Joint associations of 25-hydroxyvitamin D and physical activity with hypertension: Evidence from the ELSA study and genome-wide data

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Abbreviations

25(OH)D: 25-hydroxyvitamin D;

PA: physical activity;

ELSA: English Longitudinal Study of Ageing;

OR: odds ratio;

CI: confidence interval;

SBP: systolic blood pressure;

DBP: diastolic blood pressure;

BMI: body mass index;

MET: metabolic equivalents of task;

RERI: relative excess risk due to interaction;

AP: attributable proportion;

S: synergy index;

PAF: population attributable fraction;

MR: Mendelian randomization;

IVW: inverse-variance weighted;

GWAS: genome-wide association studies;

UKB: UK Biobank;

EBI: European Bioinformatics Institute.

Abstract

The interaction between 25-hydroxyvitamin D [25(OH)D] and physical activity (PA) in influencing hypertension remains underexplored. This study aimed to examine their independent and joint associations with hypertension risk among 5,327 participants aged ≥50 years from the English Longitudinal Study of Ageing. Participants were categorized by 25(OH)D status (sufficient, ≥50 nmol/L; insufficient, ≥30 to <50 nmol/L; deficient, <30 nmol/L) and self-reported PA levels. Multivariable logistic regression, adjusting for the season of measurement and sociodemographic confounders, showed that sufficient 25(OH)D (OR = 0.66, 95% CI: 0.56–0.78) and higher PA (OR = 0.82, 95% CI: 0.71–0.94) were independently associated with reduced hypertension prevalence. In joint analyses, the group combining higher PA and sufficient 25(OH)D exhibited the lowest odds of hypertension (OR = 0.55, 95% CI: 0.43–0.70) compared to the lower PA and deficient group. A significant synergistic interaction was identified, indicating that the combined protective effect of these factors was greater than the sum of their individual associations. These results were corroborated by Mendelian randomization analysis, which identified inverse causal associations between genetically predicted 25(OH)D, vigorous PA, and hypertension risk across independent datasets. These findings emphasize that vitamin D sufficiency acts in synergy with an active lifestyle to enhance cardiovascular protection. This relationship underscores the critical importance in nutritional science of integrating micronutrient status with physical activity to develop more effective, multifaceted lifestyle-based strategies for hypertension management in middle-aged and older populations.

Keywords: Vitamin D, Physical activity, Hypertension, Joint association, Mendelian randomization

Introduction

Hypertension is a leading global health challenge, affecting more than 1.28 billion adults worldwide, with a substantial proportion remaining undiagnosed or poorly controlled(1). In addition to being a major risk factor for cardiovascular conditions including heart disease and stroke, hypertension damages organs in a number of different systems, highlighting the need for better treatment methods(2). Although hypertension cannot be fully cured, it can be managed effectively through lifestyle modifications, such as regular physical activity, dietary adjustments, stress reduction, and improved sleep quality, combined with consistent monitoring of blood pressure. These measures, alongside appropriate medical treatments, are crucial in controlling hypertension and mitigating the risk of associated health complications(3-5).

Vitamin D serves both as a nutrient and a hormone, integral to numerous physiological processes. It is mostly produced by the skin when exposed to UVB rays, and it is also obtained through diet from foods like egg yolks, oily seafood, and fortified meals(6, 7). Its active form, 1,25(OH)D, provides regulatory effects on the immune system and other cellular pathways and is essential for preserving the calcium and phosphate balance necessary for bone health(8-10). A lack of vitamin D is increasingly being linked to poor cardiovascular outcomes. It is believed that low vitamin D levels contribute to the pathophysiology of cardiovascular disease by mechanistically upsetting calcium homeostasis, compromising endothelial function, and fostering systemic inflammation(11-13). Furthermore, deficiencies have been linked to hypertension, possibly as a result of high blood pressure-raising processes including arterial stiffness and increased vascular resistance. The wider function of vitamin D in vascular health and its possible consequences for the prevention and treatment of hypertension are highlighted by these findings(14, 15).

Vitamin D deficiency can be effectively addressed by adopting a healthy lifestyle that incorporates routine exercise, optimizing sun exposure, and consuming a nutrient-dense diet(16). Frequent exercise is especially important as it improves vascular health by enhancing endothelial function, regulating sympathetic nervous system activity, and decreasing systemic vascular resistance (17, 18). While physical activity is well-established as beneficial for reducing risks of cardiovascular diseases (19-21), its relationship with hypertension, as well as the combined effects of physical activity and 25(OH)D, remains insufficiently explored. Therefore, this study aims to investigate their joint influence on

hypertension risk.

