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Associations between vitamin D deficiency, musculoskeletal health, and cardiometabolic risk among community-living people in Taiwan

Age and sex-specific relationship

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Abstract

The role of serum vitamin D (Vit D) in cardiometabolic and muscle health remains unclear. The study aimed to evaluate associations of Vit D and factors of healthy aging among community-living middle-aged and older people in Taiwan. Analytic data on 1839 community-living older adults were excerpted from I-Lan Longitudinal Aging Study. All participants were collected demographic characteristics, serum Vit D, functional assessment, and cardiometabolic risk factors. The prevalence of Vit D insufficiency and deficiency in this study was 50.5% and 33.6%, respectively. Among 617 participants with Vit D deficiency, 72.3% of them were women. In multivariate logistic regression, the independent risk factors of Vit D deficiency were male gender (odds ratio [OR]: 0.266; 95% confidence interval [CI]: 0.213–0.333; $P<0.001$), higher BMI (OR: 1.036; 95% CI: 1.005–1.067; $P=0.022$), high total cholesterol (OR: 1.437; 95% CI: 1.160–1.779; $P=0.001$), and high triglyceride (OR: 1.865; 95% CI: 1.446–2.404; $p<0.001$). In multinomial logistic regression for 3-level Vit D status analysis, similar trend was found among participants with Vit D insufficiency. Insulin resistance increased in 2.31 and 1.71-folds in Vit D deficiency and insufficiency groups. Besides, association between Vit D deficiency and osteopenia was found only in women. In conclusion, Vit D deficiency was more common in women, and associated with poorer musculoskeletal health and higher cardiovascular and metabolic risk, including higher BMI, DBP, insulin resistance, total cholesterol, and triglyceride.

Abbreviations: HDL-C = high-density lipoprotein cholesterol, HOMA-IR = Homeostatic model assessment-insulin resistance, ILAS = I-Lan Longitudinal Aging Study, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride, Vit D = vitamin D.

Keywords: cardiometabolic risk, musculoskeletal health, vitamin D

1. Introduction

Vitamin D (Vit D) was composed by a group of secosteroids, which was responsible for intestinal absorption of calcium, magnesium, and phosphate .[1] The major physiological function of Vit D was to maintain calcium homeostasis and metabolism, hence, deficiency of Vit D may result in impaired bone mineralization, subsequent rickets in children, osteomalacia and osteoporosis in adults .[2] A number of risk factors for Vit D deficiency had been reported, including older age, malnutrition, obesity, insufficient sun exposure, living conditions, critical illnesses, and others.[3] In addition to bone metabolism, Vit D also played active roles in maintaining physiological function of other organ systems. Owing to the impact of Vit D on multiple organ systems, Vit D deficiency has been reported to be associated with various dysfunctions, including musculoskeletal system (such as osteoporosis[4] and sarcopenia, [5] physical function,[6] cognitive function,[7] and cardiovascular risk).[8,9] A study of 12,644 participants from the Third US National Health and Nutrition Examination Survey (NHANES III) showed inverse association between Vit D level and SBP.[9] However, a randomized controlled trial of supplementation with 2800 IU of Vit D3 per day for 8 weeks did not reveal any significant treatment effects on blood pressure, cholesterol, or insulin resistance. Evidences support that Vit D receptors expressed throughout the cardiovascular system, and activations of Vit D receptor in molecular level demonstrate antiatherosclerotic and protective effects on cardiovascular risk factors.[10] However, mechanism for low Vit D may improve cardiovascular risk remained unclear, and more well-designed randomized controlled trials are needed.[11] There are several potential hypotheses including

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negative downregulation of the renin–angiotensin–aldosterone system on blood pressure, directly improving vascular compliance or improvement of glycemic control.[12] Interestingly, though previous work found similar prevalence of Vit D deficiency with only minor differences by gender or age, the associated multimorbidities actually showed prevalence diversity between genders of diabetes, hypertension, peripheral vascular disease, coronary artery disease, myocardial infarction, and stroke.[13] Age, gender, and body size also affected seasonal variation of Vit D levels.[14]

Internationally, approximately 1 billion people may be Vit D insufficient or deficient, including healthy community-living people, and even patients receiving medical treatment for osteoporosis .[2] Although supplementation of Vit D was expected to reverse the adverse impact of Vit D deficiency, the evidence was inconsistent.[8,15] The ineffectiveness of Vit D supplementation to prevent adverse outcomes may be resulted from some possibilities: the existence of hidden confounding factors that biased the association between Vit D deficiency and pathology, the lack of comprehensive data collection of study participants in evaluating those associations, and longer period of Vit D supplementation may needed to reverse the adverse impact. Therefore, the main aim of this study was to clarify the associations between serum Vit D status, musculoskeletal health condition, and cardiometabolic risk factors by using a cohort of community-living middle-aged and older adults with comprehensive data collection. Further, gender and age were analyzed in relation to the aforementioned dependent variables.

