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Vitamin D receptor gene polymorphisms modify the association of serum 25-hydroxyvitamin D levels with handgrip strength in the elderly in Northern China

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ABSTRACT

Objectives: The aim of this cross-sectional study was to investigate the association of serum 25-hydroxyvitamin D (25[OH]D) levels and vitamin D receptor (VDR) genotypes with skeletal muscle mass and function in elderly subjects in northern China.
Methods: A total of 275 men and 510 women, ages 63.1 to 72.5 y, in two randomly selected communities in Beijing were investigated. The investigation included a questionnaire, physical measurements, muscle mass and function measurements, serum 25(OH)D levels, and VDR gene polymorphisms analysis.
Results: In the group with 25(OH)D levels <10.0 ng/mL, the proportion with low handgrip strength was 3.04 times higher than that in the group with 25(OH)D levels >20.0 ng/mL for men (odds ratio: 3.04; 95% confidence interval, 1.13-8.20) but not for women. The general linear model showed that higher 25(OH)D levels and having T allele of Fok1 and the bb genotype of Bsm1 were significantly associated with more handgrip strength. The regression coefficients (β) were 1.80 ($P < 0.01$), 1.26 ($P < 0.01$), and 2.90 ($P < 0.01$), respectively. There was a significant interaction between 25(OH)D and VDR gene polymorphisms for handgrip strength for both Fok1 ($\beta = 2.86$; $P < 0.01$) and Bsm1 ($\beta = 3.14$; $P = 0.02$) after adjustment for potential confounders (sex, age, body mass index, fat mass, physical activity, sun exposure, energy, and protein intake).
Conclusions: 25(OH)D levels are associated with handgrip strength for men and this relationship could be modified with the interaction between 25(OH)D and VDR gene polymorphisms (Fok1 and Bsm1).

Introduction

A loss in skeletal muscle mass (SMM) and muscle function leads to significant physical functional deterioration, metabolic impairments, disability, and even death in the elderly population [1,2]. Although environmental and genetic factors related to sarcopenia such as growth hormones, resistance training, adequate protein intake, serum vitamin D level, and genotypic variations (e.g., Bsm1, Fok1, and Taq1 translation site) have been proposed as related to this loss [3–6], many uncertainties remain and are currently under investigation [7]. Vitamin D insufficiency has been shown as a potential risk factor for skeletal muscle weakness and atrophy of type 2 muscle fibers [6,8–11]. In addition, the vitamin D receptor (VDR) gene polymorphisms (e.g., Bsm1 and Fok1) are deemed one of the genetic factors related to the deterioration in SMM and functional loss [12–15]. However, the contribution of different genotypes has not been clearly identified [16].

Meanwhile, vitamin D deficiency is reported to affect more than 1 billion people worldwide [17] and China is not an exception [18], especially in the elderly population. However, when studying the relationship between serum vitamin D level and muscle mass and function, the consideration of VDR gene polymorphisms is very limited.

Thus, to obtain further understanding of the relationship between serum vitamin D levels, VDR gene polymorphisms, and muscle mass loss and functional deterioration, we conducted this cross-sectional study in the northern urban area of China.

Materials and methods

Study design and subjects

A total of 277 men and 518 women, ages ≥60 y, were recruited in a cross-sectional study in two randomly selected communities in Beijing, northern China.

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During the recruitment phase, we excluded some volunteers who had serious diseases that may lead to vitamin D deficiency [19] such as heavy liver disease, renal disease, skin disease, neural disease, cardiovascular disease, and hyperthyroidism. We also excluded 10 participants who were taking antiepileptic drugs, which was disclosed on the questionnaire survey. Finally, data from 275 men and 510 women were used for our statistical analysis. This study included a questionnaire, physical measurements, muscle mass and functional measurements, and a biochemical analysis.

All participants were interviewed in accordance with the study protocols, which were approved by the ethical review committee of the National Institute for Nutrition and Health at the Chinese Center for Disease Control and Prevention. Written informed consent was obtained from all participants.

