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Received: 10 September 2020 | Revised: 15 February 2021 | Accepted: 18 February 2021

DOI: 10.1002/dmrr.3457

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RESEARCH ARTICLE

Vitamin D insufficiency is associated with metabolic syndrome independent of insulin resistance and obesity in young adults - The Berlin Aging Study II

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Funding information
German Federal Ministry of Education and Research, Grant/Award Number: #16SV5536K, #16SV5537, #16SV5538, and #16SV5837; Max Planck Institute for Human Development
Open access funding enabled and organized by Projekt DEAL

Abstract

Purpose: Age-related changes affect vitamin D absorption and metabolism. Low 25-hydroxyvitamin D concentrations have been reported as risk factor for the development of metabolic syndrome (MetS). However, recent evaluations suggest this association might be explained by obesity or insulin resistance (IR) in subjects with MetS. Our aim was to analyze associations between vitamin D insufficiency and MetS in a young cohort without diabetes and two senior cohorts with and without diabetes.

Methods: Four hundred sixteen young and 1357 older BASE-II participants were analyzed. Type 2 diabetes (T2D) was defined according to European Society of Cardiology (ESC) guidelines, MetS as suggested by International Diabetes Federation/American Heart Association/National Heart, Lung and Blood Institute (IDF/AHA/NHLBI 2009). Vitamin D insufficiency was defined as 25-hydroxyvitamin D concentrations <50 nmol/L. Among other confounders, BMI and IR were taken into account.

Results: MetS was prevalent in 7.7% of the young and in 35.6% of the older BASE-II participants and T2D occurred in 12.7% of the older participants. In young subjects without diabetes, vitamin D insufficiency was associated with an independent 3.2-fold increased odds of having MetS (OR: 3.2 CI: 1.0–8.7; $p = 0.042$). However, in the older participants, this association was lost once BMI was taken into account among those with diabetes, and once IR was taken into account among those without diabetes.

Conclusion: Independent associations between vitamin D insufficiency and MetS were only found among young subjects without diabetes. In the older adults, BMI annihilated these associations among subjects without diabetes as did HOMA-IR among subjects with diabetes.

KEYWORDS
diabetes, dietary vitamin D intake, metabolic syndrome, vitamin D

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1 | INTRODUCTION

Vitamin D, a prohormone, is essential for bone mineral metabolism but several non-skeletal functions are being recognized, as vitamin D receptors have been identified in various tissues such as muscle and pancreatic tissue.[1-3] Low 25-hydroxyvitamin D concentrations have consequently been associated with a variety of diseases such as obesity, insulin resistance (IR), sarcopenia, immune deficiency, cancer, cardiovascular disease, and increased fall risk.[4-8] Vitamin D—in contrast to other vitamins—can be produced in the skin and is found in certain foods such as oily fish and eggs. Nevertheless, vitamin D insufficiency is common, due to a low vitamin D content in most foods and a lack of UVB-induced vitamin D synthesis at high latitudes.[9-11] In older adults in particular, dietary deficiency of vitamin D is particularly common, especially in the case of malnutrition or alcohol consumption.[12,13] Besides the inadequate dietary intake, diminished exposure to sunlight, reduced skin thickness and impaired intestinal absorption in the old lead to an increased risk for vitamin D insufficiency.[12,14,15] In addition, impaired hydroxylation of 25-hydroxyvitamin D in the liver and kidney leads to altered metabolism of vitamin D in the old.[13] The metabolic syndrome (MetS) is a cluster of at least three out of five important cardiovascular risk factors: these risk factors include hypertension, dyslipidemia, elevated waist circumference, and hyperglycemia. The prevalence of MetS increases with age[16] and has been linked to a variety of diseases such as diabetes, osteoporosis, lung function decline, or cardiovascular disease and outcomes.[16-21]