2. Materials and methods

2.1. Study participants

I-Lan Longitudinal Aging Study (ILAS) recruited community-dwelling people aged 50 years and older living in Yilan County of Taiwan, and the study protocol has been published in several previous studies.[16–20] ILAS aimed to investigate the complex interrelationship between aging, frailty, sarcopenia and cognitive declines. The inclusion criteria were: inhabitants of Yilan County with no intentions of relocating in the near future; and aged 50 years or older. ILAS excluded subjects as follows: unable to communicate with the interviewer or to sign the informed consent; unable to complete a 6-m walk within a reasonable time; with major illness, such as cancer, with life expectancy of less than 6 months; or currently institutionalized at the time of screening. Overall, 1839 participants received face-to-face interviews by the research staff, and all of them received subsequent body composition tests and physical examinations. All participants signed the written informed consent before they were enrolled for study. The institutional review board of the National Yang Ming University approved the study protocol. The study was designed and conducted in accordance with the principles of the Declaration of Helsinki; the cross-section and observational design and reporting format follow the STROBE guidelines.[21] The datasets generated during and/or analyzed during the current study are available from the Institutional Data Access of the National Yang-Ming University/Ethics Committee for researchers who meet the criteria for access to confidential data.

2.2. Demography and functional assessment

For all participants, the research nurses completed the questionnaire of demographic characteristics, past medical history, and personal health behavior. In addition, comprehensive functional assessment was performed for all participants, including Center for Epidemiologic Studies Depression Scale for depressive symptoms,[22] Charlson's comorbidity index for disease severity,[23] short-form mini-nutritional assessment for nutritional status;[24] Mini-Mental State Examination for cognitive status,[25] and Functional Autonomy Measurement System for functional status.[26]

Participants were defined as weakness in those who had lowest quintile of handgrip strength (measured using the Smedley Dynamometer; TTM, Tokyo, Japan), and as slowness in those who had slow walking speed in 6-m walking test. Weakness and slowness referred to those performances lower than the gender-specific lowest 20% of study population. [27]

2.3. Bone quality and appendicular muscle measurement

A whole body dual-energy X-ray absorptiometry scan was performed on each participant to measure their appendicular skeletal muscle mass by using a Lunar Prodigy instrument (GE Healthcare, Madison, WI), which was calculated as the sum of the lean soft tissue mass of all four limbs. Appendicular skeletal muscle mass index was adjusted by height (m) square (ASM/height^2, kg/m^2). Bone marrow density at the lumbar spine and bilateral hip joints was measured for analysis.

2.4. Laboratory measurements

All participants received venipuncture for blood sampling after 10-h overnight fast. Serum concentrations of fasting glucose (mg/dL), total cholesterol (TC, mg/dL), triglyceride (TG, mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/dL), high-density lipoprotein cholesterol (HDL-C, mg/dL) were measured by using an automatic analyzer (ADVIA 1800, Siemens, Malvern, PA). Whole-blood glycated hemoglobin A1c was measured by enzymatic method using the Tosoh G8 HPLC Analyzer (Tosoh Bioscience, Inc., San Francisco, CA). Serum insulin level (uIU/mL) was measured by the chemiluminescence immunoassay analyzer (ADVIA Centaur, Siemens). Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated as (glucose (mg/dL) $\times$ insulin (uIU/mL))/405.[28]

2.5. Definition of Vit D status

Serum level less than 20 ng/mL was defined as "deficiency," [2] whereas serum level was between 20 and 30 ng/mL was defined as "insufficiency," and those serum level more than (or equal to) 30 ng/mL was classified as "normal."[2,29]

2.6. Definition of cardiometabolic risk

In this study, cardiometabolic risk factors were defined as follows: high blood pressure was defined as "SBP $\geq$130 mm Hg" or "DBP $\geq$85 mm Hg," TC $\geq$200 mg/dL as "high TC," serum HDL-C $<$40 mg/dL in men or $<$50 mg/dL in women as "low HDL-C," serum TG $\geq$150 mg/dL as "high TG," serum LDL-C $\geq$130 mg/dL as "high LDL-C," and waist circumference $\geq$ 90 cm in men and $\geq$80 cm in women as "abnormal waist circumference.".[30] We defined "high HOMA-IR" as highest quintile from the population in this study.

