4.13)	0.71	0.87 (0.40–1.86)	0.90	1.06 (0.43–2.61)	0.19	4.71 (0.46–48.16)
Alle.: T *vs.* C	0.67	0.95 (0.77–1.18)	0.15	0.86 (0.71–1.06)	0.45	0.91 (0.71–1.17)	0.28	1.43 (0.74–2.76)
Fok1 (rs2228570)								
Add.: BB *vs.* AB *vs.* AA	0.48	0.93 (0.75–1.15)	0.08	0.84 (0.68–1.02)	0.80	1.03 (0.81–1.32)	**0.02**	2.25 (1.12–4.52)
Dom.: BB + AB *vs.* AA	0.80	0.96 (0.66–1.37)	0.32	0.84 (0.60–1.18)	0.60	1.12 (0.73–1.73)	0.22	2.53 (0.58–11.06)
Rec.: BB *vs.* AB + AA	0.43	0.88 (0.63–1.21)	0.07	0.75 (0.56–1.02)	0.91	0.98 (0.67–1.43)	**0.03**	2.73 (1.11–6.70)
Hom.: BB *vs.* AA	0.83	1.09 (0.51–2.34)	0.82	1.09 (0.52–2.29)	0.79	1.13 (0.46–2.74)	0.78	0.75 (0.10–5.83)
Alle.: B *vs.* A	0.45	0.92 (0.74–1.14)	0.16	0.87 (0.71–1.06)	0.58	1.07 (0.84–1.38)	0.10	1.82 (0.90–3.70)
Taq1 (rs731236)								
Add.: GG *vs.* AG *vs.* AA	0.64	1.13 (0.68–1.85)	0.69	1.10 (0.69–1.76)	0.32	0.73 (0.39–1.37)	0.65	0.71 (0.15–3.24)
Dom.: GG + AG *vs.* AA	0.69	1.12 (0.66–1.90)	0.74	1.09 (0.66–1.79)	0.44	0.77 (0.40–1.48)	0.84	0.85 (0.19–3.94)
Rec.: GG *vs.* AG + AA	0.79	1.34 (0.16–11.27)	0.46	2.42 (0.24–24.75)	1.00	0.00 (0.00–NA)	1.00	0.00 (0.00–NA)
Hom.: GG *vs.* AA	NA	NA (NA–NA)	NA	NA (NA–NA)	NA	NA (NA–NA)	NA	NA (NA–NA)
Alle.: G *vs.* A	0.62	1.14 (0.68–1.90)	0.66	1.11 (0.69–1.80)	0.32	0.72 (0.38–1.37)	0.70	0.74 (0.17–3.34)

Note. Abbreviations: Add.: additive model; Alle.: allelic model; B: degenerate base standing for C, G, and T; *CI*: confidence interval; Dom.: dominant model; HDLC: high-density lipoprotein cholesterol; Hom.: homozygous model; LDLC: low-density lipoprotein cholesterol; NA: not available; *OR*, odds ratio; Rec.: recessive model; SNPs: single nucleotide polymorphisms; TC: total cholesterol; TG: triglyceride; *VDR*: vitamin D receptor gene.

Relationship between Circulating 25OHD and Lipid Profiles

In men, lg TG (β = −0.003, P < 0.001), LDLC (β = −0.003, P = 0.006), and HDLC (β = −0.001, P = 0.025) were inversely associated with the 25OHD concentration while in women, none of the lipid profiles showed a significant correlation with the 25OHD concentration (P ≥ 0.05, Supplementary Table S11, available in www.besjournal.com).

Interaction between VD Nutritional Status and VDR SNPs on the Occurrence of Dyslipidemia

According to the logistic regression results (see Tables 2 and 3) and the simple linear regression results (see Supplementary Table S11), VD and *VDR* SNPs had some parameters that were related to the results of dyslipidemia. Therefore, we further explored whether VD and *VDR* SNPs were synergistic or antagonistic to the results of dyslipidemia. The results (see Table 4) further showed that in men, the combined effect of VD, *Fok1* BB (P = 0.02, *OR* = 1.03, 95% *CI*: 1.01–1.06), and *Cdx2* TT (P = 0.02, *OR* = 1.03, 95% *CI*: 1.01–1.06) synergistically led to a decrease in HDLC levels while in women, there was no significant difference in the interaction between VD and *Fok1* or *Cdx2* (*OR* < 1 and P ≥ 0.05) on the lipid profiles.

DISCUSSION

Cellular and animal studies have demonstrated that both VD and VDR play important roles in adipocyte differentiation[25,26]. VD activates VDR to inhibit the differentiation of pre-adipocytes into mature adipocytes *in vitro* at an early stage[27,28], and gene expression data showed that the abundance of *VDR* mRNA was changed in the process of adipocyte differentiation[29-31]. In *Vdr* knockout mice, VD could not block the expression of peroxisome proliferator-activated receptor γ (PPARγ) and the corresponding adipocyte differentiation, which indicated that VDR was a key mediator of VD in adipocyte differentiation[27,28]. The TC level of *Vdr* knockout mice was more than 20% higher than that of wild-type mice[32]. Therefore, the existence of VDR is very important for the healthy regulation of serum lipid profiles, and it is speculated that VDR has the function of lowering TC levels. Knockout of *Vdr* in macrophages will cause insulin resistance and promote the movement of cholesterol, accelerating atherosclerosis in mice[33]. The above all suggest that the perfect function of VDR has a positive effect on the normal lipid metabolism process.