Questionnaire survey

The questionnaire mainly collected basic demographic information in addition to information the lifestyle, behavior, and dietary habits of the study subjects. The general population information of the subjects included sex, age, education, occupation, and economic income. The lifestyle survey asked about physical activity (number of days and duration of moderate [3-6 metabolic equivalents] or heavy physical activity [≥6 metabolic equivalents] per week during previous year) and sun exposure (duration of sun exposure in summer and winter in 1 d). The dietary survey was conducted using the semiquantitative food frequency method. Reliability and validity tests were done for the questionnaire.

Physical measurements

Participants were asked to take off their shoes and socks and wear underwear only. Weight (0.1 kg) and height (0.1 cm) were measured using height and weight measurement instruments (DST-500). SMM, appendicular skeletal muscle mass (ASM, kg), and total fat mass (kg) were measured with a bioelectrical impendence analysis (InBody720, Biospace, Korea). Handgrip strength was measured with a handgrip dynamometer (EH101, CAMRY). Participants were asked to hold the dynamometer in their dominant hand while standing and encouraged to exert a maximum isometric effort. All participants were given two chances and 1-min rest periods were given between each attempt to minimize fatigue affects [17,20]. The muscle function was assessed with 4-m usual gait speed and participants were asked to walk at their regular speed in their regular shoes for 4 m [1].

Biochemical analysis

Participants were asked to maintain their normal dietary intake (1 wk) and avoid alcohol intake (48 h) and smoking (1 h) before collection of the fast venous blood samples. The 2-mL EDTA-K2 anticoagulant vessels and 4-mL vacuum separation gel vessels were used to collect venous blood samples (fasting for 12 h). The fasting venous blood sample was collected between 8.00AM and 9:00AM, and then centrifuged (15 min, 2500 rpm) after resting in a box to avoid sunlight for approximately 30 min. The serum fraction was divided into three aliquotes and put into cryogenic vials (0.5 mL/vial) within 1 h. All blood samples were transported in dry ice to our laboratory and stored in a refrigerator at −70°C until analyzed in the same batch.

High molecular-weight genomic DNA was isolated from whole blood using cleaved amplification, polymorphism, and sequence-tagged sites. All participants were genotyped for VDR Fok1 and Bsm1 restriction sites as previously described [21]. The serum concentration of total 25-hydroxyvitamin D (25[OH]D) was measured by radioimmunoassay kits (DiaSorin-RIA; DiaSorin Inc., Stillwater, MN). The reference range for 25(OH)D is 2.5 to 44.3 ng/mL, and the intra- and interassay coefficients of variation for 25(OH)D were 4.7% and 9.1%, respectively. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is widely known as the standardized method for serum vitamin D measurement, but some studies have reported that the DiaSorin-RIA method was in acceptable agreement with the LC-MS/MS method [22–24].

Data manipulation

In this study, the relative skeletal muscle mass index (RSMI) was calculated as ASM divided by the squared value of height (m). According to the Japanese cutoff rates, low ASM was defined as RSMI <7.0 kg/m^2 for men and <5.8 kg/m^2 for women. Low handgrip strength was defined as <26 kg for men and <18 kg for women. Low gait speed was defined as <0.8 m/s for both sexes [1]. Sarcopenia was defined in accordance with the consensus reported by the Asian Working Group for Sarcopenia [1]. Participants who had low ASM with either low handgrip strength or low 4-m gait speed were defined as having sarcopenia. According to the widely used criteria [14], the ranges for the classification of serum 25(OH)D status were: Severe deficiency <10.0 ng/mL; deficiency 10.0 to 19.9 ng/mL; insufficiency 20.0 to 29.9 ng/mL, and normal range ≥30.0 ng/mL.

Statistical analysis

The database was established using Epidata version 3.0 and all analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). Means ± standard deviation (normal distribution) or median (quartile: Q1–Q3; skewed distribution) was used to describe quantitative data and frequency (proportion) to describe qualitative data. An analysis of covariance (with age, height, body mass index, fat mass, physical activity, and sun exposure as covariates) was used to analyze the differences of RSMI, ASM, handgrip strength, and 4-m usual gait speed between the categories of 25(OH)D.

