The Interaction and Mediation of Physical Activity of Body Mass Index with Cardiovascular Disease: Evidence from NHANES and MR Analysis

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BASIC SCIENCES

ABSTRACT

ZHAO, L., D. ZHANG, T. ZHANG, C. WANG, S. HAN, T. ZHANG, Z. HE, and J. WANG. The Interaction and Mediation of Physical Activity of Body Mass Index with Cardiovascular Disease: Evidence from NHANES and MR Analysis. *Med. Sci. Sports Exerc.*, Vol. 57, No. 7, pp. 1326–1332, 2025. **Background:** Both insufficient physical activity (PA) and excess body weight are important risk factors for cardiovascular disease (CVD), and PA is closely related to body weight. However, it remains unclear whether PA modifies or mediates the association of body mass index (BMI) with CVD. **Methods:** We conducted a cross-sectional study of 35,406 adults participating in the National Health and Nutrition Examination Survey. The mediation and interaction effects of PA were assessed using a four-way decomposition approach. An additional two-step Mendelian randomization analysis was performed to verify the potential causal mediation effect. **Results:** A strong association was observed between PA and lower odds of CVD after adjusting for all confounders (odds ratio, 0.84; 95% confidence interval, 0.74–0.95). Increased BMI was associated with higher odds of CVD (odds ratio, 1.04; 95% confidence interval, 1.03–1.04). PA showed interaction and mediation effects on the association of BMI with CVD. The overall proportion attributable to interaction was −37.5%, whereas the overall proportion attributable to mediation was 22.2%. Mendelian randomization analysis further confirmed that PA causally mediated the pathway from BMI to CVD. **Conclusions:** PA modified the association of BMI with CVD, suggesting that sufficient PA is needed to lower the impact of high BMI on CVD risk. Moreover, we found that PA served as a causal influence on the association of BMI with CVD, indicating that higher BMI led to a lower level of PA, which in turn increased the risk of CVD. **Key Words:** PHYSICAL ACTIVITY, BODY MASS INDEX, CARDIOVASCULAR DISEASE, MEDIATION ANALYSIS, MENDELIAN RANDOMIZATION

Cardiovascular disease (CVD) is an umbrella term for a range of related pathologies affecting the heart and blood vessels. CVD is a significant and growing global health issue. In 2021, it accounted for 20.5 million deaths worldwide, representing one-third of all mortality (1). CVD is not only a leading cause of death but also the primary cause of loss of disability-adjusted life years globally (2). Although the global death rate from CVD decreased from 354.5 deaths per 100,000 people in 1990 to 239.9 per 100,000 in 2019, this reduction varied significantly by region, with high-income countries experiencing the most rapid decline in death rates (3). Therefore, CVD still poses a serious threat around the world, particularly in low- and middle-income countries.

There is strong evidence from epidemiological studies that excess body weight contributes directly to the risk of CVD (4). Individuals who are overweight tend to have increased CVD mortality and morbidity (5). Because both CVD and excess body weight lead to poor quality of life, effective measures should be taken to prevent and manage them. Numerous studies have shown that regular physical activity (PA) reduces the risk of CVD, and PA is recognized as a powerful preventive therapy (6,7). Moreover, PA has been demonstrated to be an important behavioral factor in promoting long-term weight loss and minimizing weight regain (8). Although PA can be beneficial for many critical health markers among individuals with excess body weight, independent of changes in body mass index (BMI), individuals who are overweight and obese are generally less active and expend less energy in PA than lighter individuals (9).

Hence, we hypothesized that there are interaction and mediation effects of PA on the association of BMI with CVD. Based on cross-sectional data from the National Health and

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Nutrition Examination Survey (NHANES), we decided to use a four-way decomposition method, an analysis technique that explores interaction and mediation effects simultaneously, to clarify the interaction and mediation of PA between BMI and CVD (10). Moreover, we performed additional Mendelian randomization (MR) analysis to confirm the potential causal mediation effect.