As SNPs of a gene may impact gene expression, as well as the structure and function of the encoded protein and the consequent phenotypes, *VDR* polymorphisms have been found to modify the risk of metabolic diseases[34]. Among the SNPs of *VDR*, *Fok1* is the most widely studied. Some studies have found that the AA (complementary to TT, i.e., *ff*) carriers of *Fok1* had higher TC in Arab adults[35], lower HDLC and higher TG in Moroccans[36], and

Table 4. Interactions between plasma 25OHD concentrations and SNPs of *VDR*, *Cdx2* (rs11568820) and *Fok1* (rs2228570) on the occurrence of dyslipidemia

Genotype	Female		Male	
	LDLC, ≥ 3.4 *vs*. < 3.4 mmol/L		HDLC, < 1.0 *vs*. ≥ 1.0 mmol/L	
	P	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)
Cdx2				
CC	–	–	0.11	1.02 (1.00–1.05)
CT	–	–	0.28	1.02 (0.99–1.05)
TT	–	–	**0.02**	1.03 (1.01–1.06)
Fok1				
AA	0.08	0.99 (0.98–1.00)	0.46	1.01 (0.98–1.05)
AB	0.13	0.99 (0.98–1.00)	0.17	1.02 (0.99–1.05)
BB	0.58	1.00 (0.99–1.01)	**0.02**	1.03 (1.01–1.06)

Note. Abbreviations: 25OHD: 25-hydroxyvitamin D; B: degenerate base standing for C, G, and T; *CI*: confidence interval; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; *OR*: odds ratio; SNPs: single nucleotide polymorphisms; TG: triglyceride; –: interaction analyses were not conducted due to negative findings in the logistic regression analyses for the genotypes.

higher LDLC in Chinese individuals[37]. Moreover, *Fok1* A allele carriers had a higher risk of having coronary heart disease, and patients with a BB (or *FF*, e.g., GG) genotype had a higher level of HDLC[38]. The genetic benefits of AA (*ff*) or risk of BB (*FF*) or their alleles were also reported for other lipid parameters, or even the same lipid parameters, in different studies. In adult male Poles, the AA (*ff*) genotype carriers had lower fasting insulin and higher HDLC[39]. Similarly, in the men in our study, the AA (*ff*) genotype carriers had higher HDLC. In the Han Chinese population, the risk of dyslipidemia was associated with the BB (e.g., CC) genotype in the elderly male T2D patients of Beijing[40] and with the B (e.g., C) allele in a community-based population in Nanjing[37]. Largely consistent with these findings, we found that the B allele was positively associated with LDLC in women and that the BB genotype was negatively associated with HDLC in men.

The other three *VDR* SNPs, *Cdx2*, *Apa1*, and *Taq1*, were also reported to be associated with lipid profiles. For example, regarding the *Cdx2* polymorphism of *VDR* in a Lebanese student cohort, CC (GG) or CT (AG) carriers of both genders had higher LDLC than the TT (AA) carriers[41]. Higher TC and LDLC levels were also observed in the *Apa1* A allele (T or *A*) (Russian)[42] and *Apa1* CA (GT) (Chinese)[43] carriers than in the CC (GG) carriers. The *VDR Taq1* AA (TT) genotype was associated with increased TG and HDLC levels compared to the genotypes of GG (CC) and GA (CT) in obese Greek subjects[44]. However, *Taq1* GA and GG genotypes were associated with higher TC and LDLC levels in T2D patients (Arab)[45], and the GA genotype exhibited a higher TC concentration compared with the AA genotypes (Arab)[46]. However, Karonova and colleagues[42] noted that no difference was found regarding the association between *Taq1* and any lipid parameter. These findings suggested that the associations between *VDR* SNPs and the individual lipid parameters differed among various races or health conditions.

In general, gender differences and sexual dimorphism also affect the genotype and phenotype association. Studies from Lebanon, Poland, and Brazil concluded that men with *Fok1* B (*F*) had lower HDLC and higher TG levels[39,41,47] while female students with the A allele (*f*) had higher TC and LDLC[41]. By analyzing genotypic frequencies of the four *VDR* SNPs between the DL and ND groups in our study, we found that *Fok1* showed significant differences between the two groups. Adjusting for age and BMI, we found that *VDR Fok1* B (C, G, and T) alleles were related to the occurrence of high LDLC in the female group and low HDLC in the male group. Moreover, *VDR Cdx2* T was related to low HDLC in the male group. Gender-specific differences between *VDR* SNPs and various cardiovascular risk factors and adiponectin[41] also suggest that *VDR* SNPs may be a predictor of cardiovascular diseases. Thus, based on our findings, *Fok1* B in both sexes and *Cdx2* T in men may serve as predictors for dyslipidemia and related diseases, including cardiovascular diseases.

Though it has been widely acknowledged that plasma or serum 25OHD levels are inversely correlated with TG, TC, and/or LDLC[14,48-53], the relationship between VD and HDLC is complicated[3]. We previously found that oral supplementation of VD (50,000 IU/week for eight weeks) induced a decrease in HDLC in male adults[54]. In interpreting the discrepancy in gender, age, and physiological status that might be involved, we found that sunlight exposure also seemed to affect the association between 25OHD and HDLC. Specifically, at lower sunlight exposure (< 1 h/d), a positive relationship was observed, while at higher sunlight exposure (> 2 h/d), 25OHD was negatively associated with HDLC[55]. In our present study, the men in the DL group had a lower level of VD than the men in the ND group, and plasma 25OHD was inversely associated with lg TG, LDLC, and HDLC in men. There was no significant difference in the distribution of VD concentration among the various *VDR* SNPs genotypes, but we noticed that the women in the DL group were much older than the women in the other groups, which may affect the VD levels among the groups. Other possible reasons, such as the population selection, dietary VD, time spent outdoors for sun exposure, menopause, etc., may also have complicated the results.