Notably, several studies suggested that vitamin D insufficiency increases the risk for MetS in children, adolescents, and older people.[22-29] Although, recent studies suggested that this association may be indirect and mainly driven by the frequently increased BMI and/or IR among individuals who are affected by the MetS. For example, in a large Korean study among 5559 adult participants, the association between vitamin D status and MetS vanished when BMI was included in the multivariate model.[30] Similarly, Huang et al. reported that after adjustment for IR and BMI, the inverse relationship between vitamin D status and prevalence of the MetS disappeared among young subjects without diabetes.[25] Thus, to date, the association between vitamin D and MetS remains unclear. Moreover, the influence of age on the association between vitamin D status and MetS has not been studied conclusively.[31]

To point out age-specific differences, within the current study of Berlin Aging study II (BASE-II) data, we assessed the odds of the MetS in vitamin D insufficiency among young (n = 416; age 22–37 years) and older adults (n = 1357; age 60–84 years, with and without T2D) including important covariate information on BMI, IR, and dietary as well as supplement-based vitamin D intake.

2 | METHODS

2.1 | Study population

For the current cross-sectional analysis, we included 1773 participants (a young cohort [n = 416; 52.4% female] and an old cohort [n = 1357; 51.6% female]) of BASE-II, a prospective epidemiological study described previously in detail elsewhere.[32,33] In brief, BASE-II is a population-based sample of community-dwelling participants, living in the greater metropolitan area of Berlin, Germany (the latitude of Berlin is 52°31′27″ N). All subjects gave written informed consent to participate in the study. The study was conducted according to the Declaration of Helsinki. The study was approved by the ethics committee of Charité–University Medicine Berlin (project number: EA2/029/09).

2.2 | Exclusion criteria

Only subjects with complete data on MetS (waist circumference, triglycerides, high-density lipoprotein [HDL] cholesterol, blood pressure, glucose, HbA1c, and T2D) were included in the data analysis. This resulted in a sample of 1357 participants with and without T2D, aged between 60 and 84 years, and 416 young subjects without diabetes (20–37 years old). In order to prevent bias due to disease state, we analysed anamnestic information on history of Cushing disease, hyperparathyroidism, or severe liver disease, however no participant in the collected sample reported such a disease. With respect to the regression models calculated, we excluded subjects taking vitamin D supplements and subjects with potentially severe hypo-/hyperthyroidism (fT3 <1,80 or fT3 >5,70 pg/ml).

2.3 | Diabetes mellitus (T2D)

T2D was defined according to the guidelines of the European Society of Cardiology (ESC),[34] MetS was defined as suggested by the International Diabetes Federation/American Heart Association/National Heart, Lung and Blood Institute (IDF/AHA/NHLBI 2009).[16] Vitamin D insufficiency was defined as 25(OH)D below 50 nmol/L according to the Institute of Medicine (IOM) guidelines.[35] Blood pressure was measured with an electronic sphygmomanometer (boso-medicus memory, Jung Willingen, Germany), waist circumference was assessed using a non-elastic tape measure at the level of the umbilicus and elevated waist circumference was classified as ≥94 cm in men and ≥80 cm in women.[16]

2.4 | Laboratory measurements

After a fasting period of at least 8 h, blood was collected from the subjects, subsequently stored at 4°C–8°C and prepared for transport