METHODS

Participants

NHANES is a large, nationwide cross-sectional survey designed to evaluate the health and nutrition status of the noninstitutionalized civilian population in the United States (11). The survey includes information on health conditions and behaviors, physical examination findings, and laboratory results. The study protocols were approved by the Ethics Review Board of the National Center for Health Statistics, and all participants provided written informed consent before undergoing a household interview, followed by a clinical examination at a mobile examination center. NHANES data are released in 2-yr cycles, and for this study, we combined data from 2007–2008 to 2017–2020 (prepandemic), as PA was assessed using a different scale before 2007.

A total of 63,010 participants completed the interview and physical examination between 2007–2008 and 2017–2020. Of these, 38,594 were adults 18 yr or older. Subsequently, 404 participants were excluded due to pregnancy, and 2784 were excluded due to missing information on PA, BMI, or CVD. This left a total of 35,406 participants for the final analysis.

Measures

Assessment of PA, BMI, and CVD. In NHANES 2007–2008 to 2017–2020, PA was assessed using the Global Physical Activity Questionnaire. The questionnaire measured PA across three domains: leisure-time, work-related, and transportation-related PA. The leisure-time and work-related domains included questions evaluating the intensity (moderate or vigorous), frequency (per week), and duration (in minutes) of PA during a typical week. The transportation-related domain included questions regarding the number of days per week and the average duration per day participants engaged in the activity. In NHANES, a metabolic equivalent score of 4.0 was assigned to moderate-intensity and transportation-related PA, and a score of 8.0 was assigned to vigorous-intensity PA. Therefore, transportation-related PA was considered equivalent to moderate-intensity PA. The total amount of PA per week was calculated as the sum of min spent on moderate-intensity PA plus twice the minutes spent on vigorous-intensity PA. According to recent guidelines, participants who engaged in at least 150 min of moderate-intensity PA per week were classified as having sufficient PA (12).

During the physical examination, weight and height were measured, and BMI was calculated as the ratio of weight in kilograms to height in meters squared. Obesity was defined as a BMI of 30 $kg \cdot m^{-2}$ or higher. During the interview, participants provided self-reported information on a range of health conditions. For CVD, five different questions were asked to determine self-reported physician diagnoses of congestive heart failure, coronary heart disease, angina, myocardial infarction, and stroke. Participants who reported having at least one of these conditions were classified as having CVD.

Assessment of covariates. Important covariates were identified from the literature on PA, BMI, and CVD. We collected information on age, gender, race/ethnicity (Mexican American, non-Hispanic White, non-Hispanic Black, and other), education level (less than high school, high school graduate, and college or higher), and income (measured by the family poverty index ratio, which is calculated by dividing the annual family income by the poverty threshold, adjusted for family size and inflation). Additional covariates included hypertension, diabetes, dyslipidemia, alcohol use, and smoking status. Hypertension was defined as a systolic blood pressure of 130 mm Hg or higher, diastolic blood pressure of 80 mm Hg or higher, or the use of antihypertensive medications. Diabetes was defined as a hemoglobin A_{1c} level of 6.5% or higher, fasting plasma glucose of 126 $mg \cdot dL^{-1}$ or higher, or the use of diabetes medications. Dyslipidemia was defined as total cholesterol of 240 $mg \cdot dL^{-1}$ or higher, or the use of lipid-lowering drugs. Alcohol use was categorized as nondrinker or abstainer, 1–4 drinks per day, and over 5 drinks per day. Smoking status was classified as "never" for participants who had never smoked, "current" for participants who were actively smoking, and "former" for participants who had smoked at least 100 cigarettes in their lifetime.