Multiple logistic regression was used to analyze the risk factors for sarcopenia, low handgrip strength, and low 4-m gait speed between the different 25(OH)D level groups after adjusting for potential confounders. The generalized linear model was used to describe the association between 25(OH)D level and VDR genotype with handgrip strength (normal distribution, dependent variable) including interactions between 25(OH)D level and VDR genotypes. Different multiple linear regression models were used to analyze the association between 25(OH)D levels and handgrip strength in the population with varied VDR genotypes.

Results

Participant characteristics

As shown in Table 1, men were ages 63.2 to 72.5 y and women ages 63.1 to 71.9 y in this study, with no significant differences in terms of 25(OH)D levels and frequency of VDR genotypes ($P > 0.05$). However, the values of ASM, handgrip strength, 4-m usual gait, and sun exposure were significantly higher in men than in women. Physical activity was higher in women than in men ($P < 0.01$).

Serum 25-hydroxyvitamin D level with skeletal muscle mass and function

As shown in Table 2, handgrip strength was much higher ($P < 0.01$) and the proportion of participants with low handgrip strength was lower ($P = 0.02$) significantly in the higher group of 25(OH)D for men. In the group with serum 25(OH)D levels <10.0 ng/mL, the proportion of participants with low handgrip strength was 3.04 times higher than in the group with serum 25(OH)D levels >20.0 ng/mL for men (odds ratio: 3.04; 95% confidence interval, 1.13-8.20). However, there was no association between the 25(OH)D categories and ASM, 4-meter usual gait speed, prevalence of sarcopenia, or the proportion with low 4-meter usual gait speed (Table 2). Moreover, higher sun exposure was observed in the higher group of 25(OH)D for men ($P = 0.01$ for summer; $P = 0.04$ for winter) and varied energy intake in different categories of 25(OH)D for women ($P = 0.02$). However, body mass index, fat mass, and physical activity did not have a significant difference among the 25(OH)D categories (Table S1).

Association of serum 25(OH)D levels and vitamin D receptor genotypes with handgrip strength

As shown in Table 1, VDR Fok1 allele frequencies and Bsm1 genotypes were both in Hewq ($P > 0.05$). Table 3 shows that older age, female sex, and more fat masses were significantly associated with lower handgrip strength and the regression coefficients (β) were −14.12 ($P < 0.01$), −0.35 ($P < 0.01$), and −0.29 ($P < 0.01$), respectively. After adjustment for confounders, the general linear model showed that higher 25(OH)D levels, T allele of Fok1, and bb genotype of Bsm1 were significantly associated with more handgrip strength with $\beta = 1.80$ ($P < 0.01$), $\beta = 1.26$ ($P < 0.01$), and $\beta = 2.90$ ($P < 0.01$), respectively. Physical activity, sun exposure, and energy and protein intake were not associated with handgrip strength in this model ($P > 0.05$).

Table 1
Participant characteristics

Characteristic	Men (n = 275)	Women (n = 510)	t/χ^2	*P*-value
Age (y)*	66.6 (63.2–72.5)	66.8 (63.1–71.9)	0.76	0.40
Height (cm)*	170.0 (165.0–174.0)	157.0 (153.0–161.0)	160.0 (156.0–167.0)393.4	<0.01
BMI (kg/m^2)*	25.1 (23.3–27.1)	25.0 (22.8–27.9)	0.02	0.86
PA (h/d)*	1.0 (0.3–2.0)	1.5 (1.0–2.3)	27.8	<0.01
SEW (h/d)*	2.0±1.3	1.7±1.2	3.14	<0.01
SES (h/d)*	2.3±1.5	2.0±1.3	2.59	<0.01
ASM (kg)*	22.1 (19.7–24.4)	15.6 (14.2–17.2)	414.1	<0.01
Handgrip strength (kg)*	36.1 (29.9–41.7)	23.2 (20.1–26.2)	348.1	<0.01
4-m usual gait speed (m/s)*	1.0 (0.87–1.17)	0.99 (0.82–1.12)	7.47	<0.01
25(OH)D (ng/mL)*,†	12.4 (7.1–19.5)	12.7 (7.2–18.5)	0.12	0.79
n(%)				
Severe deficiency	98(35.5)	195(38.2)	1.18	0.74
Deficiency	111 (40.2)	207 (40.7)		
Insufficiency	39 (14.2)	67 (13.1)		
Sufficiency	27 (9.8)	41 (8.0)		
Sarcopenia(%)†	51 (18.6)	117 (22.9)	2.44	0.12
Bsm1†				
bb (G/G)	238 (86.6)	455 (89.2)	0	0.23
Bb (A/G)	37 (13.4)	55 (10.8)		
BB (A/A)	0	0		
Fok1†				
CC	85 (30.9)	173 (33.9)	169 (21.5)	0.65
CT	129 (46.9)	229 (44.9)		
TT	61 (22.2)	108 (21.2)		