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and measurement on the same day. The laboratory parameters were analyzed by a certified laboratory (Labor 28 GmbH, Berlin and Labor Berlin). Serum triglycerides and HDL cholesterol were measured with enzymatic colour tests (Roche/Hitachi Modular; device: ACN 435 und ACN 781). Insulin concentrations (NaF-tube) were analyzed by chemiluminescence measurements; IR was calculated using fasting glucose and insulin concentrations in the homeostasis model of insulin resistance (HOMA-IR) as (fasting glucose (mg/dl) × fasting insulin (mu/ml))/405.[36] 25-hydroxyvitamin D serum concentrations were assessed with two different methods (Serum-tubes): Automated chemiluminescence immunoassays (IDS-iSYS 25-Hydroxy Vitamin D Immunoassay [IDS] and LIAISON 25 OH Vitamin D TOTAL Assay [DiaSorin]). A within-assay CV of 8%–21% and a between-assay CV of 8%–34% for DiaSorin and an intraassay CV <7.3% and an interassay CV <8.9% for IDS have been described previously.[37] Moreover, variations between these two methods have been described.[38,39] The measurement of 25-hydroxyvitamin D serum concentrations was conducted by Labor Berlin, which performed a method comparison on 74 samples. An adjustment factor based on regression models was calculated and we performed an adjustment as: 25-hydroxyvitamin D serum concentrations (IDS) = 1.617 × 25-hydroxyvitamin D serum concentrations (Diasorin). Serum concentrations of C—reactive protein were analyzed using immunological turbidity test.

2.5 | Co-variables

Regular alcohol intake (yes/no), current smoking status (yes/no), and physical activity (yes/no) were assessed by standardized questions. As part of the medical examination, diagnoses were obtained through participant reports, with select diagnosis (e.g., diabetes mellitus) being verified by additional laboratory tests. Diagnoses were used to compute a morbidity index largely based on the categories of the Charlson index, which is a weighted sum of moderate to severe, mostly chronic physical illnesses, including cardiovascular (e.g., congestive heart failure), cancer (e.g., lymphoma), and metabolic diseases (e.g., diabetes mellitus).[40,41] The medical examination included an anamnestic assessment of medications including vitamin D supplementation. To estimate dietary vitamin D intake, participants completed a validated, self-administered 146-item food frequency questionnaire (European Prospective Investigation into Cancer and Nutrition).[42,43]

2.6 | Statistical analysis

The statistical analysis was carried out using the software package SPSS 21 for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0). We used the Kolmogorov-Smirnov test to examine normal distribution of all included variables. Normally distributed variables were analyzed using the parametric Student's *t*-test, variables with a skewed distribution were analyzed with the non-parametric Mann-Whitney-U-Test. Groups were compared by Chi2-test or Fisher's exact test. Regarding Tables 1 and 2, data are either shown as mean ± SD or number (%). *p*-values in Table 1 refer to the comparison of subjects with 25-hydroxyvitamin D serum concentrations <50 nmol/L and subjects with 25-hydroxyvitamin D serum concentrations ≥50 nmol/L, independently calculated for the young cohort and the old cohort. Subjects with vitamin D supplementation and potentially difficult hypo-/hyperthyroidism (fT3 <1,80 or fT3 >5,70 pg/ml) were excluded from the regression models. *p*-values in Table 2 refer to the comparison of subjects with MetS and without MetS independently calculated for the young cohort (subjects without diabetes) and the two old cohorts (subjects with diabetes and without diabetes). Finally, binary logistic regression models with MetS as a dependent variable were calculated to assess the association of vitamin D insufficiency with MetS (Table 3; *p*-values from binary logistic regression models excluding subjects with vitamin D supplementation). Regression models were independently calculated for the young cohort (subjects without diabetes) and the two old cohorts (subjects with diabetes and without diabetes). In a first step, we adjusted for an increasing number of potential co-variables. Model 1 is adjusted for age, and sex; Model 2 is additionally adjusted for physical activity, smoking status, alcohol intake, total energy intake/day, dietary vitamin D intake/day, morbidities, and CRP. Models for subjects with diabetes were additionally adjusted for antidiabetic medication (none, insulin, metformin, other oral antidiabetic medication). Moreover, we recalculated these models including HbA1c as a proxy for metabolic control of patients with T2D (Model 5). Finally, we included HOMA-IR and BMI in these binary logistic regression models (Model 3, Model 4, and Model 5) to work out the influence of obesity and IR on the association between MetS with vitamin D insufficiency. *p*-values for the association between BMI with MetS and for the association between HOMA-IR with MetS are from binary logistic regression models (adjusted for age, sex, physical activity, smoking status, alcohol intake, total energy intake/day, dietary vitamin D intake/day, morbidities, and CRP).