Statistical Analysis

All statistical analyses were conducted using R (R Development Core Team, Version 4.1.3). Primary sampling units, strata variables, and appropriate sampling weights were applied to account for the complexity of the survey design using the 'Survey' package (Version 4.4-2), as recommended by NHANES (13). Continuous variables were expressed as means (compared using Student's *t*-test), and categorical variables were expressed as percentages (compared using the chi-square test). All statistical tests were two-sided and considered significant at $P < 0.05$. The detailed R code has been provided in the Supplemental Material (Supplemental Digital Content 3, http://links.lww.com/MSS/D178).

In the current study, we used VanderWeele's four-way decomposition method to perform mediation and interaction analysis (10). This method divides mediation and interaction effects into four components: controlled direct effect (CDE), the effect of exposure on the outcome is due to neither mediation nor interaction; reference interaction effect (INT_{ref}), the effect is due to just interaction; mediated interaction effect (INT_{med}), the effect is due to both mediation and interaction; and pure mediated effect (PIE), the effect is due to just mediation. Compared with evaluating mediation and interaction separately, the four-way decomposition method provides

better insight into the relationships between exposure effects, mediation effects, and outcomes (14,15). The following four potential contributors are defined in this study: 1) CDE: BMI has a direct effect on CVD, which does not go through PA; 2) INT_{ref}: the effect on CVD is due to the interaction between BMI and PA; 3) INT_{med}: the effect on CVD is due to both mediation and interaction between BMI and PA; and 4) PIE: the effect of BMI on CVD goes purely through PA. Figure 1 illustrates the interaction and mediation of PA between BMI and CVD. The four-way decomposition method was performed by the "CMAverse" package (Version 0.1.0) (16).

MR Analysis

The NHANES is a cross-sectional observational survey and therefore cannot establish causal inferences between BMI, PA, and CVD. MR analysis is an innovative statistical approach that uses genetic variation as an instrumental variable (IV) to assess the causal effect of exposure factors on outcomes. It can eliminate the potential unmeasured confounders and reverse causation as the genetic variants are assigned randomly at conception (17). By using MR, we intend to estimate the causal effects of BMI on CVD and investigate the potential causal mediation role of PA between them. We performed the MR according to the guidelines of STROBE-MR (Supplemental Material, Supplemental Digital Content 2, http://links.lww.com/MSS/D179) (18).

The data used in the current study were derived from publicly available GWAS summaries. GWAS data on BMI were obtained from a meta-analysis of genome-wide association studies for height and BMI involving 681,275 individuals of European ancestry (19). This summary study identified 941 SNPs associated with BMI. Data for PA were obtained from a genome-wide meta-analysis involving up to 606,820 individuals (20). Similar to NHANES, moderate-to-vigorous PA was measured using domain- and intensity-specific questions. Moderate-to-vigorous PA was defined as a binary variable, with categories of physically active and inactive. Genetic instruments for CVD (177,923 cases and 306,675 controls) were obtained from the UK Biobank (https://gwas.mrcieu.ac.uk/, GWAS ID: ebi-a-GCST90038595) (21). All study participants were of European descent.

Single nucleotide polymorphisms (SNPs) were defined as IVs. The IVs used as instruments satisfied three assumptions: 1) associated with exposure, 2) independent of the outcome given the exposure, and 3) independent of all confounders of exposure and outcome. We included SNPs that were genome-wide significant ($P < 5 \times 10^{-8}$). To identify independent IVs, these SNPs were clustered based on linkage disequilibrium (window size = 10,000 kb and $r^2 < 0.001$) using the European 1000 Genomes reference panel (22). The PhenoScanner tool (http://www.phenoscanner.medschl.cam.ac.uk/) was then used to exclude any SNPs associated with confounding factors of the outcome. Moreover, the robustness of the included IVs was quantified using *F*-statistic, with an *F*-statistic value exceeding 10 deemed suitable for MR analysis.

We performed MR analysis using the "TwoSampleMR" package (version 0.5.6) in R software. Statistical power for MR was calculated using mRnd (https://cnsgenomics.Shinyapps.io/mRnd/). We used the inverse-variance weighted (IVW) method as the primary analytic approach. It uses meta-analysis to combine the Wald ratios of causal effects for each SNP (23). MR-Egger and weighted-median methods were used as a complement to IVW.