Methods

Study population

The present study utilized data from Wave 6 of the English Longitudinal Study of Ageing (ELSA)(22), a representative sample of the English population aged 50 years and older. Wave 6 was specifically selected for this analysis as it provided the necessary data on blood 25-hydroxyvitamin D [25(OH)D] levels. Of the 8,054 participants in Wave 6, we excluded individuals aged under 50 years (n=164), those with missing data on 25(OH)D levels or physical activity (n=1,942), those without hypertension information (n=327), and those lacking data on other relevant covariates (n=294). The final analytic sample consisted of 5,327 participants. Supplementary Figure 1 illustrates the detailed flow of participant selection.

Ethical criteria

This study was conducted in accordance with the guidelines of the Declaration of Helsinki. Ethical approval was granted by the NRES Committee South Central - Berkshire on 28th November 2012 (11/SC/0374). Written informed consent was obtained from all participants.

Assessment of exposures

Blood samples were obtained from participants during Wave 6's health check, which was the first to measure 25(OH)D concentrations. Participants on anticoagulant therapy (e.g., warfarin), those with a history of seizures, those with bleeding problems (e.g., hemophilia or low platelet counts), and those without written consent were excluded. The DiaSorin Liaison® immunoassay was used to analyze the samples. According to the Institute of Medicine's (IOM) standards, participants were classified based on their 25(OH)D levels as sufficient, insufficient, or deficient, with thresholds of ≥50 nmol/L, ≥30 to <50 nmol/L, and <30 nmol/L, respectively(23).

The three intensity categories of physical activity—light, moderate, and vigorous—were reported by the participants. Using the following choices—"more than once a week," "once a week," "1–3 times per month," and "rarely/never"—they indicated how frequently they

participated, with sample activities included for each intensity. We estimated a monthly 'bout' score for each intensity, assuming 4.3 weeks each month, in order to quantify these activities. The following is the conversion of the frequency categories: 8.6 bouts per month were associated with "more than once a week," 4.3 with "once a week," 2.0 with "1–3 times per month," and 0 with "rarely/never." The overall physical activity score was then calculated by multiplying the scores by the corresponding metabolic equivalents of task (MET) values for each activity level. Supplementary Table 1 contains comprehensive information on the weight computation, which adheres to accepted procedures from earlier research(24, 25). To improve clarity in reporting, participants were grouped into tertiles based on their physical activity scores, with the higher two tertiles combined and compared to the lowest tertile.

Assessment of outcome

A systematic approach was followed for taking blood pressure readings. A manual sphygmomanometer was used to collect three measurements at 30-second intervals following a 5-minute rest period. The mean of these measurements was used to compute systolic and diastolic values. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or a self-reported hypertension diagnosis, including antihypertensive drug usage(26).

Assessment of other covariates

Sociodemographic covariates included age, sex, marital status (married/partnered vs. single/other), wealth (tertiles of non-pension wealth), education level, and ethnicity (White vs. Non-White). Health behaviors included smoking status (current vs. non-smoker), alcohol consumption frequency, sleep duration (short <6h, optimal 6-8h, long >8h), and BMI (kg/m²). Medical history included diabetes, cancer, lung disease, cardiovascular conditions, arthritis, stroke, and high cholesterol. Information on the season of blood measurement (Spring, Summer, Autumn, Winter) was also recorded to account for seasonal variations in vitamin D levels.

Statistical analysis

Baseline characteristics were compared between normotensive and hypertensive groups using t-tests for continuous variables and chi-square tests for categorical variables. Comparisons were also conducted between included and excluded participants to assess potential selection bias. Multivariable logistic regression models were employed to estimate

odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of 25(OH)D and PA with hypertension. Models were fully adjusted for age, sex, ethnicity, education, marital status, wealth, smoking, alcohol consumption, sleep duration, BMI, comorbidities, and the season of measurement. We assessed the joint effects of 25(OH)D and PA, incorporating an interaction term to evaluate multiplicative interaction, while the Relative Excess Risk due to Interaction (RERI) was calculated to assess additive interaction. Population attributable fractions (PAFs) were estimated to determine the potential public health impact. To handle missing data on covariates, we performed multiple imputation by chained equations (MICE) to generate 5 imputed datasets, assuming data were missing at random. Pooled results from the imputed datasets were used for sensitivity analysis (Supplementary Table 4). All statistical analyses were performed using R software (version 4.2.2).