25(OH)D, 25-hydroxyvitamin D; ASM, appendicular skeletal muscle mass; BMI, body mass index; PA, physical activity; SES, sun exposure in summer; SEW, sun exposure in winter

* The *t* test (normal distribution) and Wilcoxon rank test (skewed distribution) were used for difference analyses.

† The χ^2 test was used for difference analysis to qualitative data.

Interaction of serum 25(OH)D levels and vitamin D receptor genotypes on handgrip strength

Table 4 shows that there was a significant interaction between 25(OH)D levels and VDR genotypes for both Fok1 ($\beta = 2.86$; $P < 0.01$) and Bsm1 ($\beta = 3.14$; $P = 0.02$) after adjustment for potential confounders. However, the Bsm1 genotypes (Bb/bb) did not have a significant difference with handgrip strength after the addition of the 25(OH)D category interaction with Bsm1 genotypes ($P > 0.05$).

As shown in Table 5, the standardized regression coefficients (β') were 0.20 ($P < 0.001$) for men and 0.02 ($P = 0.49$) for women when the Fok1 genotypes were not considered, but the association between serum 25(OH)D levels and handgrip strength increased in the TT and bb groups after Fok1 (β' = 0.27; $P = 0.001$ for men and β' = 0.16; $P = 0.02$ for women) and Bsm1 (β' = 0.22; $P < 0.001$ for men) genotypes were taken into consideration.

Participants with bb genotypes were divided into three subgroups by Fok1 genotype. The TT-bb group had a significant partial regression coefficient in men ($\beta = 0.27$; $P < 0.001$) but not in the CC-bb and CT-bb groups or for women. Moreover, β' values for men in the TT-bb, TT, and bb group models were 0.33, 0.27, and 0.22, respectively.

Discussion

Some scholars have focused on genetic factors related to the deterioration in SMM and functional loss such as VDR gene polymorphisms (e.g., Bsm1, Fok1, and Taq1 translation site), but they only investigated the association between VDR genotypes and SMM and function [21,25–27]. In this study, we paid more attention to the association between 25(OH)D levels and VDR genotypes with SMM and function, and we especially examined whether this relationship was modified by VDR gene polymorphisms.

The effects of vitamin D on muscle have been examined at large by previous studies [6,28–30]. Many observational studies, mainly in elderly people, indicate that 25(OH)D levels are positively associated with muscle mass, strength [9,12,21,31–34], and physical performance [8], but some studies did not get similar results

Table 2
Skeletal muscle mass and function by categories of 25(OH)D in the elderly*

	Men 25(OH)D (ng/mL; n = 275)					Women 25(OH)D (ng/mL; n = 510)				
	<10.0 (n = 98)	10.0–19.9 (n = 111)	>20.0 (n = 67)	F/χ^2	*P*-value	<10.0 (n = 195)	10.0–19.9 (n = 207)	>20.0 (n = 108)	F/χ^2	*P*-value
ASM (kg)†	21.7 ± 2.2	20.6 ± 3.1	22.3 ± 1.9	0.78	0.38	15.9 ± 2.2	15.6 ± 2.0	15.9 ± 1.8	1.64	0.20
Handgrip strength (kg)†	34.0 ± 8.6	36.4 ± 8.1	38.7 ± 7.2	9.65	<0.01	23.0 ± 4.9	23.1 ± 5.1	23.3 ± 4.6	3.06	0.08
4-m usual gait speed (m/s)†	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.2	0.12	0.70	1.0 ± 0.3	0.97 ± 0.22	0.99 ± 0.24	0.37	0.54
Sarcopenia, n(%)†	16 (16.3)	26 (23.4)	9 (13.4)	0.81	0.37	40 (20.5)	59 (28.5)	20 (18.4)	0.13	0.71
Low handgrip strength, n(%)‡	23 (23.5)	14 (12.6)	8 (11.9)	6.29	0.01	21 (10.8)	31 (15.0)	11 (10.1)	0.57	0.45
Low 4-m usual gait speed, n(%)‡	18(18.37)	20(18.02)	5(7.58)	4.56	0.03	35(18.1)	42(20.4)	22(20.2)	0.07	0.83