In addition, *VDR* polymorphisms may affect the responses of metabolic parameters to VD supplementation. After VD supplementation, *Apa1* CC (*aa*) as compared to *Apa1* AA (*AA*) or *Cdx2* TT (AA) as compared to *Cdx2* CC (GG) was associated with a greater decrease in plasma LDLC[56]. A previous study conducted in New Zealand found that after VD supplementation in women with VD deficiency, the *VDR* SNP genotypes of *Apa1* AA (*AA*) and *Taq1* GG (*tt*) were predicted to show greater improvement in insulin resistance[57]. Thus, it was easy to understand that different genotypes of *VDR* may have an impact on VD levels and biochemical metabolic indicators[58-60]. For example, the *Fok1* AA (TT, i.e., *ff*) genotype was associated with

lower 25OHD levels and higher LDLC levels in the aforementioned Chinese population[37]. Nevertheless, we failed to find such differences in the plasma 25OHD concentration between the genotypes for each of the four SNPs in our examination center-based population. According to the logistic regression and simple linear regression results, some parameters of VD and *VDR* SNPs were related to results of dyslipidemia. Therefore, we further explored whether VD and *VDR* SNPs were synergistic or antagonistic to the results of dyslipidemia. The results showed that in men, the combined effect of VD and *Fok1* BB or *Cdx2* TT did not optimize HDLC parameters but synergistically decreased HDLC levels, which tend to be unhealthy. This suggests that, in men, in particular those who carry the *Fok1* BB or *Cdx2* TT genotypes, supplementation of VD may not help improve their low-HDLC dyslipidemia; however, further studies are needed to confirm this.

Aside from the inconsistent results of the epidemiological evidence due to complicated confounders existing in real life, the fundamental biological aspects of some SNPs of *VDR* have been interpreted. The *Fok1* restriction enzyme site as $GGATGN_{(9)}$^ at the 5'-end of *VDR* in exon 2 has two ATG triplets that can serve as the initial codon for the long or short isoforms of the VDR protein, respectively. The impaired nuclear uptake of $1,25(OH)_2D$ in fibroblasts was related to the conversion of the A (complementary to T in the first ATG triplet of *VDR*) allele to B (e.g., C) for the *Fok1* polymorphism[61], which initiated the translation from the downstream ATG for the smaller VDR protein (49.5 kD), three amino acid residues shorter than the longer form. Further analysis of the VDR molecular model found that the *Fok1* B-allele changed the structure and stability of VDR and its binding energy with its ligand[37] but is more effective in activating the VD target genes[62]. However, the expression and migration efficiency of the two VDR isoforms have not yet been determined. The *Cdx2* polymorphism is located in the promoter region of the *VDR* gene, and its minor allele T (or A on its complementary strand) resulted in a higher transcriptional activity of *VDR*[63]. But these mechanisms remain to be studied for the polymorphisms of *Apa1* located in the 8th intron and *Taq1* in the 9th exon, causing a nonsense variation.

LIMITATIONS AND STRENGTHS

This study is the first to propose that different genotypes of *VDR* SNPs affect serum lipid profiles with gender differences. This can be useful for improving preventive strategies for dyslipidemia and related diseases in populations with a specific gender and genetic makeup. However, attention should be paid to our findings considering at least the following aspects: 1) the participants were recruited from a health examination center where the dyslipidemia prevalence was lower than that indicated in an epidemiological study of the entire Shenzhen population (27% *vs*. 34.6%), and larger population and multi-center studies are needed to further confirm the relationship between *VDR* SNPs and different lipid parameters; 2) identification and quantification of confounding factors, especially sex, age, and lifestyle factors, need more comprehensive consideration in interpreting the relationship between dyslipidemia and *VDR* polymorphisms, as well as serum VD levels.

CONCLUSIONS

Cdx2, *Fok1* polymorphisms of *VDR* were sex-differentially associated with lipid profiles in Han Chinese adults. In women, *Fok1* B was positively correlated with LDLC, indicating that *Fok1* B is a risk factor of high-LDLC-dyslipidemia, while in men, *Cdx2* T and *Fok1* B were negatively correlated with HDLC, suggesting that *Cdx2* T and *Fok1* B are risk factors of low-HDLC-dyslipidemia. In men, the VD status interacted with *Cdx2* TT and *Fok1* BB in association with low-HDLC levels.

CONFLICTS OF INTEREST

None of the authors have any conflicts of interest to declare.

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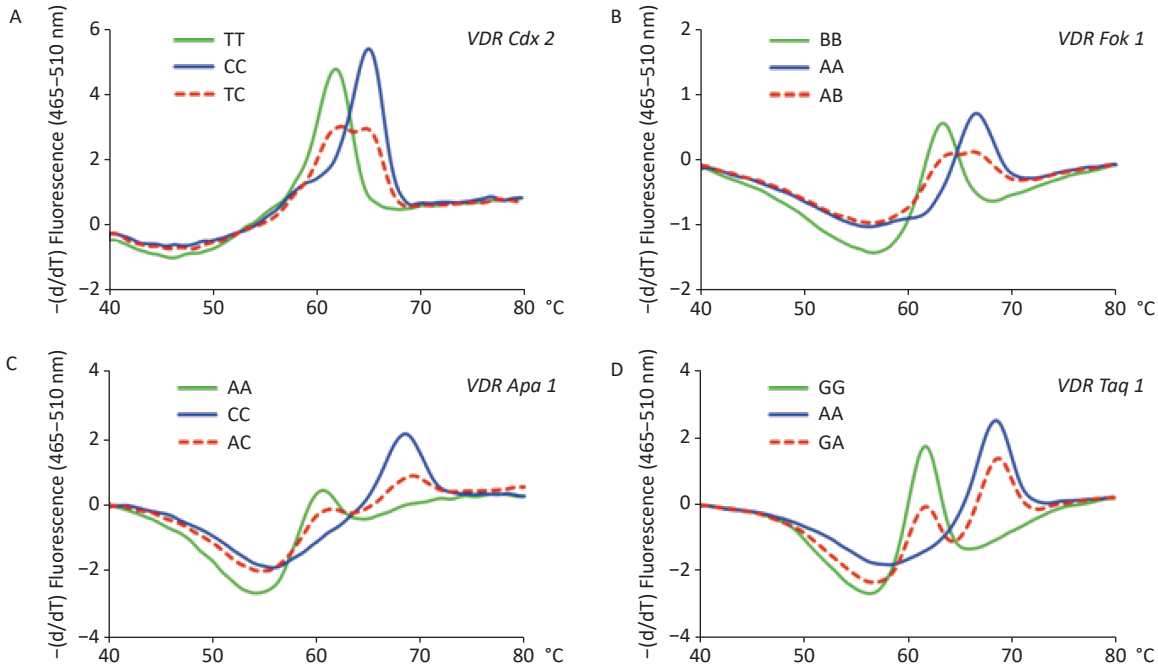