MR analysis

We employed a two-sample Mendelian randomization (MR) design to investigate the causal associations between 25(OH)D levels, physical activity, and hypertension. This approach leverages genetic variants as instrumental variables to reduce confounding and reverse causation biases. Three core assumptions were satisfied: relevance, independence, and exclusion restriction. Summary-level data were restricted to individuals of European ancestry. Genetic instruments were selected based on genome-wide significance ($P < 5\times10^{-6}$) and independence ($R^2 < 0.01$ within a 10,000 kb window). The primary causal estimates were calculated using the random-effects inverse-variance weighted (IVW) method. Crucially, since both the physical activity exposures and the primary hypertension outcome were derived from the UK Biobank, there was substantial sample overlap. To explicitly address the potential bias (winner's curse and weak instrument bias) arising from this overlap, we applied the MRlap method to correct the IVW estimates. Sensitivity analyses including MR-Egger, weighted median, and MR-PRESSO were conducted to detect pleiotropy and heterogeneity. All statistical analyses were performed using R software (version 4.2.2) with the TwoSampleMR, MRPRESSO, and MRlap packages. Detailed methodology regarding data sources and instrument selection is provided in Supplementary Appendix 1.

Results

Baseline characteristics

A total of 5,327 participants aged 50 years and older were included in this cross-sectional analysis. Of these, 2,441 (45.8%) were classified as normotensive, while

2,886 (54.2%) were identified as hypertensive. The mean age of participants in the hypertensive group was significantly higher than that in the normotensive group (68.4 ± 8.58 vs. 63.6 ± 8.11 years). Males comprised 47.9% of the hypertensive group, a significantly higher proportion compared to 42.4% in the normotensive group. Demographic characteristics, lifestyle behaviors, and health conditions differed significantly between the normotensive (reference) and hypertensive groups (Table 1). Participants with hypertension were more likely to be older, male, of non-White ethnicity, and to have lower socioeconomic status (indicated by lower educational attainment and non-housing wealth). Furthermore, this group was characterized by lower physical activity levels, higher BMI, and a greater prevalence of comorbidities—including diabetes, arthritis, and cardiovascular conditions—whereas rates of current smoking and weekly alcohol consumption were lower compared to normotensive participants (Table 1).

Association of PA and 25(OH)D levels with Hypertension

Table 2 presents the associations of PA and 25(OH)D levels with hypertension. After adjusting for sociodemographic factors, lifestyle behaviors, comorbidities, and season of measurement, higher 25(OH)D levels were significantly associated with reduced odds of hypertension. Compared to the deficient group, the multivariable-adjusted ORs were 0.81 (95% CI: 0.69–0.96) for insufficient levels and 0.66 (95% CI: 0.56–0.78) for sufficient levels. Similarly, higher PA was independently associated with a lower risk of hypertension (OR: 0.82, 95% CI: 0.71–0.94). Population attributable fraction (PAF) analysis estimated that maintaining sufficient vitamin D levels and higher PA could potentially lower the prevalence of hypertension by 25% and 15%, respectively.

Joint association PA and 25(OH)D with hypertension

Joint association of PA and 25(OH)D with hypertension Figure 1 illustrates the combined association of PA and 25(OH)D with the prevalence of hypertension after multivariable adjustment. Compared to the reference group (lower PA and vitamin D deficiency), participants with higher PA and sufficient 25(OH)D levels exhibited the lowest odds of hypertension (OR = 0.55, 95% CI: 0.43–0.70). A significant inverse dose-response relationship was observed, with the likelihood of hypertension decreasing as the combination of PA and 25(OH)D levels improved (*P* for trend < 0.001). Further analyses revealed a significant additive interaction between these factors (RERI = 0.61; AP = 0.24; S = 1.65),

indicating a synergistic effect where the combined risk exceeds the sum of individual risks (Supplementary Table 3). No multiplicative interaction was observed.

Sensitivity and Subgroup analyses

Subgroup analyses (Figure 2) indicated generally consistent associations between 25(OH)D, PA, and hypertension across most strata, with a significant interaction observed among alcohol users ($P < 0.05$). Regarding data completeness, significant differences in baseline characteristics were found between included and excluded participants (Supplementary Table 2). However, analyses based on multiple imputation datasets yielded results consistent with the primary analysis (Supplementary Table 4). Additionally, in analyses stratified by antihypertensive medication use, the inverse associations of higher physical activity and sufficient 25(OH)D with hypertension remained statistically significant among participants not taking medication (Supplementary Table 5).