25(OH)D, 25-hydroxyvitamin D; ASM, appendicular skeletal muscle mass

* Participants were divided into three groups by standard, defined, cut points of serum vitamin D levels. Age, height, body mass index, fat mass, physical activity, sun exposure, and energy and protein intakes are considered as confounders.

† Analysis of covariance was used to difference analysis for quantitative variants.

‡ Multiple logistic regression was used to factors analysis for category variables.

Table 3
Results of generalized linear model of 25(OH)D category and VDR genotype on handgrip strength*

			95% confidence interval			
	β	SE	Lower limit	Upper limit	F value	*P*-value
Sex†	−14.12	0.81	−15.71	−12.53	302.85	<0.01
Age (y)	−0.35	0.06	−0.47	−0.23	36.32	<0.01
BMI (kg/m2)	0.69	0.20	0.30	1.08	11.86	<0.01
Fat mass (kg)	−0.29	0.10	−0.49	−0.09	8.22	<0.01
PA (h/d)	0.73	0.53	−0.31	1.77	1.90	0.17
SEW (h/d)	0.07	0.45	−0.81	0.95	0.02	0.89
SES (h/d)	0.11	0.52	−0.91	1.13	0.05	0.83
Energy (kcal/d)	<0.01	<0.01	<0.01	<0.01	2.42	0.12
Protein (g/d)	−0.02	0.03	−0.08	0.04	0.53	0.47
VD†	1.80	0.48	0.86	2.74	14.25	<0.01
Fok1‡	1.26	0.47	0.34	2.18	7.30	<0.01
Bsm1§	2.90	1.07	0.80	5.00	7.33	<0.01
Intercept	50.46	6.33	38.05	62.87	7.97	<0.01

25(OH)D, 25-hydroxyvitamin D; β, regression coefficient; BMI, body mass index; PA, physical activity; SE, standard error; SES, sun exposure in summer; SEW, sun exposure in winter; VD, vitamin D

* Sex, age, height, BMI, fat mass, PA, SES, SEW, and energy and protein intakes were taken as confounders.

† Sex: 1 = men, 2 = women.

† VD: 1 = 25(OH)D <10.0 ng/mL; 2 = 10.0–20.0 ng/mL; 3 = 25(OH)D >20.0 ng/mL.

‡ Fok1: 1 = CC; 2 = CT; 3 = TT.

§ Bsm1: 1 = Bb; 2 = bb.

Table 4
Results of generalized linear model of 25(OH)D category and VDR genotype on handgrip strength including interactions*

			95% confidence interval			
	β	SE	Lower limit	Upper limit	T-value	*P*-value
VD†	4.25	1.35	1.60	6.90	3.14	0.00
Fok1‡	4.20	1.25	1.76	6.65	3.37	0.00
Fok1*VD†,‡	2.86	0.62	1.65	4.08	4.61	<0.01
VD†	4.34	2.65	0.86	9.53	1.64	0.10
Bsm1§	2.85	2.72	2.48	8.18	1.05	0.29
Bsm1*VD†,§	3.14	1.39	0.41	5.86	2.25	0.02

25(OH)D, 25-hydroxyvitamin D; β, regression coefficient; BMI, body mass index; SE, standard error; VD, vitamin D; VDR, vitamin D receptor

* Fok1*VD added into the Fok1-model and Bsm1*VD into the Bsm1-model. Sex, age, height, BMI, fat mass, physical activity, sun exposure in summer, sun exposure in winter, energy and protein intakes were considered into confounders.