3 | RESULTS

Mean 25(OH) concentrations were 52.1 ± 27.9 nmol/L in the young cohort and 53.5 ± 26.0 nmol/L in the old cohort. MetS was prevalent in 7.7% of the young and 35.6% of the old cohort and T2D occurred in 12.7% of the old cohort. We found that the distribution of MetS parameters differed between young and old. Whereas elevated blood pressure (93.8%), elevated waist circumference (87.5%), and low HDL (71.9%) were the most frequently identified parameters in young subjects with MetS, elevated waist circumference (99.1% of old subjects without diabetes, 99.3% of old subjects with diabetes), IR (60.6% of old subjects without diabetes, 100% of old subjects with diabetes) and elevated blood pressure (97.3% of old subjects without diabetes, 98% of old subjects with diabetes) were predominant in the old with MetS. Vitamin D insufficiency was present in 49.3% of the young and in 44.9% of the old ($p = 0.064$). Dietary intake of vitamin D was significantly lower in the old cohort with vitamin D

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TABLE 1 Baseline characteristics of study participants according to vitamin D insufficiency and age

	Young subjects (n = 415)			Old subjects (n = 1357)		
	Vitamin D <50 nmol/L (n = 211)	Vitamin D ≥50 nmol/L (n = 205)	p Value	Vitamin D <50 nmol/L (n = 609)	Vitamin D ≥50 nmol/L (n = 748)	p Value
Age [years]	28 ± 3	28 ± 3	0.872	68 ± 4	68 ± 3	0.248
BMI [kg/m^2]	23.6 ± 4.6	23.0 ± 3.9	0.305	27.3 ± 4.5	26.4 ± 3.8	0.001
Waist circumference [cm]	83.9 ± 12.6	80.2 ± 10.5	0.003	97.7 ± 12.3	94.7 ± 11.3	0.001
Vitamin D [nmol/L]	73.8 ± 21.9	29.7 ± 10.0	0.001	71.5 ± 20.6	31.4 ± 10.0	0.001
SBP [mmHg]	124 ± 15	120 ± 14	0.009	145 ± 19	141 ± 20	0.001
DBP [mmHg]	79 ± 10	77 ± 10	0.006	84 ± 11	82 ± 12	0.040
HOMA - IR	1.5 ± 1.8	1.7 ± 1.7	0.098	2.9 ± 4.9	2.2 ± 2.9	0.001
TAG [mg/dl]	96 ± 54	89 ± 47	0.250	118 ± 63	106 ± 61	0.001
HDL [mg/dl]	59 ± 17	62 ± 16	0.028	61 ± 17	64 ± 17	0.001
MetS [n; %]	22 (10.7)	10 (4.7)	0.017	251 (41.2)	232 (31.0)	0.001
T2D [n; %]	-	-	-	84 (13.8)	88 (11.8)	0.150
Smoking status [n; %]	57 (27.8)	71 (33.6)	0.257	69 (11.3)	57 (7.6)	0.064
Regular alcohol intake [n; %]	188 (91.7)	191 (90.5)	0.410	533 (87.5)	687 (91.8)	0.006
Self-reported physical inactivity [n; %]	19 (9.5)	18 (8.6)	0.438	73 (12.1)	52 (7.1)	0.001
Energy intake [kcal/d]	2420 ± 806	2297 ± 798	0.151	2288 ± 750	2222 ± 671	0.224
Dietary vitamin D intake [µg/day]	4.1 ± 2.7	4.1 ± 2.5	0.976	4.8 ± 2.7	5.2 ± 3.0	0.001
CRP [mg/L]	1.4 ± 2.2	1.9 ± 4.3	0.683	2.1 ± 2.7	1.8 ± 2.7	0.002

Note: Data are either mean ± SD or number (%).