Results of MR analysis

The primary Mendelian randomization analysis using the inverse-variance weighted (IVW) method identified significant inverse causal associations between 25(OH)D levels (OR 0.99, 95% CI 0.98–1.00; $P = 0.001$) and the risk of hypertension, as illustrated in Figure 3. Similarly, a genetic predisposition to vigorous physical activity was associated with a marked reduction in hypertension risk (OR 0.98, 95% CI 0.97–0.99; $P < 0.001$). As shown in Figure 3, other specific physical activities—including light household tasks, walking for pleasure, other exercises, heavy physical tasks, and strenuous sports—also demonstrated significant protective effects (all $P < 0.001$). Crucially, to address potential bias arising from sample overlap within the UK Biobank, we applied MRlap correction (Supplementary Table 6). This rigorous adjustment confirmed the consistency of our findings, yielding robust causal estimates and indicating even stronger effect sizes for vigorous physical activity and strenuous sports after accounting for overlap structure.

Validation in the independent EBI dataset largely corroborated these protective associations (Supplementary Table 7). The causal effects remained statistically significant for 25(OH)D (OR = 0.99, $P = 0.022$), vigorous physical activity (OR = 0.98, $P = 0.023$), light household tasks, other exercises, and strenuous sports. However, the associations for walking for pleasure and heavy physical tasks did not reach statistical significance in the replication cohort. To further ensure the validity of these causal inferences, comprehensive sensitivity

analyses were performed. We found no evidence of significant horizontal pleiotropy or heterogeneity based on MR-Egger intercept tests and Cochran's Q statistics, respectively. Additionally, visual inspection of leave-one-out plots confirmed that the observed associations were not driven by any single influential variant (Supplementary Figures 3–16).

Discussion

This study identified associations between physical activity, 25(OH)D levels, and the prevalence of hypertension. Notably, the interaction between physical activity and 25(OH)D was observed, with the combined presence of sufficient vitamin D levels and physical activity showing a stronger protective effect against hypertension. Additionally, MR analysis provided further evidence supporting the relationship between physical activity, 25(OH)D, and hypertension risk.

Our findings on the protective role of vitamin D are consistent with prior epidemiological meta-analyses that report an inverse dose-response association between serum 25(OH)D and hypertension risk(27). Earlier evidence indicates that a 25 nmol/L increase in 25(OH)D corresponds to an approximate 7% reduction in hypertension likelihood(28). In contrast to studies assessing vitamin D status alone, our results show that individuals who also engage in regular physical activity derive greater cardiovascular benefit, suggesting that behavioral factors may modify the magnitude of vitamin D-related protection. The convergence of observational and genetic evidence supports the reliability of this relationship, while highlighting the need to evaluate multiple modifiable exposures jointly rather than independently(29-32).

Evidence has consistently shown that regular physical activity is associated with lower blood pressure and reduced hypertension risk(33). Lu et al. reported that individuals achieving the recommended 150 minutes per week of moderate-intensity activity had a 6% lower hypertension risk compared with sedentary individuals(34). Exercise interventions in other cohorts have documented SBP reductions of 2.4–5.2 mmHg and DBP reductions of 2.2–4.1 mmHg(35-37). Unlike previous research focusing on isolated lifestyle effects, our findings suggest that considering activity frequency alone may underestimate its preventive value, particularly when micronutrient status is not simultaneously accounted for. The additional mental-health benefits of physical activity reported in earlier studies(17, 18) may also contribute indirectly to a more favorable cardiovascular risk profile, supporting the

broader systemic value of physical activity in chronic disease prevention.

The synergistic interaction between physical activity and vitamin D status constitutes a central finding of clinical and public health relevance. Although vitamin D sufficiency is associated with a substantially lower risk of hypertension, our results indicate that individuals who also maintain regular physical activity demonstrate the most favorable cardiovascular risk profile. Importantly, the additive interaction analysis shows that physical inactivity and vitamin D deficiency jointly confer a disproportionately elevated risk of hypertension, exceeding the expected sum of their individual effects. This supra-additive risk pattern underscores that physical activity remains a relevant protective exposure regardless of vitamin D status and is essential for a more comprehensive risk reduction strategy. This interaction also has practical implications, particularly for populations in which vitamin D deficiency is common, as outdoor physical activity may simultaneously support cardiovascular conditioning and increase opportunities for solar UVB exposure, a key contributor to endogenous vitamin D synthesis. Evaluating these modifiable factors jointly rather than independently provides a more realistic framework for understanding hypertension vulnerability and helps inform integrated lifestyle-based prevention strategies(38-40).