† VD: 1 = 25(OH)D <10.0 ng/mL; 2 = 10.0–20.0 ng/mL; 3 = 25(OH)D >20.0 ng/mL.

‡ Fok1: 1 = CC; 2 = CT; 3 = TT.

§ Bsm1:1 = Bb; 2 = bb.

Table 5
Association of serum 25(OH)D levels with handgrip strength in different VDR genotyped groups*

	Men (n = 275)			Women (n = 510)		
	β (95%CI)	β†	*P*-value	β (95% CI)	β†	*P*-value
Total	0.16 (0.07–0.25)	0.20	<0.001	0.01(−0.03 to 0.05)	0.02	0.49
Fok1						
CC(n = 258)	0.12(−0.07 to 0.31)	0.14	0.95	−0.05(−0.12 to 0.02)	−0.13	0.18
CT(n = 358)	0.14(0.02–0.26)	0.19	0.34	−0.01(-0.06-0.04)	−0.02	0.80
TT(n = 169)	0.24(0.05–0.43)	0.27	0.001	0.09(0.02–0.18)	0.16	0.02
Bsm1						
Bb(n = 92)	0.08(−0.14 to 0.32)	0.13	0.15	0.10(−0.05 to 0.25)	0.18	0.20
bb(n = 693)	0.18(0.08–0.28)	0.22	<0.001	−0.01(−0.05 to 0.03)	−0.01	0.83
Fok1-Bsm1						
CC-bb(n = 226)	0.10(−0.10 to 0.30)	0.13	0.33	−0.06(−0.14 to 0.02)	−0.14	0.16
CT-bb(n = 313)	0.13(−0.02 to 0.28)	0.16	0.09	−0.02(−0.10 to 0.08)	−0.04	0.56
TT-bb(n = 155)	0.27(0.08–0.46)	0.33	<0.001	0.09(0.01–0.17)	0.15	0.05

25(OH)D, 25-hydroxyvitamin D; β, regression coefficient; β', standardized regression coefficient; BMI, body mass index; CI, confidence interval; SE, standard error; VD, vitamin D; VDR, vitamin D receptor

* Age, BMI, fat mass, sun exposure, and physical activity were taken as confounders.Table 5.

† β' were 0.20 ($P < 0.001$) for men and 0.02 ($P = 0.49$) for women when the Fok1 genotypes were not considered, but the association between serum 25(OH)D levels and handgrip strength strengthen in the TT and bb groups after the Fok1 (β' = 0.27; $P = 0.001$ for men and β' = 0.16; $P = 0.02$ for women) and Bsm1 (β' = 0.22; $P < 0.001$ for men) genotypes were taken into consideration. Participants with bb genotypes were divided into three subgroups by Fok1 genotype, and the TT-bb group had a significant partial regression coefficient in men (β = 0.27; $P < 0.001$), but not in the CC-bb or CT-bb group or for women. Moreover, the β' values for men of the TT-bb, TT, and bb group models were 0.33, 0.27, and 0.22, respectively.

[17,35]. Despite limited evidence available at the present time, vitamin D might have an anabolic effect on myotubes by modulating multiple intracellular signaling pathways including genomic and nongenomic mechanisms [6].

For genomic mechanism, vitamin D binds to VDR and is transported to the nucleus [36], which can promote muscle fiber proliferation and related protein synthesis [37]. Therefore, we could infer that because VDR expression affects myocytes and muscle fiber, Fok1 genotypes are associated with handgrip strength and muscle mass in this study. According to nongenomic mechanism, vitamin D can activate the pathways of the calcic endoplasmic reticulum to increase the storage of calcium in myogenous cells to regulate muscle strength and function through the second messenger pathway [38,39]. Because of these reasons, the association between lower 25(OH)D levels and lower skeletal muscle strength in Chinese elderly men (Tables 2 and 3) as well as the interaction between 25(OH)D levels and VDR (i.e., vitamin D binds to VDR; genomic pathway) could be explained.