Supplementary Figure S1. Melting curve analyses on the polymorphisms of vitamin D receptor gene (*VDR*). Panel A: Melting curve of *VDR Cdx2* (rs11568820, A). Panel B: Melting curve of *Fok1* (rs2228570, B). Panel C: Melting curve of *VDR Apa1* (rs7975232, C). Panel D: Melting curve of *VDR Taq1* (rs731236, D).

Supplementary Table S1. The information of molecular beacon probes and primers for genotyping the four single nucleotide polymorphisms (SNPs) of vitamin D receptor gene (*VDR*)

NCBI rs ID	SNP name	Alleles[a]	Position[b]	Oligo name	Oligo sequence, 5'–3' direction[c]	Length of amplicon, bp
rs11568820	*Cdx2*	C > T	promoter region, chr12:47908762	Probe	cctgaTTACTGTGACCTAGTTTACTCAGG	179
				Forward primer	CAATGAAAGCAAACCAAGGGGTCTTC	
				Backward primer	AGGAAGGAAAAGAGGATAGAGAAAAT	
rs2228570	*Fok1*	A > B[d]	exon 2, chr12:47879112	Probe	ccgcGGGATGGAGGCAATGGCGG	178
				Forward primer	CACTGACTCTGGCTCTGACCGT	
				Backward primer	GCAGCCTTCACAGGTCATA	
rs7975232	*Apa1*	C > A	intron 8, chr12:47845054	Probe[e]	ctTGGGCCCCTCACTGCTCAAg	185
rs731236	*Taq1*	A > G	exon 9, chr12:47844974	Probe[e]	cgcGGATGGCCTCAATCAGCGCG	
				Forward primer	GGCGGCAGCGGATGTACG	
				Backward primer	GCCGTTGAGTGTCTGTGT	

Note. [a]The usages of these alleles are consistent to those used in the NCBI dbSNP database. [b]Location of the allelic bases on the *VDR* and chromosome 12. [c]In the probe sequence, the lowercase letters at the 5' or 3' end are adaptor bases, and the highlighted letters are one of the alleles in the SNP locus. [d]B, degenerate base standing for C, G, and T, i.e. not A. [e]*Apa1* and *Taq1* were detected with their respective probe on the same qPCR amplicon.

Supplementary Table S2. Hardy-Weinberg equilibrium tests on the vitamin D receptor gene polymorphisms, *Cdx2* (rs11568820), *Fok1* (rs2228570), *Apa1* (rs7975232), and *Taq1* (rs731236)

Genotype	*n*	Genotype frequency, %			χ^2	*P* value[*]
Cdx2		**TT**	**CT**	**CC**		
DL	1,142	20.0	47.0	34.0	2.06	0.15
ND	845	19.0	51.0	30.0	0.80	0.37
total	1,987	19.0	49.0	32.0	0.26	0.61
Fok1		**BB**	**AB**	**AA**		
DL	1,142	28.0	52.0	20.0	2.38	0.12
ND	845	28.0	50.0	22.0	0.06	0.81
total	1,987	28.0	51.0	21.0	1.75	0.19
Apa1		**AA**	**AC**	**CC**		
DL	1,142	10.0	39.0	51.0	4.85	**0.03**
ND	845	9.0	42.0	49.0	0.09	0.76
total	1,987	9.0	40.0	50.0	2.14	0.14
Taq1		**GG**	**AG**	**AA**		
DL	1,142	0.5	8.0	90.0	2.73	0.10
ND	845	0.5	11.0	91.0	0.60	0.44
total	1,987	1.0	9.0	90.0	3.01	0.08

Note. Abbreviations: B, degenerate base standing for C, G, and T; DL, dyslipidemia; ND, non-dyslipidemia. [*]Hardy-Weinberg equilibrium analyses test for the genotypes of the four SNPs.

Supplementary Table S3. Comparisons of the genotypic and allelic frequencies of vitamin D receptor gene polymorphisms, *Cdx2* (rs11568820), *Fok1* (rs2228570), *Apa1* (rs7975232), and *Taq1* (rs731236) between dyslipidemia (DL) and non-dyslipidemia (ND) adults

Genotype	Female				Male			
	DL, % *n* = 236	ND, % *n* = 888	χ^2	*P* value	DL, % *n* = 299	ND, % *n* = 564	χ^2	*P* value
Cdx2								
TT	17.8	19.4	0.955	0.620	20.4	19.1	0.390	0.823
CT	50.0	51.6			43.8	45.9		
CC	32.2	29.1			35.8	34.9		
T	42.8	45.2	0.841	0.359	42.3	42.1	0.006	0.937
C	57.2	54.8			57.7	57.9		
Fok1								
AA	15.3	23.3	11.658	**0.003**	16.7	21.6	3.871	0.144
AB	48.7	50.2			53.2	52.8		
BB	36.0	26.5			30.1	25.5		
A	39.6	48.4	11.618	**0.001**	43.3	48.0	3.528	0.060
B	60.4	51.6			56.7	52.0		
Apa1								
AA	9.3	9.9	0.120	0.942	8.7	9.0	0.304	0.859
AC	41.1	40.1			41.5	39.5		
CC	49.6	50.0			49.8	51.4		
A	29.9	30.0	0.001	0.972	29.4	28.8	0.073	0.787
C	70.1	70.0			70.6	71.2		
Taq1								
AA	91.5	88.9	1.496	0.476	91.0	91.3	0.256	0.921
AG	8.1	10.7			8.7	8.2		
GG	0.4	0.5			0.3	0.5		
A	95.6	94.2	1.305	0.253	95.3	95.4	0.005	0.946
G	4.4	5.8			4.7	4.6		

Note. Abbreviations: B, degenerate base standing for C, G, and T.