This study has several strengths. First, the inclusion of a large, representative sample enabled a detailed analysis of vitamin D levels in the UK population. Second, we rigorously adjusted for the season of measurement to minimize environmental confounding. Furthermore, the application of MR methods significantly enhances the reliability of our causal inferences.

However, there are limitations to acknowledge. The cross-sectional design of the observational analysis limits strict causal interpretation, and potential reverse causality cannot be fully excluded, as individuals with hypertension may reduce activity due to comorbidities or treatment-related factors. Our analysis captured physical activity frequency but not duration or intensity, and self-reported measures may introduce recall bias. It is noteworthy that the ELSA physical activity questionnaire did not distinguish between indoor and outdoor activities. Therefore, the proposed mechanism linking outdoor activity, UVB exposure, and vitamin D synthesis should be interpreted with caution. The absence of data on vitamin D supplementation prevented direct adjustment for this confounder, although MR findings provided partial mitigation by leveraging genetic proxies less susceptible to behavioral or

environmental bias. Finally, replication in longitudinal and ethnically diverse cohorts is warranted to confirm external generalizability.

Conclusion

In conclusion, this study indicated that regular exercise and sufficient 25(OH)D are associated with a lower risk of hypertension. A realistic strategy for preventing hypertension is to combine regular exercise with maintaining appropriate vitamin D levels. These results provide credence to the creation of lifestyle modifications targeted at effective hypertension management.

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Table 1. Baseline characteristics of participants

Characteristic	Non-hypertensive participants (n= 2,441)	Hypertensive participants (n= 2,886)	*P value*
Age	63.6 ± 8.11	68.4 ± 8.58	< 0.001
Sex			< 0.001
Male	1,034 (42.4%)	1,381 (47.9%)	
Female	1,407 (57.6%)	1,505 (52.1%)	
Race or ethnicity			0.019
White	2,386 (97.7%)	2,789 (96.6%)	
Non-White	55 (2.25%)	97 (3.36%)	
Married or partnered	1,732 (71.0%)	1,942 (67.3%)	0.004
Current smoker	276 (11.3%)	258 (8.94%)	0.005
Reports weekly alcohol consumption	1,447 (59.3%)	1,558 (54.0%)	< 0.001
Sleep duration			0.006
Short (<6 h)	322 (13.2%)	471 (16.3%)	
Optimal (6–8 h)	1,942 (79.6%)	2,211 (76.6%)	
Long (>8 h)	177 (7.25%)	204 (7.33%)	
Non-housing wealth tertile			<0.001
First (lowest wealth)	704 (28.8%)	1,065 (36.9%)	
Second (intermediate wealth)	793 (32.5%)	986 (34.2%)	
Third (highest wealth)	944 (38.7%)	835 (28.9%)	
Education			<0.001
Less than secondary	994 (40.7%)	2,771 (96.0%)	
Secondary or above secondary	1,447 (59.3%)	115 (3.98%)	
Physical activity			< 0.001
Lower	522 (21.4%)	917 (31.8%)	
Higher	1,919 (78.6%)	1,969 (68.2%)	
BMI, kg/m^2	26.9 ± 4.58	29.1 ± 5.20	< 0.001
Comorbidities			
Diabetes	66 (2.70%)	325 (11.3%)	< 0.001
Cancer	50 (2.05%)	83 (2.88%)	0.066
Lung disease	53 (2.17%)	95 (3.29%)	0.017
Cardiovascular condition	35 (1.43%)	98 (3.40%)	< 0.001
Arthritis	633 (25.9%)	1,066 (36.9%)	< 0.001
Stroke	29 (1.19%)	102 (3.53%)	< 0.001
High cholesterol	633 (25.9%)	1,091(36.9%)	< 0.001
Season of Measurement			0.018
Winter	665 (27.2%)	746 (25.8%)	
Spring	216 (8.85%)	200 (6.93%)	
Summer	559 (22.9%)	669 (23.2%)	
Autumn	1001 (41.0%)	1271 (44.0%)	
25(OH)D level			< 0.001
<30 nmol/L (Deficient)	485 (19.9%)	748 (25.9%)	
≥30 and <50 nmol/L (Insufficient)	761 (31.2%)	963 (33.4%)	
≥50 nmol/L (Sufficient)	1,195 (49.0%)	1,175 (40.7%)	
Systolic blood pressure (mmHg)	122 ± 10.5	141 ± 17.0	< 0.001
Diastolic blood pressure (mmHg)	71.3 ± 8.11	76.4 ± 11.5	< 0.001

Continuous variables are expressed as means ± standard deviations or medians (interquartile ranges) and categorical variables are expressed as percentages. BMI, body mass index; 25(OH)D: 25-hydroxyvitamin D

Table 2. Association of 25(OH)D levels and PA with hypertension among participants.