Heterogeneity between SNPs was assessed using Cochran's *Q*-test. IVW with a multiplicative random effect would be performed if heterogeneity was observed (24). MR-Egger intercept method was used to examine the possibility of directional

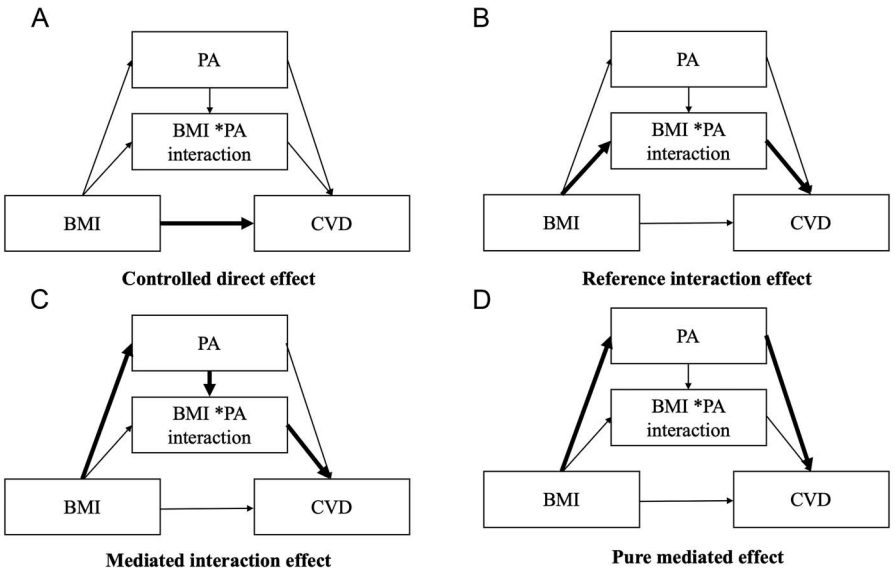

FIGURE 1—Schematic of the four-way decomposition method. Thick lines identify the specific pathway of different effects. Thin lines identify all the potential pathways. CDE: the effect of exposure on the outcome is due to neither mediation nor interaction. INT_{ref}: the effect is due to just interaction. INT_{med}: the effect is due to both mediation and interaction. PIE: the effect is due to just mediation.

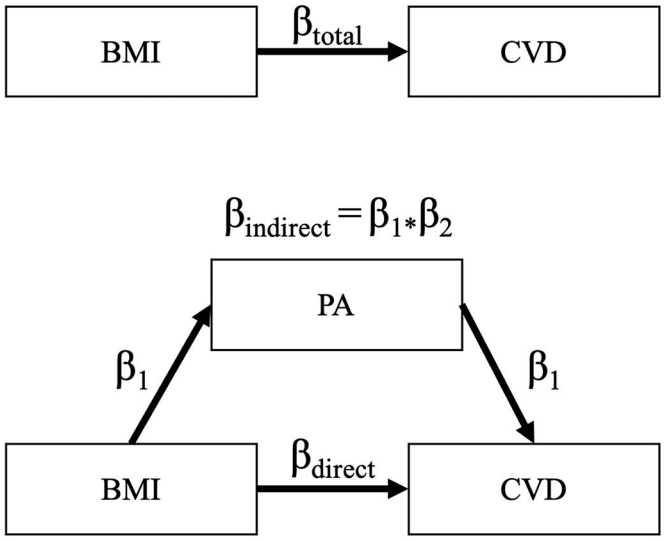

FIGURE 2—Schematic of the two-step MR. β_{total}: total effect of BMI on CVD; β_1: effect of BMI on PA; β_2: effect of PA on CVD. The total effect was decomposed into the indirect effect ($\beta_{indirect}$: the effect mediating through PA and calculated as $\beta_1 * \beta_2$) and direct effect (β_{direct}: the effect not mediating through PA and calculated as $\beta_{total} - \beta_{indirect}$).

horizontal pleiotropy between SNPs and outcome. Correction of pleiotropy would be performed via outlier removal if horizontal pleiotropy was detected. Furthermore, leave-one-out analysis was used to validate the effect of each SNP on the overall causal estimates the reliability and robustness of the evaluation results.