Abbreviations: BMI, Body Mass Index; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; SBP, systolic blood pressure; T2D, diabetes mellitus; TAG, triglycerides; vitamin D insufficiency, vitamin D <50 nmol/L.

insufficiency. Basic and clinical characteristics of both age groups according to vitamin D insufficiency are summarized in Table 1. Subjects with T2D had significantly higher BMI and HOMA-IR concentrations compared to old and young subjects without diabetes ($p < 0.001$). In addition, subjects with T2D had higher concentrations of triglycerides, exhibited more parameters of MetS, had higher CRP concentrations and lower concentrations of HDL ($p < 0.001$, data not shown).

Irrespective of age group, participants with vitamin D insufficiency were more frequently diagnosed with MetS, as waist circumference and blood pressure were significantly higher in these subjects, and HDL-concentrations were lower. In addition, old participants with vitamin D insufficiency had higher concentrations of HOMA-IR, higher BMI, higher triglyceride concentrations, higher CRP-concentrations and reported more frequently to be physically inactive and to consume alcohol on a regular basis (Table 1).

In both age groups and independent from T2D, participants with MetS suffered more frequently from vitamin D insufficiency (Table 2). BMI, HOMA-IR and waist circumference were higher in subjects with MetS independent from age group or T2D. Young subjects without diabetes and old subjects with MetS moreover reported more frequently to be physically inactive and had higher concentrations of CRP, whereas these differences were not observed between the old subjects with diabetes and with or without MetS (Table 2).

To assess the association between vitamin D insufficiency and MetS, we calculated different regression models adjusted for an increasing number of covariates. As summarized in Table 3, in adjusted models, vitamin D insufficiency increased the risk for MetS in all cohorts (Models 1 and 2). In the young subjects without diabetes, vitamin D insufficiency was associated with higher odds of having MetS even in the fully adjusted model, that is, independent from HOMA-IR and BMI (Model 5). However, these results were not observed in the old cohort with diabetes, when BMI was taken into account (Model 3) and neither seen in the old cohort without diabetes after adjustment for HOMA-IR (Models 4 and 5). HOMA-IR showed a significant association with MetS (Model 5) in young subjects without diabetes ($p = 0.011$), in old subjects without diabetes ($p < 0.001$), but not in old subjects with diabetes ($p = 0.122$), whereas BMI had a significant association with MetS (Model 5) in young subjects without diabetes ($p < 0.001$), in old subjects without diabetes ($p = 0.003$) and in old subjects with diabetes ($p < 0.006$).

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TABLE 2 Baseline characteristics of study participants according to metabolic syndrome, diabetes, and age