2.7. Statistical analysis

Continuous variables were expressed as mean (standard deviation), and categorical data were expressed as frequency and percentage. Regarding basic characteristics analysis,

Table 1

Baseline sex stratified characteristics of participants.

	All (n = 1839)	Male (n = 873)	Female (n = 966)	*P* value
Age (years)	63.9 (9.3)	65.0 (9.7)	62.8 (8.7)	<0.001
BMI (kg/m^2)	24.9 (3.6)	24.9 (3.3)	24.8 (3.8)	0.433
Education (years)	6.2 (5.0)	7.1 (5.0)	5.4 (4.8)	<0.001
Current cigarette smoker	336 (18.3%)	306 (35.1%)	30 (3.1%)	<0.001
Current alcohol drinker	607 (33.0%)	435 (49.8%)	172 (17.8%)	<0.001
Serum vitamin D level, (ng/mL)	23.4 (7.1)	26.1 (7.4)	20.9 (5.8)	<0.001
Vitamin D deficiency	617 (33.6%)	171 (19.6%)	446 (46.2%)	<0.001
Vitamin D insufficiency	929 (50.5%)	479 (54.9%)	450 (46.6%)	<0.001
Charlson comorbidity index	1.0 (1.3)	1.0 (1.2)	1.0 (1.3)	0.959
Hypertension	762 (41.4%)	368 (42.2%)	394 (40.8%)	0.552
Type 2 diabetes mellitus	309 (16.8%)	143 (16.4%)	166 (17.2%)	0.645
Dyslipidemia	143 (7.8%)	53 (6.1%)	90 (9.3%)	0.009
Coronary artery disease	95 (5.2%)	38 (4.4%)	57 (5.9%)	0.134
T-score (L-spine)	−0.7 (1.5)	−0.3 (1.1)	−1.1 (1.4)	<0.001
T-score (Hip)	−0.9 (1.1)	−0.6 (1.1)	−1.1 (1.1)	<0.001
CES-D	2.4 (4.6)	2.0 (3.7)	2.8 (5.2)	<0.001
MNA-SF	13.4 (1.0)	13.4 (1.0)	13.3 (1.0)	0.051
MMSE	25.6 (4.0)	26.2 (3.5)	25.1 (4.4)	<0.001
SMAF	−0.2 (1.6)	−0.2 (1.8)	−0.2 (1.5)	0.575

CES-D = Center for Epidemiological Studies-Depression, MNA-SF = Mini Nutritional Assessment-Short Form, MMSE = Mini-Mental State Examination, SMAF = Functional Autonomy Measurement System.

comparisons between categorical variables were performed by Chi-square or Fisher's exact test when appropriate; comparisons between continuous variables were performed by Student *t* test. While analyzing variables between different serum Vit D levels, one-way analysis of variance was used to compare continuous variables between multiple categories. Analysis of covariance was applied to evaluate the association between serum Vit D level and physical function, musculoskeletal health, and cardiometabolic risk factors adjusted for age and sex.

Binary logistic regressions were used to explore the independent associative factors for Vit D deficiency, and factors with potential association ($P < 0.10$) were used for multivariate logistic regression model with Backward Wald method. Further, building the modeling of Vit D insufficiency and deficiency (reference group: participants with normal Vit D levels), multinomial logistic regression model was used to evaluate the independent association between parameters of cardiovascular system and musculoskeletal system after adjustment of potential confounding factors. Confounding factors including age and gender were adjusted to evaluate the odds ratio in different models. All statistical analyses were performed by statistical software SPSS 22.0 (SPSS, Chicago, IL). For all *P* value less than 0.05 was considered as statistically significant.