We utilized two-step MR rather than multivariable MR to evaluate the mediation role of PA as two-step MR can better demonstrate the causal effect from exposures to mediators and then to the outcomes (25,26). Figure 2 shows a schematic summary of the two-step MR. We first calculated the total effect of BMI on CVD (β_{total}), and this total effect could be decomposed into the indirect effect (mediating through PA, $\beta_{indirect}$) and direct effect (not mediating through PA, β_{direct}). We then estimated the effect of BMI on PA (β_1) and the effect of PA on CVD (β_2) independently. The indirect effect was calculated as $\beta_1 * \beta_2$, and the percentage of mediation effect was calculated as $(\beta_1 * \beta_2)/\beta_{total}$. The results from IVW were used to estimate the causal effect in two-step MR.

RESULTS

The baseline characteristics of participants are presented in Table 1. Participants with sufficient PA tended to be younger,

TABLE 1. Baseline characteristics of study population by PA and CVD.

		PA			CVD		
	Total	Insufficient	Sufficient	*P*	Absent	Present	*P*
Unweighted sample size	35,406	14,205	21,201		21,663	13,743	
Age, yr	47.7 (0.2)	52.8 (0.3)	45.0 (0.3)	<2.2e−16	46.0 (0.2)	64.8 (0.2)	<2.2e−16
Male sex, %	48.5 (0.3)	38.0 (0.6)	54.2 (0.4)	<2.2e−16	48.0 (0.3)	54.0 (1.2)	1.954e−06
Race, %				1.80e−12			7.66e−16
Hispanic	14.6 (0.9)	15.4 (1.1)	14.2 (0.9)		15.2 (0.9)	8.3 (0.8)	
Non-Hispanic White	67.7 (1.3)	62.5 (1.5)	67.4 (1.3)		65.0 (1.4)	72.9 (1.5)	
Non-Hispanic Black	14.3 (0.8)	16.1 (1.0)	13.3 (0.8)		14.3 (0.8)	14.4 (1.0)	
Others	5.4 (0.3)	6.0 (0.4)	5.0 (0.3)		5.5 (0.3)	4.4 (0.5)	
Educational level, %				<2.2e−16			<2.2e−16
Less than high school	15.1 (0.5)	20.1 (0.7)	12.5 (0.5)		14.4 (0.5)	22.3 (0.9)	
High school graduate	23.6 (0.5)	25.2 (0.7)	22.7 (0.6)		23.1 (0.6)	28.7 (1.0)	
College or higher	61.3 (0.9)	54.7 (0.9)	64.8 (1.0)		62.5 (0.9)	49.0 (1.2)	
Income-to-poverty ratio <1.3, %	20.2 (0.6)	23.1 (0.8)	18.7 (0.6)	1.24e−11	19.7 (0.6)	25.4 (1.0)	<2.2e−16
BMI ≥30, %	38.1 (0.5)	44.7 (0.6)	34.6 (0.6)	<2.2e−16	37.1 (0.5)	48.1 (1.1)	<2.2e−16
Hypertension, %	47.5 (0.5)	57.1 (0.6)	42.3 (0.6)	<2.2e−16	44.4 (0.6)	78.7 (1.1)	<2.2e−16
Diabetes, %	12.1 (0.3)	18.0 (0.5)	9.0 (0.3)	<2.2e−16	10.0 (0.3)	33.7 (1.0)	<2.2e−16
Dyslipidemia, %	29.0 (0.4)	35.4 (0.6)	25.7 (0.5)	<2.2e−16	25.7 (0.4)	62.6 (1.1)	<2.2e−16
Alcohol consumption, %				<2.2e−16			<2.2e−16
Never or abstainer	22.7 (0.6)	30.5 (0.8)	18.9 (0.6)		21.7 (0.6)	34.6 (1.2)	
1–4 drinks	66.2 (0.8)	61.6 (0.9)	68.5 (0.8)		66.8 (0.8)	59.3 (1.4)	
≥5 drinks	11.1 (0.4)	7.9 (0.4)	12.6 (0.5)		11.5 (0.4)	6.1 (0.6)	
Smoking, %				1.07e−01			<2.2e−16
Never	56.0 (0.6)	55.8 (0.7)	56.1 (0.7)		57.6 (0.6)	39.7 (1.2)	
Former	24.8 (0.4)	25.6 (0.6)	24.3 (0.5)		23.3 (0.4)	39.1 (1.3)	
Current	19.2 (0.5)	18.6 (0.6)	19.6 (0.5)		19.0 (0.5)	21.2 (1.1)	