	Non-diabetic young (n = 415)			Non-diabetic old (n = 1185)			Diabetic old (n = 172)		
	No MetS (n = 383)	MetS (n = 32)	p	No MetS (n = 852)	MetS (n = 333)	p	No MetS (n = 22)	MetS (n = 150)	p
Age [years]	28 ± 3	29 ± 3	0.593	68 ± 4	68 ± 4	0.944	68 ± 3	68 ± 4	0.587
BMI [kg/m^2]	22.7 ± 3.6	29.8 ± 5.24	0.001	25.5 ± 3.6	28.6 ± 4.1	0.001	25.1 ± 4.2	30.1 ± 4.4	0.001
Waist circumference [cm]	80.6 ± 10.6	99.5 ± 10.7	0.001	92.2 ± 10.8	102.1 ± 10.1	0.001	89.5 ± 12.2	105.5 ± 9.9	0.001
Vitamin D [nmol/L]	53.1 ± 28.1	39.5 ± 22.0	0.003	55.2 ± 25.9	51.4 ± 26.7	0.072	59.3 ± 27.8	48.0 ± 24	0.003
Vitamin D insufficiency [n; %]	182 (47.5)	22 (68.8)	0.021	352 (41.3)	173 (52.0)	0.001	6 (27.3)	78 (52.0)	0.030
Vitamin D supplementation [n; %]	-	-		59 (6.9)	19 (5.7)	0.447	-	7 (4.7)	-
Current smoker [n; %]	119 (31.1)	9 (28.1)	0.416	79 (9.3)	27 (8.1)	0.369	4 (18.2)	16 (10.7)	0.590
Regular alcohol intake [n; %]	350 (91.4)	28 (87.5)	0.459	759 (89.1)	309 (92.8)	0.054	19 (86.4)	133 (88.7)	0.753
Self-reported physical inactivity [n; %]	30 (8.0)	7 (23.3)	0.005	56 (6.7)	42 (12.9)	0.001	4 (20.0)	23 (15.4)	0.601
Energy intake [kcal/d]	2361 ± 814	2306 ± 689	0.865	2206 ± 676	2360 ± 755	0.001	2360 ± 604	2252 ± 766	0.257
Dietary vitamin D intake [µg/day]	4.1 ± 2.6	4.4 ± 2.7	0.481	5.0 ± 2.9	5.1 ± 2.9	0.644	3.2 ± 4.9	4.9 ± 2.7	0.134
HOMA - IR	1.5 ± 1.6	3.2 ± 2.3	0.001	1.6 ± 0.8	3.1 ± 2.0	0.001	3.7 ± 5.2	6.1 ± 10.3	0.001
CRP [mg/L]	1.5 ± 3.45	3.4 ± 2.9	0.001	1.7 ± 2.6	2.3 ± 2.9	0.001	2.0 ± 2.4	2.5 ± 2.5	0.278

Note: Data are either mean ± SD or number (%).

Abbreviations: BMI, Body Mass Index; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; T2D, diabetes mellitus type II; vitamin D insufficiency, vitamin D <50 nmol/L.

TABLE 3 Association of vitamin D insufficiency and metabolic syndrome according to diabetes and age

	Young participants without diabetes (n = 415)		Old participants without diabetes (n = 1126)		Old participants with diabetes (n = 165)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Model 1	2.3 (1.1–5.0)	0.036	1.6 (1.2–2.1)	0.002	3.7 (1.3–11.1)	0.018
Model 2	2.8 (1.2–7.0)	0.026	1.5 (1.1–2.1)	0.006	7.4 (1.4–39.4)	0.019
Model 3	2.9 (1.0–8.2)	0.043	1.5 (1.1–2.1)	0.014	4.4 (0.9–27.0)	0.072
Model 4	3.2 (1.2–8.4)	0.019	1.3 (0.09–1.8)	0.216	9.3 (1.5–56.0)	0.015
Model 5	3.2 (1.0–8.7)	0.042	1.3 (0.9–1.8)	0.203	6.1 (1.0–36.8)	0.047

Note: Data show OR and 95% CIs. p for trend is from binary logistic regression models. Models were calculated excluding subjects with vitamin D supplementation and subjects with fT3 <1,80 or fT3 >5,70 pg/ml.

Model 1: adjusted for age, sex, antidiabetic medication (in subjects with diabetes); Model 2: Model 1 + physical activity, smoking status, alcohol intake, energy intake/day, dietary vitamin D intake, co-morbidities (modified Charlson morbidity index), CRP; Model 3: Model 2 + BMI; Model 4: Model 3 + HOMA-IR; Model 5: Model 2 + BMI + HOMA-IR.