Supplementary Table S4. Genetic model comparison of *Cdx2* (rs11568820) in vitamin D receptor gene between dyslipidemia (DL) and non-dyslipidemia (ND) adults

Gene	Additive model			Dominant model		Recessive model		Homozygous model		Allelic model	
models	TT	CT	CC	TT + CT	CC	TT	CT + CC	TT	CC	T	C
DL											
n	103	249	183	352	183	103	432	103	183	455	615
%	19.3	46.5	34.2	65.8	34.2	19.3	80.7	36.0	64.0	42.5	57.5
ND											
n	280	717	455	997	455	280	1,172	280	455	1,277	1,627
%	19.3	49.4	31.3	68.7	31.3	19.3	80.7	38.1	61.9	44.0	56.0
Total											
n	383	966	638	1,349	638	383	1,604	383	638	1,732	2,242
%	19.3	48.6	32.1	67.9	32.1	19.3	80.7	37.5	62.5	43.6	56.4
χ^2	1.54			1.48		0.00		0.38		0.67	
P value	0.46			0.22		0.99		0.54		0.41	

Supplementary Table S5. Genetic model comparison of *Apa1* (rs7975232) in vitamin D receptor gene between dyslipidemia (DL) and non-dyslipidemia (ND) adults

Gene models	Additive model			Dominant model		Recessive model		Homozygous model		Allelic model	
	AA	AC	CC	AA + AC	CC	AA	AC + CC	AA	CC	A	C
DL											
n	48	221	266	269	266	48	487	48	266	317	753
%	9.0	41.3	49.7	50.3	49.7	9.0	91.0	15.3	84.7	29.6	70.4
ND											
n	139	579	734	718	734	139	1,313	139	734	857	2,047
%	9.5	39.9	50.6	49.4	50.6	9.6	90.4	15.9	84.1	29.5	70.5
Total											
n	187	800	1,000	987	1,000	187	1,800	187	1,000	1,174	2,800
%	9.4	40.3	50.3	49.7	50.3	9.4	90.6	15.8	84.2	29.5	70.5
χ^2	0.40			0.11		0.17		0.10		0.01	
P value	0.82			0.74		0.68		0.79		0.94	

Supplementary Table S6. Genetic model comparison of *Taq1* (rs731236) in vitamin D receptor gene between dyslipidemia (DL) and non-dyslipidemia (ND) adults

Gene models	Additive model			Dominant model		Recessive model		Homozygous model		Allelic model	
	GG	AG	AA	GG + AG	AA	GG	AG + AA	GG	AA	G	A
DL											
n	2	45	488	47	488	2	533	2	488	49	1,021
%	0.4	8.4	91.2	8.8	91.2	0.4	99.6	0.4	99.6	4.6	95.4
ND											
n	7	141	1,304	148	1,304	7	1,445	7	1,304	155	2,749
%	0.5	9.6	89.9	10.2	89.8	0.5	99.5	0.5	99.5	5.3	94.7
Total											
n	9	186	1,792	195	1,792	9	1,978	9	1,792	204	3,770
%	0.5	9.4	90.2	9.8	90.2	0.5	99.5	0.5	99.5	5.1	94.9
χ^2	0.89			0.88		0.00		0.11		0.92	
P value	0.64			0.35		1.00		0.74		0.34	

Supplementary Table S7. Logistic regression analyses of lipids with SNPs of *VDR* in adult females with adjustment for age, body mass index, dietary 25-hydroxyvitamin D, and the sunshine time per week