3. Results

Overall, data of 1839 participants were obtained for study. The mean age and prevalence of chronic illness were similar compared to the Taiwan Longitudinal Study on Ageing survey. [31]Table 1 summarized the baseline characteristics and demographic characteristics of all participants. The prevalence of Vit D deficiency in this study was 33.6%, and 50.5% for Vit D insufficiency. A significant sex difference was identified in this study that 72.3% of subjects with Vit D deficiency was women, and only 23.9% subjects with normal Vit D level was women. Compared to men, women were significantly younger, having lower educational level, lower bone mineral density, higher score of center for epidemiological studies depression, higher score of mini-mental status examination, and higher prevalence of dyslipidemia (Table 1).

Table 2 compared subjects with different status of serum Vit D. Adjusted for age and sex, people with Vit D deficiency had significantly poorer physical function and nutritional status. Considering cardiometabolic parameters, subjects with Vit D deficiency had higher BMI, higher waist circumference, more abnormal blood pressure, higher insulin resistance, and higher serum levels of TC, LDL-C, and TG. However, no statistical difference was identified in depressive mood, comorbidity, mean carotid intima media thickness, or serum level of high sensitive C-reactive protein between groups.

Table 3 showed the associative factors for Vit D deficiency in univariate analysis that age, gender, BMI, high waist circumference, slowness (low walking speed), weakness (low grip strength), osteoporosis, mean carotid intima media thickness, high TC, high LDL-C, high TG, and high HOMA-IR were all significantly associated with Vit D deficiency. In multivariate logistic regression, we found that male gender (odds ratio [OR]: 0.266; 95% confidence interval [CI]: 0.213–0.333; $P < 0.001$), higher BMI (OR: 1.036; 95% CI: 1.005–1.067; $P = 0.022$), high TC (OR: 1.437; 95% CI: 1.160–1.779; $P = 0.001$), and high TG (OR: 1.865; 95% CI: 1.446–2.404; $P < 0.001$) were associative factors for Vit D deficiency. Meanwhile, slowness (low walking speed) showed borderline association (OR: 1.697; 95% CI: 0.980–2.939; $P = 0.059$).

Further, adjusted for potential confounders and compare the 3 levels of vitamin status (deficiency, insufficiency, and normal), Vit D deficiency was significantly associated with higher malnutrition risk (OR: 2.02; 95% CI: 1.10–3.71; $P = 0.023$), poorer functional status (OR: 3.78; 95% CI: 1.57–9.13; $P = 0.003$), high waist circumference (OR: 1.54; 95% CI: 1.13–2.08; $P = 0.006$), high serum TC (OR: 2.35; 95% CI: 1.71–3.24; $P < 0.001$), high LDL-C (OR: 1.96; 95% CI: 1.41–2.72; $P < 0.001$), and high TG (OR: 2.88; 95% CI: 1.98–4.19; $P < 0.001$)(Table 4). Interestingly, higher SBP seemed to be a protective factor (OR: 0.71; 95% CI: 0.53–0.96; $P = 0.025$). Moreover, insulin resistance was significantly associated with Vit D status, and the lower the Vit D level was, the higher odds ratio and the stronger correlation was.

Table 2

Comparison between groups of different serum vitamin D status.

Serum vitamin D status	Deficiency (n = 617)	Insufficiency (n = 929)	Normal (n = 293)	*P* trend	*P* value adjusted*
Age (years)	63.0 (9.0)	64.0 (9.2)	65.4 (9.6)	<0.001	0.028
Men (%)	27.7%	51.6%	76.1%	<0.001	<0.001
BMI (kg/m^2)	25.21 (3.81)	24.84 (3.53)	24.17 (3.19)	<0.001	<0.001
High WC (%)	55.8	49.5	38.9	<0.001	0.008
CES-D	2.56 (5.15)	2.33 (4.17)	2.42 (4.43)	0.663	0.657
Charlson comorbidity index	0.95 (1.19)	1.04 (1.33)	1.10 (1.23)	0.089	0.331
Low MNA-SF (%)	4.7	5.5	7.8	0.071	0.029
Low SMAF (%)	5.3	4.2	2.4	0.041	0.001
Slowness (%)	5.5	2.2	5.1	0.218	0.075
Weakness (%)	20.1	15.0	18.4	0.200	0.373
Osteopenia (%)	42.2	45.1	38.5	0.008	0.823
Osteoporosis (%)	18.0	14.3	12.9		
Low ASMI (%)	18.1	16.2	15.4	0.264	0.608
High SBP (%)	48.3	48.8	53.6	0.194	0.035
High DBP (%)	21.4	21.5	17.1	0.215	0.011
High total cholesterol (%)	51.9	42.8	27.0	<0.001	<0.001
Low HDL-C (%)	25.0	20.6	17.1	0.004	0.301
High LDL-C (%)	39.1	36.5	35.4	<0.001	<0.001
High triglyceride (%)	29.7	20.2	16.7	<0.001	<0.001
Mean Carotid intima media thickness (cm)	0.68 (0.13)	0.70 (0.15)	0.71 (0.16)	0.002	0.471
Abnormal fasting glucose (%)	36.6	35.5	29.8	0.069	0.064
High hemoglobin A1c (%)	18.6	18.6	15.4	0.314	0.418
High HOMA-IR (%)	25.1	19.2	11.6	0.001	<0.001
High sensitive C-reactive protein (%)	0.21 (0.49)	0.21 (0.43)	0.23 (0.44)	0.536	0.567