The continuous data were presented as mean (standard error) and compared using the Student's *t*-test. The categorical variables were presented as percentages (standard error) and compared using the chi-square test.

TABLE 2. Interaction and mediation of PA on the association of BMI with CVD.

	Excessive Relative Risk (×100)		Proportional Attributable (%)	
	Estimated (95% CI)	P	Estimated (95% CI)	P
Overall population				
CDE	3.3 (2.4–4.3)	3.34e−12	115.6 (3.6–137.5)	<2e−16
INT_{ref}	−1.1 (−1.6 to −0.5)	1.18e−04	−37.7 (−54.5 to −21.0)	9.80e−06
INT_{med}	0.0 (0.0–0.0)	1.45e−04	0.2 (−0.1 to −21.0)	1.19e−05
PIE	0.6 (0.4–0.8)	4.01e−11	21.9 (15.9–27.9)	8.98e−13
Male				
CDE	5.0 (3.7–6.2)	1.44e−14	165.4 (143.2–187.7)	<2e−16
INT_{ref}	−2.3 (−3.0 to −1.7)	1.07e−12	−77.3 (−95.6 to −59.1)	<2e−16
INT_{med}	0.0 (0.0–0.0)	2.43e−09	0.3 (0.2–0.4)	8.85e−12
PIE	0.3 (0.1–0.6)	1.18e−03	11.6 (5.5–17.6)	1.84e−04
Female				
CDE	3.3 (1.9–4.6)	2.74e−06	104 (77.1–130.6)	2.98e−14
INT_{ref}	−0.9 (−1.7 to −0.2)	1.36e−02	−30.1 (−49.4 to −10.9)	2.14e−03
INT_{med}	0.0 (0.0–0.0)	1.48e−02	0.2 (0.1–0.4)	2.36e−03
PIE	0.8 (0.6–1.1)	6.97e−10	26.1 (17.2–35.0)	9.88e−09

The excessive relative risk and proportional attributable were estimated by the VanderWeele's four-way decomposition method.

male, and non-Hispanic White. They had higher levels of education and higher incomes, and were less likely to suffer from obesity, hypertension, diabetes, and dyslipidemia. In addition, they consumed more alcohol. Conversely, participants with CVD tended to be older, male, and non-Hispanic White. They had lower levels of education and lower incomes, and were more likely to suffer from obesity, hypertension, diabetes, and dyslipidemia. They consumed less alcohol and were more likely to smoke.

