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Insulin resistance mediates the association between physical activity and mortality in US adults with metabolic syndrome

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This study examines the associations between physical activity (PA) and all-cause mortality (ACM), cause-specific mortality (cancer, cardiovascular disease), and premature mortality, with a focus on the mediating role of insulin resistance. Data from the National Health and Nutrition Examination Survey (NHANES) were analyzed, including 8,460 participants. PA was quantified in metabolic equivalents (MET-h/week) and categorized into four groups: no physical activity (NOPA), low-level PA (LLPA), moderate-level PA (MLPA), and high-level PA (HLPA). Cox regression, restricted cubic splines, and Kaplan-Meier survival curves assessed the associations between PA and mortality risks. Mediation analysis evaluated the role of insulin resistance. With a median follow-up of 6.3 years, 1,147 all-cause deaths, 321 cardiovascular deaths, 274 cancer deaths, and 441 premature deaths. Compared to the NOPA group (0 MET-h/week), the LLPA (MET < 10 h/week), MLPA (10 ≤ MET < 50 h/week), and HLPA (≥ 50 MET-h/week) groups showed significant reductions in all-cause mortality risk by 39% (HR = 0.61, 95% CI: 0.51–0.73), 44% (HR = 0.56, 95% CI: 0.48–0.66), and 57% (HR = 0.43, 95% CI: 0.35–0.52), respectively. Similarly, for cardiovascular disease mortality, the risk reductions were 49% (HR = 0.51, 95% CI: 0.36–0.71), 51% (HR = 0.49, 95% CI: 0.37–0.64), and 52% (HR = 0.48, 95% CI: 0.35–0.66) across the three PA groups. In terms of cancer mortality risk, only the HLPA group showed a statistically significant 50% reduction (HR = 0.50, 95% CI: 0.34–0.74), while the LLPA and MLPA groups demonstrated non-significant reductions of 29% and 16%, respectively. A nonlinear dose-response relationship was observed for PA and mortality. Mediation analysis revealed that HOMA-IR mediated 22.1% ($P = 0.022$), 16.7% ($P = 0.002$), 15.7% ($P = 0.030$), and 10.1% ($P = 0.058$) of the association ACM, cause-specific mortality, and premature mortality, respectively. This study highlights the protective effects of PA in reducing the risks of ACM, cause-specific mortality, and premature mortality, particularly in patients with metabolic syndrome. Insulin resistance plays a significant mediating role in these relationships, underscoring the importance of targeting both PA and insulin resistance in interventions to reduce mortality risks in metabolic syndrome patients.

Keywords Insulin resistance, Physical activity (PA), Metabolic syndrome (MetS), Mediation analysis, Mortality, NHANES

Metabolic syndrome (MetS) is characterized by a cluster of metabolic abnormalities, including abdominal obesity, hyperglycemia, hypertension, and dyslipidemia, which significantly elevate the risks of cardiovascular diseases (CVD) and type 2 diabetes[1]. By 2018, over one billion people worldwide were estimated to have MetS[2]. With the aging of the global population, the prevalence of MetS is projected to rise, posing a substantial public health challenge. MetS is associated with increased risks of all-cause mortality (ACM) and CVD mortality[3,4], as well as higher mortality from malignancies such as breast, colorectal, liver, gallbladder, and pancreatic cancers[5,6]. It also contributes to premature mortality[7,8]. These associations underscore the urgent need for effective strategies to prevent MetS and reduce its associated mortality risks.

Physical activity (PA) is widely recognized for enhancing physical fitness, overall health, and quality of life[9]. A large Norwegian cohort study found that, compared to inactive MetS patients, even low levels of PA significantly reduced mortality risks, while high levels of PA were associated with a 40–50% lower risk of ACM[10]. Similarly, a 20-year follow-up study of Swedish adults aged 60 years and older showed that baseline leisure-time