Gene models	TG ≥ 1.7 *vs*. < 1.7 mmol/L		TC ≥ 5.2 *vs*. < 5.2 mmol/L		LDLC ≥ 3.4 *vs*. < 3.4 mmol/L		HDLC < 1.0 *vs*. ≥ 1.0 mmol/L	
	P	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)
Apa1 (rs7975232)								
Add.: AA *vs*. AC *vs*. CC	0.47	1.11 (0.84–1.47)	0.48	0.93 (0.76–1.14)	0.38	1.12 (0.87–1.43)	0.93	1.03 (0.52–2.04)
Dom.: AA + AC *vs*. CC	0.59	1.10 (0.77–1.59)	0.35	0.88 (0.67–1.15)	0.59	1.09 (0.79–1.50)	0.87	1.08 (0.44–2.64)
Rec.: AA *vs*. AC + CC	0.84	1.06 (0.59–1.92)	0.88	0.97 (0.63–1.49)	0.33	1.29 (0.78–2.12)	0.99	1.01 (0.23–4.45)
Hom.: AA *vs*. CC	0.16	0.21 (0.03–1.86)	0.52	1.35 (0.54–3.34)	0.16	2.09 (0.75–5.81)	0.71	1.63 (0.13–20.27)
Alle.: A *vs*. C	0.45	1.12 (0.83–1.51)	0.38	0.91 (0.73–1.13)	0.54	1.08 (0.84–1.40)	0.79	1.11 (0.53–2.33)
Cdx2 (rs11568820)								
Add.: TT *vs*. CT *vs*. CC	0.15	0.83 (0.64–1.07)	0.77	0.97 (0.81–1.17)	0.79	1.03 (0.83–1.29)	0.38	0.76 (0.40–1.42)
Dom.: TT + CT *vs*. CC	0.10	0.73 (0.50–1.06)	0.30	0.86 (0.65–1.14)	0.70	1.07 (0.76–1.49)	0.79	0.88 (0.35–2.23)
Rec.: TT *vs*. CT + CC	0.65	0.90 (0.57–1.41)	0.49	1.12 (0.81–1.55)	0.97	0.99 (0.67–1.46)	0.20	0.38 (0.09–1.68)
Hom.: TT *vs*. CC	0.42	0.66 (0.23–1.85)	0.27	1.45 (0.75–2.82)	0.51	1.32 (0.58–3.02)	0.27	0.28 (0.03–2.71)
Alle.: T *vs*. C	0.11	0.81 (0.62–1.05)	0.98	1.00 (0.83–1.21)	0.79	0.97 (0.77–1.22)	0.45	0.77 (0.40–1.50)
Fok1 (rs2228570)								
Add.: BB *vs*. AB *vs*. AA	0.57	1.08 (0.84–1.39)	0.35	1.09 (0.91–1.31)	**0.03**	1.28 (1.03–1.59)	0.68	1.13 (0.62–2.07)
Dom.: BB + AB *vs*. AA	0.51	1.16 (0.75–1.80)	0.64	1.08 (0.79–1.47)	0.18	1.31 (0.89–1.92)	0.57	0.76 (0.29–1.99)
Rec.: BB *vs*. AB + AA	0.70	1.08 (0.73–1.59)	0.29	1.16 (0.88–1.54)	**0.03**	1.45 (1.04–2.00)	0.22	1.72 (0.72–4.14)
Hom.: BB *vs*. AA	0.22	0.55 (0.21–1.44)	0.68	1.15 (0.60–2.20)	**0.02**	2.86 (1.16–7.08)	0.98	1.03 (0.14–7.63)
Alle.: B *vs*. A	0.30	1.15 (0.88–1.49)	0.27	1.11 (0.92–1.34)	0.05	1.26 (1.00–1.58)	0.37	1.36 (0.70–2.65)
Taq1 (rs731236)								
Add.: GG *vs*. AG *vs*. AA	0.08	0.55 (0.28–1.08)	0.35	0.82 (0.54–1.25)	0.85	0.95 (0.58–1.58)	0.87	0.89 (0.20–3.87)
Dom.: GG + AG *vs*. AA	0.11	0.57 (0.28–1.13)	0.41	0.83 (0.53–1.29)	0.94	0.98 (0.58–1.66)	0.98	0.98 (0.21–4.64)
Rec.: GG *vs*. AG + AA	1.00	0.00 (0.00–NA)	0.45	0.42 (0.04–3.99)	0.96	1.06 (0.11–10.06)	1.00	0.00 (0.00–NA)
Hom.: GG *vs*. AA	NA	NA (NA–NA)	NA	NA (NA–NA)	NA	NA (NA–NA)	NA	NA (NA–NA)
Alle.: G *vs*. A	0.12	0.59 (0.30–1.15)	0.27	0.79 (0.51–1.21)	0.75	0.92 (0.56–1.53)	0.86	0.87 (0.19–4.09)

Note. Abbreviations: Add., additive model; Alle., allelic model; B, degenerate base standing for C, G, and T; *CI*, confidential interval; Dom., dominant model; HDLC, high-density lipoprotein cholesterol; Hom., homozygous model; LDLC, low-density lipoprotein cholesterol; NA, not available; *OR*, odds ratio; Rec., recessive model; SNPs, single nucleotide polymorphisms; TC, total cholesterol; TG, triglyceride; *VDR*, vitamin D receptor gene.

Supplementary Table S8. Logistic regression analyses of lipids with SNPs of *VDR* in adult males with adjustment for age, body mass index, dietary 25-hydroxyvitamin D, and the sunshine time per week