	Cases (%)	Unadjusted Model		Adjusted Model		PAF% (95% CI)
		OR (95%CI)	*P value*	OR (95%CI)	*P value*	
25(OH)D						
Deficient	748 (60.1%)	1.00 [Reference]		1.00 [Reference]		
Insufficient	963 (55.8%)	0.82 (0.71, 0.95)	0.009	0.81 (0.69, 0.96)	0.012	-0.11 (-0.20, -0.07)
Sufficient	1,175 (49.5%)	0.64 (0.55, 0.73)	<0.001	0.66 (0.56, 0.78)	<0.001	-0.25 (-0.36, -0.15)
PA						
Lower	917 (63.7%)	1.00 [Reference]		1.00 [Reference]		
Higher	1,969 (50.1%)	0.58 (0.52, 0.66)	<0.001	0.82 (0.71,0.94)	0.005	-0.15 (-0.26, -0.05)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Multivariable-adjusted model: adjusted for age, sex, ethnicity, education, cohabitation status, current smoking, non-housing wealth, alcohol consumption, sleep duration, BMI, season of measurement, comorbidities (diabetes, stroke, cardiovascular diseases, chronic lung diseases, cancer, arthritis, and high cholesterol), and mutually adjusted for 25(OH)D and physical activity.

25(OH)D: 25-hydroxyvitamin D; PA: physical activity; PAF, Population attributable fraction