4 | DISCUSSION

Our results from the cross-sectional analysis within BASE-II support earlier findings on the relationship between vitamin D insufficiency with MetS. Vitamin D insufficiency was more frequent in subjects with MetS, irrespective of age group or T2D. Moreover, metabolic load (represented by lower HDL concentrations, higher HOMA-IR concentrations, higher systolic/diastolic blood pressure, and elevated waist circumference) was higher in subjects with low vitamin D concentrations. These results remained stable in the young cohort even after adjustment for multiple co-variates. However, in the old cohorts, we obtained that when BMI was

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taken into account, the relationship between vitamin D insufficiency and MetS was no longer evident in the old subjects with diabetes. Similarly, in the old subjects without diabetes, the relationship between vitamin D and MetS vanished when the analysis was adjusted for HOMA-IR as marker for IR. The differing results between the young and the old group imply that age-related factors may play a modulating role in the association between vitamin D insufficiency and MetS. However, differing effects of the covariates on the relationship between vitamin D insufficiency and MetS in our three study cohorts are not easily understood.

The majority of cross-sectional studies have reported an inverse relationship between vitamin D with MetS, diabetes and beta-cell function[7-12,23] and longitudinal studies found a subsequent higher risk for MetS in subjects with low vitamin D concentrations.[44-46] Also, studies analyzing the effect of preventive health programs promoting vitamin D supplementation found reduced risk of developing MetS with improved vitamin D concentrations.[26,31,47] Most of the authors conclude that disturbed glucose homeostasis and obesity play a decisive role and recent studies even suggested that the association between MetS and vitamin D may mainly be driven by the frequently increased BMI and/or IR among individuals with MetS.[25,31,46] Following this approach, Huang et al. found in their study on 355 young subjects without diabetes, that the association between MetS with vitamin D vanished, when BMI and HOMA-IR were taken into account.[25] This in contrast to our findings. However, in old participants, Kim et al. reported similar results. Low vitamin D concentrations were not associated with higher risk of MetS when regression models were adjusted for BMI.[30]

Vitamin D-dependent processes modulate effects of insulin,[2,4,48] that is, through upregulation of insulin dependent-receptors on muscle tissue and stimulation of receptors sensitivity to insulin.[2,8,49-51] Moreover, vitamin D receptors have been found on pancreatic beta-cells.[2,49,50] In this context, it has been shown that hyperglycemia, a key feature of Mets, leads to decreased levels of PTH, which in turn may result in lower vitamin D concentrations.[51] Thus, on the one hand, vitamin D action on pancreas may play a subordinate role in subjects with diabetes due to less functional pancreas tissue. On the other hand, an imbalance in the PTH vitamin D axis might add to the fact that in subjects with diabetes, in which vitamin D in general might be down-regulated due to imbalance in the PTH/vitamin D axis, adjustment for HOMA-IR did not change the results of the regression models. The association between vitamin D and MetS in our old cohort without diabetes, however, vanished when HOMA-IR was taken into account, supporting a stronger influence of IR on vitamin D concentrations. In our young cohort, in whom IR was less pronounced, vitamin D dependent mechanisms on IR may play a subordinate role, nevertheless, continuously low vitamin D concentrations might eventually contribute to the development of T2D.[52-54] Notably, vitamin D receptors seem to be downregulated in advanced age.[55]

An association between obesity, another key feature of MetS, and vitamin D is generally observed.[8,56] Obesity leads to diminished vitamin D uptake and distribution in these subjects and dietary habits may play an additional role in this context.[8,57,58] In our analysis highest BMI was observed in subjects with diabetes, so it seems plausible that the association between vitamin D and MetS was weak, when BMI (and not additionally HOMA-IR) was taken into account.[24,59] In addition, with regard to dietary vitamin D intake, we found a lower dietary vitamin D intake in old participants with vitamin D insufficiency, however no differences were observed with respect to MetS.