Gene models	TG ≥ 1.7 *vs*. < 1.7 mmol/L		TC ≥ 5.2 *vs*. < 5.2 mmol/L		LDLC ≥ 3.4 *vs*. < 3.4 mmol/L		HDLC < 1.0 *vs*. ≥ 1.0 mmol/L	
	P	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)
Apa1 (rs7975232)								
Add.: AA *vs*. AC *vs*. CC	0.55	1.08 (0.85–1.37)	0.95	0.99 (0.79–1.24)	0.92	0.99 (0.75–1.30)	0.11	1.72 (0.88–3.35)
Dom.: AA + AC *vs*. CC	0.49	1.12 (0.82–1.51)	0.46	0.90 (0.68–1.19)	0.74	0.94 (0.67–1.34)	0.13	2.11 (0.81–5.51)
Rec.: AA *vs*. AC + CC	0.77	1.08 (0.64–1.83)	0.23	1.35 (0.83–2.20)	0.82	1.07 (0.58–1.97)	0.51	1.54 (0.43–5.53)
Hom.: AA *vs*. CC	0.74	1.18 (0.45–3.11)	0.25	1.72 (0.69–4.29)	0.56	1.36 (0.49–3.82)	0.31	3.00 (0.37–24.68)
Alle.: A *vs*. C	0.47	1.10 (0.86–1.41)	0.66	1.05 (0.84–1.33)	0.83	0.97 (0.73–1.29)	0.35	1.39 (0.70–2.77)
Cdx2 (rs11568820)								
Add.: TT *vs*. CT *vs*. CC	0.65	0.96 (0.78–1.17)	0.09	0.85 (0.71–1.03)	0.46	0.92 (0.73–1.16)	0.12	1.62 (0.89–2.95)
Dom.: TT + CT *vs*. CC	0.88	0.98 (0.72–1.33)	0.14	0.81 (0.61–1.07)	0.64	0.92 (0.65–1.30)	0.57	1.32 (0.50–3.50)
Rec.: TT *vs*. CT + CC	0.57	0.90 (0.62–1.30)	0.20	0.80 (0.57–1.13)	0.40	0.83 (0.54–1.28)	**0.04**	2.68 (1.06–6.75)
Hom.: TT *vs*. CC	0.06	2.25 (0.97–5.23)	0.82	0.92 (0.42–1.99)	0.74	1.17 (0.47–2.95)	0.19	4.84 (0.46–51.14)
Alle.: T vs C	0.62	0.95 (0.76–1.18)	0.14	0.86 (0.70–1.05)	0.45	0.91 (0.71–1.17)	0.30	1.42 (0.73–2.73)
Fok1 (rs2228570)								
Add.: BB *vs*. AB *vs*. AA	0.50	0.93 (0.75–1.15)	0.08	0.84 (0.69–1.02)	0.77	1.04 (0.81–1.33)	**0.02**	2.26 (1.12–4.56)
Dom.: BB + AB *vs*. AA	0.75	0.94 (0.65–1.36)	0.30	0.84 (0.59–1.17)	0.63	1.11 (0.72–1.72)	0.23	2.48 (0.57–10.90)
Rec.: BB *vs*. AB + AA	0.47	0.89 (0.64–1.23)	0.08	0.76 (0.56–1.03)	0.97	0.99 (0.68–1.45)	**0.03**	2.75 (1.12–6.74)
Hom.: BB *vs*. AA	0.89	1.06 (0.48–2.35)	0.80	1.11 (0.52–2.35)	0.82	1.11 (0.45–2.73)	0.82	0.79 (0.10–6.34)
Alle.: B *vs*. A	0.50	0.93 (0.75–1.15)	0.19	0.87 (0.71–1.07)	0.53	1.08 (0.84–1.39)	0.09	1.85 (0.91–3.76)
Taq1 (rs731236)								
Add.: GG vs AG *vs*. AA	0.67	1.12 (0.67–1.86)	0.70	1.10 (0.68–1.76)	0.30	0.72 (0.38–1.35)	0.64	0.69 (0.15–3.19)
Dom.: GG + AG *vs*. AA	0.69	1.12 (0.65–1.91)	0.75	1.09 (0.66–1.79)	0.42	0.76 (0.40–1.47)	0.85	0.86 (0.19–3.97)
Rec.: GG *vs*. AG + AA	0.83	1.27 (0.15–11.06)	0.47	2.36 (0.23–24.37)	1.00	0.00 (0.00–NA)	1.00	0.00 (0.00–NA)
Hom.: GG *vs*. AA	NA	NA (NA–NA)	NA	NA (NA–NA)	NA	NA (NA–NA)	NA	NA (NA–NA)
Alle.: G *vs*. A	0.65	1.13 (0.67–1.89)	0.68	1.11 (0.68–1.79)	0.31	0.72 (0.38–1.37)	0.71	0.75 (0.17–3.37)

***Note*.** Abbreviations: Add., additive model; Alle., allelic model; B, degenerate base standing for C, G, and T; *CI*, confidential interval; Dom., dominant model; HDLC, high-density lipoprotein cholesterol; Hom., homozygous model; LDLC, low-density lipoprotein cholesterol; NA, not available; *OR*, odds ratio; Rec., recessive model; SNPs, single nucleotide polymorphisms; TC, total cholesterol; TG, triglyceride; *VDR*, vitamin D receptor gene.

Supplementary Table S9. Comparison of 25-hydroxyvitamin D concentration (nmol/L) across genotype models of *VDR* gene polymorphisms in adult males and females

Genotype	Female				Male			
comparison	*n*	Median	IQR	*P* value	*n*	Median	IQR	*P* value
Apa1 (rs7975232)								
Add: AA *vs*. AC *vs*. CC								
CC	561	58.97	[49.68–69.18]	0.35	439	63.18	[53.75–72.59]	0.83
AC	453	58.75	[49.16–68.63]		347	62.33	[52.65–73.59]	
AA	110	57.04	[48.40–65.71]		77	60.91	[52.44–73.32]	
Dom: AC + AA *vs*. CC								
AC + AA	563	58.53	[49.01–68.18]	0.47	424	62.12	[52.66–73.49]	0.54
CC	561	58.97	[49.68–69.18]		439	63.18	[53.75–72.59]	
Rec: AA *vs*. AC + CC								
AA	110	57.04	[48.40–65.71]	0.16	77	60.91	[52.44–73.32]	0.83
AC + CC	1,014	58.86	[49.50–68.82]		786	62.63	[53.24–72.72]	
Hom: AA *vs*. CC								
AA	110	57.04	[48.40–65.71]	0.15	77	60.91	[52.44–73.32]	0.74
CC	561	58.97	[49.68–69.18]		439	63.18	[53.75–72.59]	
Alle: A *vs*. C								
A	673	58.30	[48.86–67.20]	0.23	501	62.04	[52.66–73.38]	0.57
C	1,575	58.90	[49.54–68.88]		1,225	62.85	[53.38–72.66]	
Cdx2 (rs11568820)								
Add.: TT *vs*. CT *vs*. CC								
CC	334	59.17	[50.94–68.68]	0.20	304	61.79	[53.30–72.53]	0.69
CT	576	59.08	[48.96–69.29]		390	63.11	[53.50–72.93]	
TT	214	56.48	[48.30–67.03]		169	61.65	[51.85–72.31]	
Dom.: CT + TT *vs*. CC								
CT + TT	790	58.35	[48.80–68.56]	0.41	559	62.76	[53.14–72.88]	0.72
CC	334	59.17	[50.94–68.68]		304	61.79	[53.30–72.53]	
Rec.: TT *vs*. CT + CC								
TT	214	56.48	[48.30–67.03]	0.08	169	61.65	[51.85–72.31]	0.56
CT + CC	910	59.15	[49.50–69.12]		694	62.83	[53.46–72.73]	
Hom.: TT *vs*. CC								
TT	214	56.48	[48.30–67.03]	0.08	169	61.65	[51.85–72.31]	0.81
CC	334	59.17	[50.94–68.68]		304	61.79	[53.30–72.53]	
Alle: T *vs*. C								
T	1,004	58.00	[48.65–68.27]	0.13	728	62.59	[52.78–72.82]	0.93
C	1,244	59.15	[49.95–68.88]		998	62.61	[53.36–72.66]	
Fok1 (rs2228570)								
Add.: BB *vs*. AB *vs*. AA								
AA	243	57.56	[48.62–69.02]	0.83	172	63.52	[54.12–73.35]	0.47
AB	561	58.75	[49.14–69.11]		457	62.44	[53.50–72.16]	
BB	320	59.04	[49.98–67.16]		234	61.49	[51.87–72.67]	