There was a strong association between PA and lower odds of CVD after adjusting for all confounders in the general population (odds ratio (OR), 0.84; 95% confidence interval (CI), 0.74–0.95; $P = 8.00e{-}03$). The results were consistent among males (OR, 0.82; 95% CI, 0.68–0.99; $P = 3.48e{-}02$) and females (OR, 0.84; 95% CI, 0.71–0.99; $P = 4.33e{-}02$). Increased BMI was associated with higher odds of CVD in the general population (OR, 1.04; 95% CI, 1.03–1.04; $P = 1.05e{-}12$). This association was consistent among males (OR, 1.03; 95% CI, 1.01–1.05; $P = 1.15e{-}03$) and females (OR, 1.03; 95% CI, 1.02–1.05; $P = 2.44e{-}06$) as well.

Table 2 shows the results of the four-way decomposition. PA showed interaction and mediation effects on the association of BMI with CVD. The proportions attributable of CDE, INT_{ref}, INT_{med}, and PIE were 115.6%, −37.7%, 0.2%, and 21.9%, respectively. The overall proportion attributable to interaction was −37.5% (INT_{ref} + INT_{med}), and the overall proportion attributable to mediation was 22.2% (INT_{med} + PIE). This result was consistent among males and females.

The *F*-statistic values for SNPs instrumenting the relationships between BMI and PA, PA and CVD, and BMI and CVD were 64.5, 37.6, and 74.1, respectively. Statistical power for MR was 100%. The results of MR analyses are shown in Table 3 and Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/MSS/D178). The scatter plots are presented in Supplemental Figures 1–3 (Supplemental Digital Content 1, http://links.lww.com/MSS/D178). The IVW showed a causal relationship between BMI, PA, and CVD (Table 3). MR-Egger and weighted-median methods further demonstrated this result (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/MSS/D178). Cochran's *Q*-test showed heterogeneity in the analysis of the aforementioned relationships (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/MSS/D178). However, IVW with multiplicative random effects showed that the results were consistent (Supplemental Table 1, Supplemental Digital Content 1. http://links.lww.com/MSS/D178). The MR Egger intercept method did not reveal any horizontal pleiotropy (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/MSS/D178). Moreover, the leave-one-out sensitivity analysis indicated that no single SNP was likely to have influenced the causal relationship. Taken together, these findings demonstrate the robustness of the overall results. The result of two-step MR showed PA accounted for 44.7% of the association of BMI with CVD (95% CI, 12.9%–76.5%; $P = 5.82e{-}03$).

DISCUSSION

This study explored three closely related topics that significantly influence human health and longevity: PA, BMI, and CVD. Overweight and obesity increased the risk of CVD, and the potential mechanisms remain to be further elucidated. It has been suggested that biological and behavioral factors may serve as potential influences (27). Therefore, behavioral interventions are regarded as a cost-effective approach for public health. Because people with excess body weight tend to be physically inactive, which might lead to a higher risk of CVD, the association of BMI with CVD may be modified or mediated by PA.

Based on the four-way decomposition, we found a strong interaction between PA and BMI regarding the odds of CVD, with an overall proportion attributable to interaction of −37.5%. This result suggests a strong antagonistic role of increased BMI and sufficient PA on CVD, even if increased BMI is not considered to cause insufficient PA. In this study, we defined sufficient PA as participants engaging in at least 150 min of moderate-intensity PA per week, consistent with recent guidelines for physical exercise in the United States (12). Our results demonstrated that PA levels moderate the association of BMI with CVD. From a public health perspective, 150 min or more of moderate-intensity PA per week was sufficient to lower the impact of high BMI on CVD risk. This finding aligns with previous research. For example, based on

TABLE 3. The causal effects between BMI, PA, and CVD estimated by IVW (fixed effect).

Exposure	Outcome	No. of SNPs	OR (95% CI)	P
BMI	PA	419	0.89 (0.88–0.92)	5.32e−21
PA	CVD	15	0.95 (0.93–0.97)	3.69e−08
BMI	CVD	496	1.01 (1.01–1.02)	1.33e−06

NHANES data, Zhang et al. (28) also showed that PA modified the association between weight status and 10-yr CVD risk, as defined by the Framingham Risk Scores, suggesting that the cardiovascular benefits of PA differ among adults with varying weight statuses. In another study involving 6493 participants from the Nord-Trøndelag Health Study, Moholdt et al. (29) demonstrated an interaction between PA and BMI in association with all-cause mortality among participants with coronary heart disease.