ASMI = appendicular skeletal muscle index, CES-D = Center for Epidemiological Studies-Depression, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostatic model assessment-insulin resistance, LDL-C = low-density lipoprotein cholesterol, MNA-SF = Mini Nutritional Assessment Short Form, MMSE = Mini-Mental State Examination, SMAF = Functional Autonomy Measurement System, WC = waist circumference.

* *P* values adjusted for age and sex according to analysis of covariance (ANCOVA).

Insulin resistance increased in 2.31 and 1.71-fold in Vit D deficiency and insufficiency group. Besides, DBP was also significantly higher among subjects of Vit D deficiency and insufficiency group (OR: 1.68; 95% CI: 1.15–2.46; $P = 0.007$ and OR: 1.50; 95% CI: 1.06–2.12; $P = 0.024$, respectively). Table 4 also showed the associations between Vit D status and other factors in men and women. In men, there were significant associations between Vit D deficiency and cardiometabolic risk

Table 3

Independent associative factors of Vit D deficiency among community-dwelling older adults in Taiwan.

Dependent	Independent	OR (95% CI) Univariate	OR (95% CI) Multivariate
Vit D deficiency	Age group		
	50–59 y/o	Reference	
	60–69 y/o	0.844 (0.669, 1.065)	
	≥70 y/o	0.771 (0.609, 0.976)*	
	Gender		
	Women	Reference	Reference
	Men	0.284 (0.230, 0.350)**	0.266 (0.213, 0.333)**
	BMI	1.042 (1.014, 1.070)**	1.036 (1.005, 1.067)*
	High waist circumference	1.423 (1.171, 1.728)**	
	Charlson comorbidity index	0.933 (0.862, 1.009)	
	Slowness (low walking speed)	1.978 (1.221, 3.204)**	1.697 (0.980, 2.939)
	Weakness (low grip strength)	1.341 (1.045, 1.722)*	
	Osteoporosis	1.383 (1.038, 1.843)*	
	Mean Carotid intima media thickness	0.345 (0.172, 0.691)*	
	High total cholesterol	1.683 (1.384, 2.046)**	1.437 (1.160, 1.779)**
	High LDL-C	1.269 (1.039, 1.551)*	
	High triglyceride	1.752 (1.401, 2.191)**	1.865 (1.446, 2.404)**
	High HOMA-IR	1.592 (1.259, 2.013)**	

Stepwise multivariate logistic regression with variables of $P < 0.1$ employed for statistical analysis. ORs and CIs were presented only for significant variables with $P < 0.10$. CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostatic model assessment-insulin resistance, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio.

* $P < 0.05$.

** $P < 0.01$).

Table 4

Odds ratio adjusted for vitamin D status for parameters of function, musculoskeletal health, and cardiometabolic risks according to multinomial logistic regression.