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PA, even at light intensity, significantly lowered the risks of long-term mortality, CVD incidence, and ACM in MetS patients[11]. In Asia, a study involving over six million Korean adults reported that regular moderate-to-vigorous PA significantly reduced adverse cardiovascular events and ACM among individuals with MetS[12]. Another Korean study highlighted that PA's protective effects were more pronounced in MetS patients than in metabolically healthy individuals[13]. However, the generalizability of these findings is limited by differences in lifestyle, dietary patterns, healthcare systems, and MetS prevalence across countries. For instance, the prevalence of MetS in the United States increased from 25.3% (1988–1994) to 34.2% (2007–2012)[14], compared to a rise from 27.1% (2001) to 33.2% (2020) in Korea[15]. A comparative study of young adults aged 20–39 years in the U.S. and South Korea (2003–2004) found a MetS prevalence of 21.6% in the U.S. versus 6.9% in Korea[16]. Dietary differences, such as the high-calorie, processed diet common in the U.S. versus the fiber-rich Nordic diet, which improves insulin sensitivity and lipid profiles[17,18], further complicate MetS management. Racial and ethnic diversity in the U.S., along with disparities in healthcare access, socioeconomic status, and cultural contexts, also influence PA intervention outcomes[19–21]. Thus, while studies from Norway, Sweden, and Korea demonstrate the benefits of PA for MetS patients, their applicability to the U.S. population remains uncertain. Moreover, few studies have systematically evaluated the impact of PA on cancer mortality or premature mortality in MetS patients, highlighting the need for further research.

Insulin resistance, a hallmark of MetS, impairs the response of skeletal muscles, adipocytes, and the liver to insulin, leading to abnormal glucose and lipid metabolism, hyperglycemia, hyperlipidemia, central obesity, and hypertension[22]. PA plays a crucial role in improving insulin resistance. A study involving 60 obese participants found that increasing daily low-intensity PA significantly improved insulin resistance[23]. A meta-analysis of 54 studies further confirmed that exercise significantly reduced homeostasis model assessment of insulin resistance (HOMA-IR) levels in overweight or obese individuals[24]. Insulin resistance is strongly associated with multiple mortality risks and is a key factor in metabolic diseases. Lee et al. demonstrated that elevated HOMA-IR significantly increases the risks of ACM and CVD mortality[25]. Perseghin et al. similarly showed that insulin resistance significantly raises cancer mortality risk[26]. Although extensive research has examined insulin resistance, its specific mediating role in the relationship between PA and mortality risk among MetS patients remains poorly understood.

Using a nationally representative cohort, this study systematically evaluates the associations between PA and the risks of ACM, cause-specific mortality, and premature mortality among U.S. adults with MetS, while exploring the mediating role of insulin resistance. We hypothesize that (1) higher PA levels are associated with lower risks of ACM, cause-specific mortality, and premature mortality among MetS patients, potentially exhibiting a dose-response relationship; and (2) insulin resistance partially mediates these associations. This study aims to provide novel evidence on the interplay between PA, insulin resistance, and mortality risks, thereby supporting strategies for managing metabolic disorders and improving survival outcomes.

Materials and methods

Study population

This study utilized data from the National Health and Nutrition Examination Survey (NHANES), a biennial survey conducted by the Centers for Disease Control and Prevention (CDC) since 1999[27]. NHANES employs a multistage probability sampling design with cross-sectional and stratified sampling to ensure national representativeness. The study protocol was approved by the Institutional Review Board of the National Center for Health Statistics (NCHS), and all participants provided written informed consent in accordance with ethical standards.

Participants were selected based on the following inclusion and exclusion criteria: Inclusion criteria: (1) 59,842 individuals who participated in NHANES between 2007 and 2018; (2) participants who provided informed consent and agreed to follow-up. Exclusion criteria: (1) participants aged < 20 years ($n = 25,072$); (2) participants missing physical activity (PA) questionnaire data ($n = 172$); (3) participants with unclear metabolic status or without MetS due to missing data on waist circumference, triglycerides, high-density lipoprotein cholesterol, blood pressure, or fasting plasma glucose ($n = 24,557$); (5) pregnant women ($n = 25$); (6) participants with incomplete homeostasis model assessment of insulin resistance (HOMA-IR) data ($n = 123$). The final sample included 8,460 eligible participants (4,603 women, 3,857 men) (Fig. 1).

Assessment of MetS

MetS was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) guidelines[28]. A diagnosis required at least three of the following: (1) Waist circumference ≥ 102 cm (men) or ≥ 88 cm (women); (2) Triglycerides ≥ 1.7 mmol/L (150 mg/dL); (3) HDL-C < 1.03 mmol/L (40 mg/dL) in men or < 1.29 mmol/L (50 mg/dL) in women; (4) Blood pressure ≥ 130/85 mmHg (systolic/diastolic); (5) Fasting plasma glucose (FPG) ≥ 5.6 mmol/L (100 mg/dL) or a prior diagnosis of type 2 diabetes.