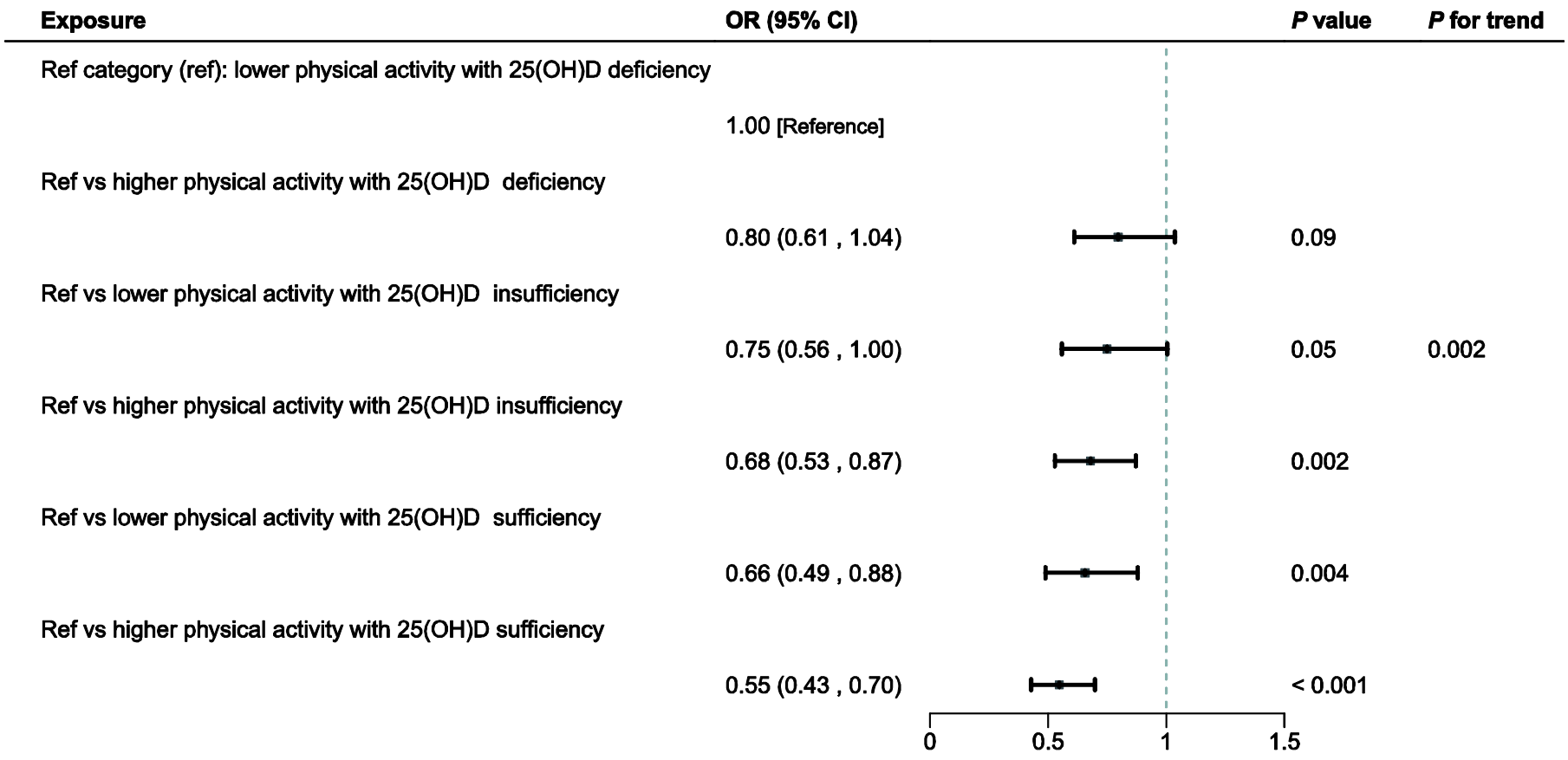

Fig. 1. Joint Association of PA and 25(OH)D levels with hypertension

Multivariable adjusted model additionally adjusted for age, sex, ethnicity, education, cohabitation status, current smoking, wealth, alcohol consumption, sleep duration, diabetes, stroke, cardiovascular diseases, chronic lung diseases, cancer, arthritis, high cholesterol, season and BMI. 25(OH)D: 25-hydroxyvitamin D; PA: physical activity.