	Total (adjusted for age and gender)				Men (adjusted for age)				Women (adjusted for age)			
	Insufficiency		Deficiency		Insufficiency		Deficiency		Insufficiency		Deficiency	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age group												
50–59 y/o	Reference		Reference		Reference		Reference		Reference		Reference	
60–69 y/o	0.91 (0.65–1.26)	0.552	0.79 (0.55–1.13)	0.189	0.85 (0.58–1.27)	0.432	0.68 (0.41–1.11)	0.122	1.11 (0.59–2.08)	0.755	0.99 (0.53–1.87)	0.982
≥70 y/o	0.82 (0.59–1.13)	0.215	0.75 (0.53–1.07)	0.110	0.93 (0.64–1.36)	0.706	0.80 (0.50–1.28)	0.348	0.58 (0.32–1.05)	0.070	0.57 (0.31–1.02)	0.060
MalnutrItion (low MNA-SF)	1.59 (0.94–2.69)	0.086	2.02 (1.10–3.71)	0.023	0.74 (0.38–1.44)	0.374	0.35 (0.11–1.07)	0.065	0.53 (0.23–1.22)	0.134	0.49 (0.21–1.15)	0.102
Functional impairment (low SMAF)	2.32 (1.00–5.39)	0.049	3.78 (1.57–9.13)	0.003	2.25 (0.89–5.66)	0.085	2.78 (0.96–8.05)	0.059	3.12 (0.39–25.0)	0.284	6.33 (0.81–49.32)	0.078
Osteopenia	1.29 (0.96–1.74)	0.093	1.14 (0.82–1.59)	0.441	1.06 (0.75–1.49)	0.736	0.90 (0.59–1.39)	0.643	2.64 (1.38–5.05)	0.003	2.33 (1.21–4.47)	0.011
Osteoporosis	1.04 (0.66–1.66)	0.855	1.11 (0.67–1.83)	0.684	1.50 (0.79–2.83)	0.216	0.91 (0.38–2.17)	0.838	1.14 (0.54–2.41)	0.740	1.41 (0.67–2.98)	0.368
High waist circumference	1.36 (1.03–1.79)	0.031	1.54 (1.13–2.08)	0.006	1.43 (1.02–1.99)	0.037	1.74 (1.15–2.62)	0.008	1.22 (0.73–2.06)	0.447	1.33 (0.79–2.25)	0.280
High SBP	0.77 (0.59–1.01)	0.058	0.71 (0.53–0.96)	0.025	0.68 (0.49–0.94)	0.020	0.56 (0.37–0.83)	0.005	1.08 (0.64–1.81)	0.787	1.05 (0.62–1.76)	0.869
High DBP	1.50 (1.06–2.12)	0.024	1.68 (1.15–2.46)	0.007	1.53 (1.03–2.28)	0.037	1.79 (1.11–2.89)	0.017	1.44 (0.70–2.95)	0.324	1.56 (0.76–3.21)	0.223
High total cholesterol	1.82 (1.35–2.44)	<0.001	2.35 (1.71–3.24)	<0.001	1.51 (1.07–2.15)	0.020	1.84 (1.20–2.81)	0.005	3.04 (1.68–5.50)	<0.001	3.96 (2.19–7.17)	<0.001
High LDL-C	1.77 (1.31–2.41)	<0.001	1.96 (1.41–2.72)	<0.001	1.70 (1.19–2.43)	0.004	1.87 (1.21–2.89)	0.005	2.00 (1.09–3.67)	0.026	2.19 (1.19–4.02)	0.011
High triglyceride	1.46 (1.02–2.07)	0.037	2.88 (1.98–4.19)	<0.001	1.26 (0.85–1.86)	0.250	2.75 (1.76–4.31)	<0.001	3.24 (1.14–9.17)	0.027	5.73 (2.04–16.10)	0.001
High HOMA-IR	1.71 (1.15–2.55)	0.008	2.31 (1.52–3.51)	<0.001	2.34 (1.38–3.96)	0.002	3.63 (2.03–6.51)	<0.001	0.97 (0.53–1.80)	0.932	1.25 (0.68–2.31)	0.469

HOMA-IR = homeostatic model assessment-insulin resistance, LDL-C = low-density lipoprotein cholesterol, MNA-SF = mini-nutrition assessment-Short Form, SMAF = the Functional Autonomy Measurement System.

including high waist circumference (OR: 1.74; 95% CI: 1.15–2.62; $P = 0.008$), high DBP (OR: 1.79; 95% CI: 1.11–2.88; $P = 0.017$), high TC (OR: 1.84; 95% CI: 1.20–2.81; $P = 0.005$), high LDL-C (OR: 1.87; 95% CI: 1.21–2.89; $P = 0.005$), and high TG (OR: 2.75; 95% CI: 1.76–4.31; $P < 0.001$). In women, however, the associations between Vit D deficiency and cardiometabolic risk were weaker. Besides, the association between serum Vit D status and bone health was only seen in osteopenia in women (OR: 2.33; 95% CI: 1.21–4.47; $P = 0.011$ in Vit D deficiency group and OR: 2.64; 95% CI: 1.38–5.05; $P = 0.003$ in Vit D insufficiency group).