Calculation of MET and quantification of PA

The metabolic equivalent of task (MET) is a crucial metric for assessing energy metabolism and exercise intensity, representing the oxygen required to maintain resting metabolism in a quiescent state[29]. PA was assessed using the Global Physical Activity Questionnaire (GPAQ) in NHANES. MET values were assigned based on activity type: vigorous work-related or leisure activities (8 MET), moderate-intensity work-related activities or transportation (walking/cycling) (4 MET), and moderate-intensity leisure activities (4 MET). Weekly MET-hours (MET-hours/week) were calculated by multiplying the MET value, weekly frequency, and daily duration of each activity[30,31]. Participants were categorized into four PA levels: (1) no physical activity (NOPA): 0 MET-hours/week; (2) low-level physical activity (LLPA): <10 MET-hours/week; (3) moderate-level physical activity (MLPA): 10 to < 50 MET-hours/week; (4) high-level physical activity (HLPA): ≥50 MET-hours/week[32].

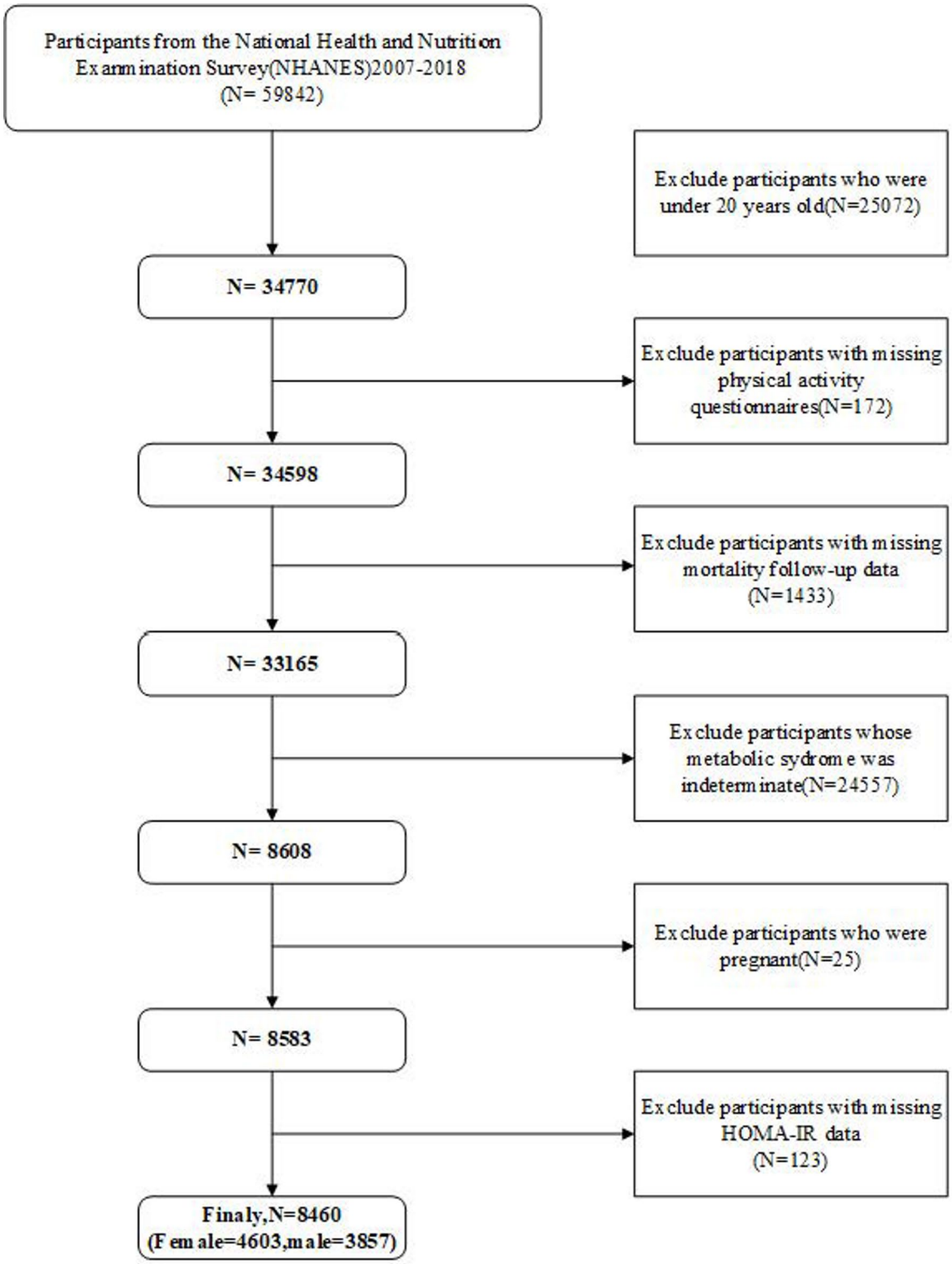

Fig. 1. The sample selection flowchart is based on NHANES 2007–2018 data.