We also performed a mediation analysis to explore the potential mechanism by which BMI leads to CVD. Our study found that PA has a mediation effect on the association of BMI with CVD. According to the four-way decomposition based on the NHANES database, the overall proportion attributable to mediation was 22.2%. In addition, we performed two-step MR analysis to explore the potential causal mediation role of PA and found that PA accounted for 44.7% of the association of BMI with CVD. Biological mechanisms linking excess body weight to a higher risk of CVD are often attributed to the ability of excess adiposity to directly alter the structure and function of the heart and blood vessels (30). Together, our results suggest that, beyond traditional biological mechanisms, behavioral mechanisms such as PA also serve as potential causal influences. This means that higher BMI causally led to a lower level of PA, which in turn increased the risk of CVD. However, the relationship between PA, BMI, and CVD is more complex. For example, in a prospective study of 27,055 healthy women, the authors compared the hazard ratios for the most active women with those for the least active, with and without adjustment for BMI (31). They found that 10.1% of the PA-related reduction in CVD risk was attributable to BMI, indicating that BMI also serves as an important mediator in the association between PA and CVD. These results highlight that PA and BMI are interdependent, and both play crucial roles in controlling CVD.

Strengths of the present study include the large number of participants, which is representative of the general US population. The reliability of the NHANES data has been validated by numerous studies. Another major strength of our study is the estimation of a potential pathway from BMI to CVD through PA using the four-way decomposition method. This method, which has been increasingly applied in clinical studies over the past decade, divides mediation and interaction effects into more detailed components, giving us better insight into the third party's role in the relationship between exposure and outcome (32). Moreover, to address the limitation of cross-sectional study designs, which cannot establish causal inference, we used MR analysis as a complementary approach and demonstrated the causal mediation effect of PA. Finally, it has been reported that the inverse association between PA and CVD is primarily limited to myocardial infarction and subarachnoid hemorrhage (33). Our study demonstrated that PA is inversely associated with overall CVD, contributing new knowledge to the field of MR analysis in CVD research. However, we were unable to perform the MR analysis for PA with different categories of CVD due to the lack of more detailed phenotypes in this GWAS database (21).

There are several limitations to this study. First, the PA assessment in NHANES is self-reported. Misclassification is sometimes inevitable, leading to under- or over-estimation of the association between PA and CVD. However, studies have validated the accuracy of self-reported questionnaires (34,35). Second, we attempted to use MVMR for the mediation analysis to rule out potential confounding effects between the mediator and outcome. However, no appropriate common SNPs were obtained for PA, and we are not able to perform MVMR using the current GWAS summary statistics. Nevertheless, the mediation analysis in the four-way decomposition had already demonstrated the mediation effect of PA after adjusting for potential confounders only without knowing the causal direction. Using two-step MR would be more appropriate than MVMR as MVMR made no assumption about the direction of causality between exposure and mediator (25,26). Third, there are certain sample overlaps among the GWAS summary statistics due to the participants coming from the UK Biobank. This might lead to weak instrument bias. However, the *F*-statistic value for exposures was larger than 10, suggesting that weak instrument bias induced by sample overlap was minimal (36).

In conclusion, our study showed that PA modified the association of BMI with CVD, suggesting that at least 150 min of moderate-intensity PA per week is needed to lower the impact of high BMI on CVD risk. Moreover, we found that PA serves as a causal influence on the association of BMI with CVD.

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Data availability: The data are publicly available on https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. All the statistical analyses and source of data could be found in the provided R code.

Ethical approval and consent to participate: The study protocol for the NHANES was approved by the National Center for Health Statistics Institutional review board. All participants provided written informed consent. Institutional review board approval was exempted for this study because of the publicly available and deidentified data.

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