4. Discussion

Findings from the study showed the inverse association between Vit D deficiency and cardiovascular risk factors including TC, TG, LDL-C, and insulin resistance. In addition, Vit D deficiency was associated with muscle strength and performance as handgrip strength and walking speed, respectively.

The prevalence of Vit D deficiency was 33.6%, which was significantly lower than that (66.2%) reported from the Nutrition And Health Survey in Taiwan.[32] The discrepancy may be resulted from the differences in lifestyle and living environment of study participants. Most participants in this study lived at rural communities and carried out heavy daily physical activities and sunlight exposure due to farming activities. Besides, we found significant sex differences in the associations between Vit D deficiency, musculoskeletal health, and cardiometabolic risk. Women were more commonly to be Vit D deficient than men, which was in line with results of the previous study.[33]

The reported associations between Vit D deficiency and cardiovascular risk were compatible with results of this study,[8,9] however, the sex-different associations were also noted in this study. Vit D had been shown to suppress pro-inflammatory cytokines, including tumor necrosis factor-α, and deferred the promotion of arterial stiffness,[34] which may play certain roles in the pathogenesis of cardiovascular disease. In kidney, Vit D may suppress renin production at the juxtaglomerular apparatus,[35] and further regulated the renin–angiotensin–aldosterone system to lower blood pressure. Thus, higher blood pressure may be a consequence to Vit D deficiency. Besides, Vit D also suppressed the expression of CD36 and peroxisome proliferator-activated receptor-r, and may slow the process of developing cardiovascular disease in patients with diabetes mellitus. Reduced Vit D receptor signaling may also increase foam cell formation and accelerated atherosclerosis that promoted the development of cardiovascular disease among subjects with Vit D deficiency.[36] Therefore, low serum Vit D may substantially increase the risk and development of cardiovascular diseases from multiple potential pathophysiological pathways.

The associations between Vit D deficiency and low bone mineral density had been reported in previous studies,[4] but the association was only seen in women with osteopenia in this study. Despite the association between Vit D deficiency and bone mineral density was noted in women, no association was found between skeletal muscle mass and muscle index in any age or sex-specific group. Serum levels of Vit D were not an appropriate biomarker or therapeutic targets for skeletal muscle mass when considering muscle health. [37]

Vit D deficiency may be resulted from multiple etiologies, and the negative impacts of Vit D deficiency were also associated with multiple mechanisms. Hence, the inconsistent results between Vit D supplementation in preventing adverse outcomes were not

surprising. On one hand, simple Vit D supplementation may not sufficiently reverse all the cumulative negative impacts of Vit D deficiency, and on the other hand, the potential benefits of Vit D supplementation may need a longer period of time to show.

Despite all efforts went into this study by collecting comprehensive data to clarify the association between Vit D deficiency and various clinical characteristics, there were still some limitations. First, the cross-sectional study design did not provide sufficient information to clarify the causal relationship between Vit D deficiency and clinical characteristics. Second, the duration of Vit D deficiency for the study participants remained unknown, so estimating the overall effect of Vit D deficiency on these clinical characteristics may become inaccurate. Third, participants in ILAS residing in an agriculture county, hence the difference of lifestyle of study participants between this study and other previous ones may be another confounding factor for further comparisons, and might limit the generalizability to urban population.

5. Conclusions

In conclusion, Vit D deficiency or insufficiency was very common among community-living middle-aged and older adults in Taiwan. The associations between Vit D deficiency, musculoskeletal health, and cardiometabolic risk showed a strong age and sex-different relationship. In addition, the lower the Vit D level was, the higher odds ratio and the stronger correlation was. Further longitudinal study is needed to evaluate the clinical impact of Vit D deficiency status to health of older people.

Author contributions

1) Conceived and designed the experiments: LNP, WJL, LKC
2) Performed the experiments: N/A
3) Analyzed and interpreted the data: CHC, LKL, MJC
4) Contributed reagents, materials, analysis tools or data: LKC
5) Wrote the paper: CHC
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