Assessment of mortality

To determine survival status as of December 31, 2018, mortality data for NHANES participants from 2007 to 2018 were obtained by cross-referencing unique identifiers (SEQN) with the National Death Index (NDI). Participants without recorded deaths during the follow-up period were considered alive. Death causes were categorized according to the International Classification of Diseases, Tenth Revision (ICD-10), with premature death being defined as death occurring prior to the age of 70[33]. The main study outcomes consisted of ACM, CVD mortality, cancer mortality, and premature death.

Assessment of insulin resistance

The homeostasis model assessment of insulin resistance (HOMA-IR) was first proposed by Matthews et al. in 1985 and has since become a widely used method for assessing insulin resistance and pancreatic β-cell function[34]. HOMA-IR was calculated using the following formula: $HOMA-IR=\frac{FPG\frac{mmol}{L}\times FINS\left(\frac{\mu U}{mL}\right)}{22.5}$. Fasting insulin levels were measured using immunoassay methods, such as enzyme-linked immunosorbent assay (ELISA), and fasting plasma glucose levels were determined using enzymatic methods. All blood parameters were obtained from venous blood samples collected after an overnight fast of more than 8 h. Due to its simplicity and noninvasiveness, HOMA-IR has been widely applied in both clinical and epidemiological research.

Assessment of covariates

To control for potential confounding factors, the study included the following covariates: (1) Demographic variables: age (20–44 years, 45–64 years, ≥ 65 years), sex (male, female), race (non-Hispanic white, non-Hispanic black, other Hispanic, Mexican American, other races), education level (< high school, high school graduate, some college, college or above), and marital status (married, never married, separated, divorced, widowed, cohabiting). (2) Socioeconomic variables: poverty ratio (PIR) (< 1.35, 1.35–3.00, > 3.00) and health insurance status (yes/no). (3) Lifestyle variables: smoking (never, former, current) and alcohol consumption (non-drinker, drinker). (4) Nutritional and physical status variables: energy intake (low, adequate, high) and Body mass index (BMI) (< 25, 25–30, ≥ 30).

Statistical analysis

All statistical analyses adhered strictly to NHANES guidelines, utilizing sample weights and applying stratified and clustered methods to account for the complex survey design. Participants were categorized into four PA groups: NOPA, LLPA, MLPA, HLPA. The analyses followed NHANES protocols, and weighted data were used to describe the characteristics of the study population, ensuring nationally representative estimates. Categorical variables were presented as counts (%), while continuous variables (normally distributed) were expressed as means ± standard deviation (SD). The Kruskal-Wallis test was employed to compare continuous variables across groups, and the Chi-squared test was used for categorical variables.

Survival among MetS patients was assessed at different time points using Kaplan-Meier (KM) survival curves, and group differences were evaluated by log-rank testing. Multivariable weighted Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for the associations between PA levels and ACM, cause-specific mortality, and premature mortality. HRs represented the relative risk of an event in each PA group compared to the NOPA group, accounting for time-to-event data. An HR < 1 indicated a decreased risk, while an HR > 1 indicated an increased risk. To control for potential confounders, three models were constructed: Model 1 was unadjusted; Model 2 was adjusted for age, sex, race, BMI, education level, marital status, and poverty income ratio (PIR); and Model 3 further adjusted for smoking status, drinking status, energy intake, and health insurance status. Restricted cubic spline (RCS) models were applied to examine the nonlinear associations between PA levels and mortality risks. Subgroup and interaction analyses were conducted based on sex, age, race, education level, marital status, PIR, BMI, smoking and drinking status, health insurance, and energy intake.