Our findings are consistent with those from previous studies [31,40–42]. A prospective study [34] suggested that low 25(OH)D levels may contribute to the decline in muscle strength in elderly individuals, especially in men. Clinical studies [10] have shown that vitamin D supplementation improves the skeletal muscle strength in elderly people who have a vitamin D deficiency or low-level status. However, we did not find an association between 25(OH)D levels and SMM and 4-m usual gait speed (m/s; Table 2). Baseline 25(OH)D levels (Table 1), basic characteristics of the study subject, and difference in measurements of SMM and function may be reasons why, but these still need to be confirmed. Meanwhile, there are other important factors that may impact muscle mass and 4-m usual gait speed such as hormones and the nervous system. However, the results from this study provided more evidence for the association between 25(OH)D levels and VDR genotypes with handgrip strength.

VDR Fok1 polymorphism is known to affect the translation initiation site [25,43]. Some studies have indicated a generally modest contribution of this gene to SMM and function [12,15,21]. Most previous studies [12–15,21,25,27] divided participants into several groups by VDR genotype (Fok1: FF/CC, Ff/CT, ff/TT, or Bsm1: BB/AA, Bb/AG, bb/GG) and compared differences in muscle mass and function between the two groups, but the results were inconsistent. In our study, we observed that participants with the TT genotype had more handgrip strength (Tables 3, 4, and S2) and RSMI (Table S2) compared those with CC or CT genotypes.

With regard to Bsm1, Geusens et al. [26] found that Bsm1 b/b genotype carriers had higher quadriceps and grip strength compared with B/B genotype carriers. However, some studies [15, 27] have reported opposite findings. For example, Grundberg et al. [27] found that subjects had higher strength in the B/B group compared with those who were b/b carriers. In our study, we observed that participants who bb genotype carriers exhibited more handgrip strength compared with those who were B-allele carriers (Table 3), but this result was not observed after the interaction of 25(OH)D levels with Bsm1 genotypes was taken into consideration (Table 4). From this result, we can also infer that the Bsm1 b/b genotype carriers have more handgrip strength because of the interaction between vitamin D and the b/b genotype.

Of note, there was a significant interaction between 25(OH)D category and VDR genotype for both Fok1 and Bsm1 after adjustment for potential confounders (Table 4). Moreover, β' became larger in the TT and bb groups for men than when the Fok1 or Bsm1 genotypes were not considered (Table 5). Therefore, a deduction could be made that the association between 25(OH)D levels and handgrip strength was modified by the Fok1 and Bsm1 genotypes. From the results of the Fok1-Bsm1 population (Table 5), we further inferred that the T and b allele had a synergistic effect on the association between 25(OH)D levels and handgrip strength. For these reasons, we deemed a consideration of the influence of VDR gene polymorphisms necessary when analyzing the association between 25(OH)D levels and SMM, strength, and function. To our knowledge, this is the first study to analyze the interaction between VDR Fok1/Bsm1 genotypes and 25(OH)D levels on handgrip strength.

However, the limitations of this study are important to consider. First, the level of 25(OH)D was too low and the vitamin D deficiency was very severe among the participants. The association between higher 25(OH)D levels and SMM and function was impossible for us to conclude and should be the focus in other populations in the future work. Hassan-Smith found that active serum 1, 25-dihydroxyvitamin D3, but not inactive 25-hydroxyvitamin D3, were correlated with measures of lower limb strength [44], so more serum vitamin D metabolites (e.g., 1, 25-dihydroxyvitamin D3, or 25-hydroxyvitamin D2) should be taken into consideration.

Second, some researchers report that 25(OH)D level is related to isometric knee extensor strength and vitamin D remains directly related to both isometric arm and leg strength [17,31]; thus, more measurements for muscle strength and physical performance should be adopted. Finally, the measurement method of serum 25(OH)D that should be used is LC-MS/MS.

Conclusions

Serum 25(OH)D levels were associated with handgrip strength and this association can be modified by the interaction between vitamin D and VDR gene polymorphisms (Fok1 and Bsm1). VDR T (Fok1) and b (Bsm1) alleles were also concluded to have a synergistic effect.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nut.2018.05.025.

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