Continued

Genotype comparison	Female				Male			
	n	Median	IQR	*P* value	*n*	Median	IQR	*P* value
Dom.: BB + AB *vs*. AA								
BB + AB	881	58.87	[49.43–68.55]	0.54	691	62.30	[53.17–72.33]	0.40
AA	243	57.56	[48.62–69.02]		172	63.52	[54.12–73.35]	
Rec.: BB *vs*. AB + AA								
BB	320	59.04	[49.98–67.16]	0.87	234	61.49	[51.87–72.67]	0.27
AB + AA	804	58.37	[49.03–69.07]		629	62.80	[53.64–72.82]	
Hom.: BB *vs*. AA								
BB	320	59.04	[49.98–67.16]	0.62	234	61.49	[51.87–72.67]	0.24
AA	243	57.56	[48.62–69.02]		172	63.52	[54.12–73.35]	
Alle.: B *vs*. A								
B	1,201	58.92	[49.55–68.41]	0.65	925	62.16	[52.72–72.54]	0.24
A	1,047	58.32	[49.01–69.02]		801	62.99	[53.89–72.93]	
Taq1 (rs731236)								
Add.: GG vs AG *vs*. AA								
AA	1,005	58.53	[49.43–68.66]	0.92	787	62.37	[53.24–72.59]	0.50
AG	114	60.05	[48.85–67.77]		72	64.27	[52.80–75.16]	
GG	5	53.88	[37.14–74.36]		4	67.28	[66.31–71.96]	
Dom.: AG + GG *vs*. AA								
AG + GG	119	59.98	[48.95–67.63]	0.91	76	64.98	[53.28–74.37]	0.46
AA	1,005	58.53	[49.43–68.66]		787	62.37	[53.24–72.59]	
Rec.: GG vs AG + AA								
GG	5	53.88	[37.14–74.36]	0.68	4	67.28	[66.31–71.96]	0.30
AG + AA	1,119	58.73	[49.36–68.59]		859	62.56	[53.20–72.72]	
Hom.: GG *vs*. AA								
GG	5	53.88	[37.14–74.36]	0.68	4	67.28	[66.31–71.96]	0.29
AA	1,005	58.53	[49.43–68.66]		787	62.37	[53.24–72.59]	
Alle.: G *vs*. A								
G	124	59.97	[49.01–67.61]	0.84	80	65.45	[53.57–73.86]	0.34
A	2,124	58.64	[49.41–68.64]		1,646	62.49	[53.23–72.66]	

Note. Abbreviations: Add., additive model; Alle., allelic model; B, degenerate base standing for C, G, and T; Dom., dominant model; Hom., homozygous model; IQR, interquartile range; Rec., recessive model; *VDR*, vitamin D receptor gene.

Supplementary Table S10. Comparison of 25-hydroxyvitamin D concentration (nmol/L) in abnormal and normal lipid groups of adult males and females

Genotype comparison	Female				Male			
	n	Median	IQR	*P* value	*n*	Median	IQR	*P* value
TG								
≥ 2.3 mmol/L	92	57.79	[49.43–65.74]	0.40	213	59.58	[49.47–69.60]	**< 0.01**
< 2.3 mmol/L	1,032	58.80	[49.25–68.85]		650	63.43	[54.29–73.70]	
TC								
≥ 6.2 mmol/L	151	59.19	[47.87–72.64]	0.68	111	59.18	[49.73–71.13]	0.09
< 6.2 mmol/L	973	58.56	[49.55–68.31]		752	62.92	[53.42–72.93]	
LDLC								
≥ 4.1 mmol/L	29	56.70	[45.80–66.12]	0.52	17	55.45	[45.07–74.43]	0.20
< 4.1 mmol/L	1,095	58.78	[49.41–68.66]		846	62.65	[53.27–72.72]	
HDLC								
< 1.0 mmol/L	22	67.80	[59.52–78.05]	**< 0.01**	20	69.35	[57.83–83.61]	0.11
≥ 1.0 mmol/L	1,102	58.52	[49.13–68.44]		843	62.57	[53.19–72.59]	

***Note*.** Abbreviations: HDLC, high-density lipoprotein cholesterol; IQR, interquartile range; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Supplementary Table S11. Simple linear regressions between serum 25-hydroxyvitamin D and lipid profiles

Lipid profiles	Female		Male	
	β	*P* value	*β*	*P* value
lg TG	< 0.001	0.902	−0.003	**< 0.001**
TC	0.001	0.647	−0.003	0.088
LDLC	−0.001	0.584	−0.003	**0.006**
HDLC	< 0.001	0.461	−0.001	**0.025**

***Note*.** Abbreviations: HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.