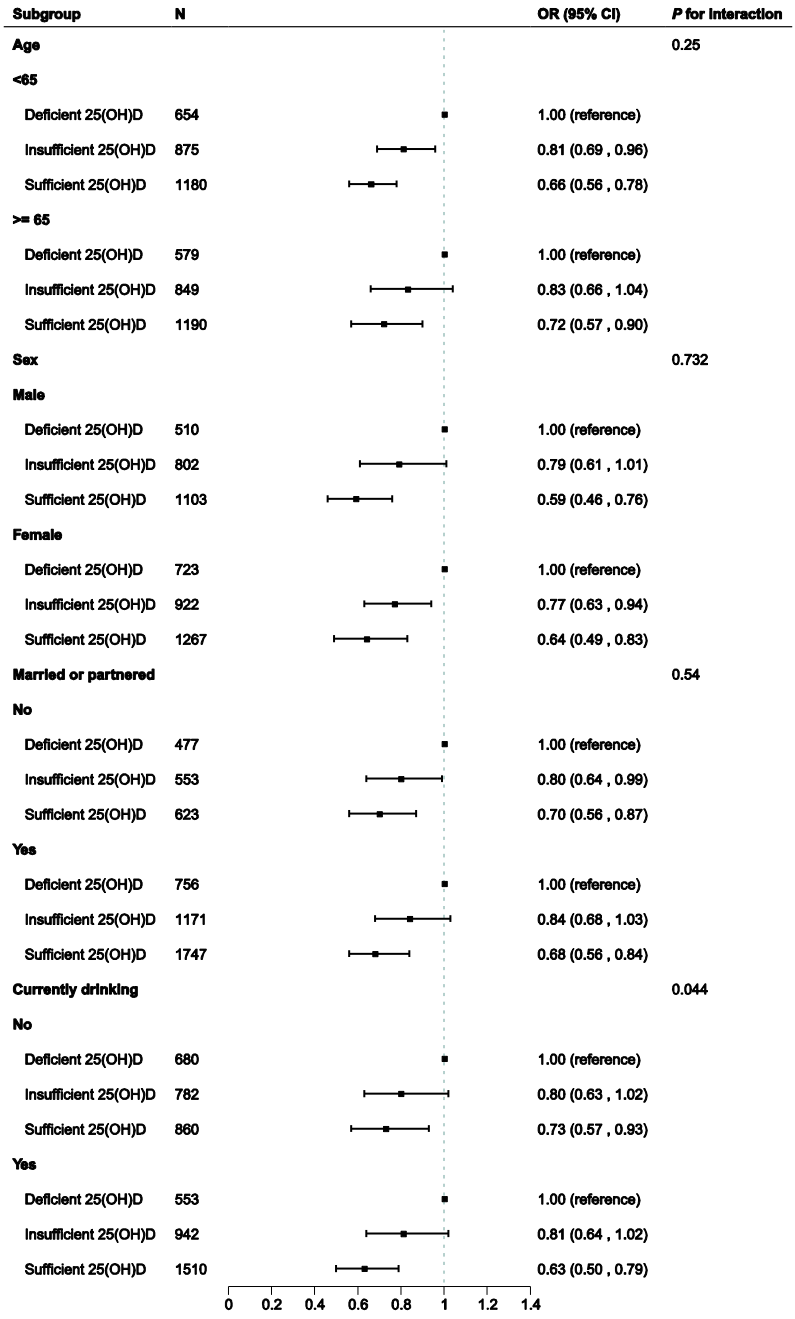

Fig. 2. Association of 25(OH)D levels and hypertension stratified by potential risk factors.

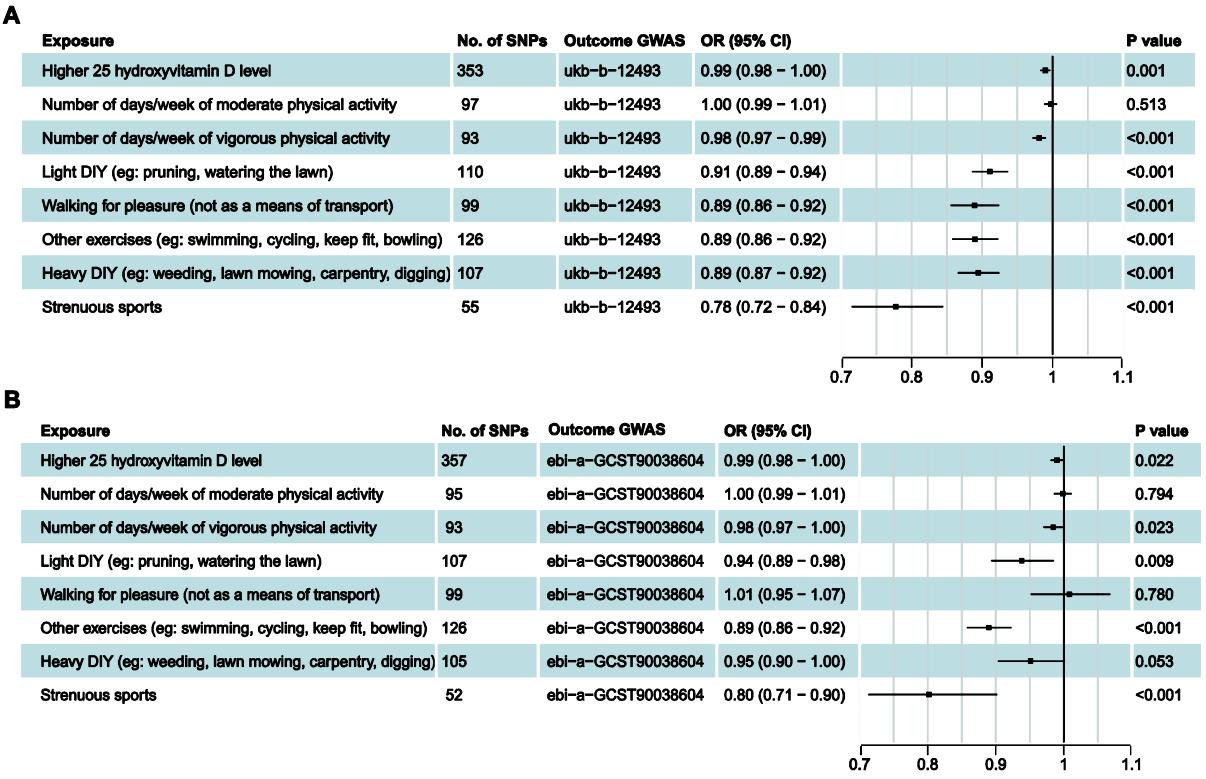

Fig. 3. MR analyses for the causal effects of PA and 25(OH)D on the risk of Hypertension by using IVW method based on GWAS of UKB (A) and EBI (B).

Abbreviations: GWAS, genome-wide association studies; EBI, European Bioinformatics Institute; MR, Mendelian randomization; IVW, inverse-variance weighted; 25(OH)D: 25-hydroxyvitamin D; PA: physical activity.