4.1 | Limitations

BASE-II is a convenience sample, the participants are on average healthier than the general population.[32,33] Nevertheless, cardiovascular risk factors which are included in the definition of MetS were frequently present in this population. Endocrine diseases as Cushing disease, hyperparathyroidism or severe liver diseases were, however, not reported in subjects included in the current analysis. Moreover, given the actual cross-sectional design of the BASE-II dataset, conclusions regarding causalities cannot be drawn. Regular alcohol intake, vitamin D substitution, dietary vitamin D and total energy intake, current smoking status, and physical activity were assessed by standardized questions. Thus, under- or over-reporting is possible even when using validated questionnaires. With respect to the statistical analysis, although we adjusted for a considerable number of confounding factors, we cannot exclude the possibility that the results may be affected by, for example, further dietary factors, latitude of the study location, outdoor activity, or medication use that we could not consider. In particular, there was no information on sun exposure, which might have been important in this context. Another example is a known association between MetS and T2D with vitamin D and calcium metabolism.[18,51] Imbalance in the PTH vitamin D axis due to hyperglycemia has been described and a role of shifted vitamin D concentrations due to this aspect cannot be ruled out. Also, 25-hydroxyvitamin D was assessed with two different methods. To provide comparable parameters, the laboratory performed a method comparison, however, even using a calculated adjustment factor might still result in imprecise conversion between methods. It has to be noted that subjects with diabetes had significantly more comorbidities (higher morbidity index), were less physically active and had higher concentrations of CRP, so the significantly lower vitamin D concentrations may also reflect these conditions. One difficulty when analyzing the concept of the MetS is that as a cluster syndrome it may represent different phenotypes. In our young subjects, the combination of 'elevated blood pressure' and 'elevated waist circumference' was most frequent, whereas in the old 'insulin resistance' and 'elevated waist circumference' were predominant. Thus, considering HOMA-IR and/or BMI might result in over-adjustment in these subjects. This is further supported by

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the fact that this adjustment did not change the results of the regression models in young subjects in whom other parameters dominate.

5 | CONCLUSION

In summary, the results of our cross-sectional analysis support an independent association between vitamin D insufficiency and MetS only among young adults of BASE-II. We, thus, observed an age-related difference, which needs further exploration. At the same time, our data suggest that among young adults at risk of MetS, the correction of vitamin D insufficiency may be warranted.

ACKNOWLEDGEMENTS

The BASE-II research project was supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) under grant numbers #16SV5536K, #16SV5537, #16SV5538, and #16SV5837 and the Max Planck Institute for Human Development (MPIHD), Berlin, Germany.

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

None declared.

ETHICS STATEMENT

The study was approved by the ethics committee of Charité – University Medicine Berlin (project number: EA2/029/09).

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work: Nikolaus Buchmann, Ilja Demuth, Elisabeth Steinhagen-Thiessen, and Kristina Norman. Acquisition, analysis, or interpretation of data for the work: Nikolaus Buchmann, Dominik Spira, Nils Eckstein, and Kristina Norman. Drafting the work or revising it critically for important intellectual content: Nikolaus Buchmann, Ilja Demuth, Elisabeth Steinhagen-Thiessen, Kristina Norman, and Nils Eckstein. Final approval of the version to be published: Nikolaus Buchmann, Ilja Demuth, Elisabeth Steinhagen-Thiessen, Kristina Norman, and Nils Eckstein. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Nikolaus Buchmann, Ilja Demuth, Elisabeth Steinhagen-Thiessen, and Kristina Norman.

DATA AVAILABILITY STATEMENT

Due to concerns for participant privacy, data are available only upon request. External scientists may apply to the Steering Committee of BASE-II for data access. Please refer to the BASE-II website (https://www.base2.mpg.de/en/project-information/data-documentation) for additional information. Please contact Katrin Schaar, scientific coordinator, at lmueller@mpib-berlin.mpg.de.

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PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/DMRR.3457.

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How to cite this article: Buchmann N, Eckstein N, Spira D, Demuth I, Steinhagen-Thiessen E, Norman K. Vitamin D insufficiency is associated with metabolic syndrome independent of insulin resistance and obesity in young adults - The Berlin Aging Study II. *Diabetes Metab Res Rev*. 2021;37(8):e3457. https://doi.org/10.1002/dmrr.3457

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