Meanwhile, to assess whether HOMA-IR mediated the association between PA and mortality risks in patients with MetS, we conducted a causal mediation analysis within a counterfactual framework. The total effect (TE) of PA on mortality risks was decomposed into the indirect effect (IE) through HOMA-IR and the direct effect (DE) after controlling for HOMA-IR. The TE represented the overall association between PA and mortality risks; the IE quantified the effect mediated through HOMA-IR; and the DE reflected the direct effect after adjusting for HOMA-IR. Given the time-to-event nature of the outcomes(mortality), Cox proportional hazards models were used to estimate the TE and DE. All models adjusted for potential confounders, including age, sex, race, BMI, education level, marital status, PIR, smoking status, drinking status, energy intake, and insurance status. The IE was estimated using the product-of-coefficients method, and statistical significance was determined by 95% confidence intervals (CIs) generated from 1,000 bootstrap samples. Mediation was considered significant if the 95% CI for the IE excluded zero. A directed acyclic graph (DAG) illustrating the causal pathways and confounding structure is provided in the Supplementary Material (Figure S1).

Additionally, to further explore whether the associations between PA and mortality risks varied by activity domain, we conducted a sensitivity analysis by disaggregating total PA into three specific domains available in the NHANES dataset: recreational PA, work-related PA, and transport-related PA. For each domain, participants were classified into four groups—NOPA, LLPA, MLPA, and HLPA—based on their weekly MET-hours, using the same thresholds as in the primary analysis. Weighted Cox proportional hazards regression models were separately constructed for each PA domain to examine their associations with all-cause, cardiovascular, cancer-specific, and premature mortality. To control for potential confounders, three weighted Cox regression models were constructed for each PA domain, following the same covariate adjustment strategy as in the main analysis.

All statistical analyses were performed using R version 4.4.0, with a two-sided P-value < 0.05 considered statistically significant.

Results

Baseline characteristics

Table 1 presents the baseline characteristics of the 8,460 participants aged 20 years and older with MetS included in this study. The cohort comprised 4,603 women (54.4%) and 3,857 men (45.6%). Participants were categorized into four groups based on PA levels: NOPA, LLPA, MLPA, and HLPA. Compared to the NOPA group, HLPA group participants were more inclined to be male, middle-aged or older, non-Hispanic white, less educated,

	Summary descriptives table by groups of 'PA_group'					
	[ALL]	NOPA	LLPA	MLPA	HLPA	
	N=8460	*N*=2955	*N*=1241	*N*=2289	*N*=1975	p.overall
Gender						< 0.001
Men	3857 (45.6%)	1127 (38.1%)	486 (39.2%)	1086 (47.4%)	1158 (58.6%)	
Women	4603 (54.4%)	1828 (61.9%)	755 (60.8%)	1203 (52.6%)	817 (41.4%)	
Age						< 0.001
20–44	1906 (22.5%)	395 (13.4%)	253 (20.4%)	557 (24.3%)	701 (35.5%)	
45–64	3482 (41.2%)	1146 (38.8%)	549 (44.2%)	949 (41.5%)	838 (42.4%)	
≥ 65	3072 (36.3%)	1414 (47.9%)	439 (35.4%)	783 (34.2%)	436 (22.1%)	
Race						< 0.001
Mexican American	1336 (15.8%)	504 (17.1%)	173 (13.9%)	322 (14.1%)	337 (17.1%)	
Other Hispanic	967 (11.4%)	359 (12.1%)	127 (10.2%)	249 (10.9%)	232 (11.7%)	
Non-Hispanic White	3710 (43.9%)	1283 (43.4%)	517 (41.7%)	1043 (45.6%)	867 (43.9%)	
Non-Hispanic Black	1710 (20.2%)	596 (20.2%)	286 (23.0%)	438 (19.1%)	390 (19.7%)	
Other Race—including multi-racial	737 (8.71%)	213 (7.21%)	138 (11.1%)	237 (10.4%)	149 (7.54%)	
Education						< 0.001
< High school	2490 (29.4%)	1121 (37.9%)	320 (25.8%)	521 (22.8%)	528 (26.7%)	
High school graduate	2071 (24.5%)	738 (25.0%)	304 (24.5%)	523 (22.8%)	506 (25.6%)	
Some college	2491 (29.4%)	719 (24.3%)	370 (29.8%)	727 (31.8%)	675 (34.2%)	
College graduate or above	1408 (16.6%)	377 (12.8%)	247 (19.9%)	518 (22.6%)	266 (13.5%)	
Marital						< 0.001
Married	4599 (54.4%)	1527 (51.7%)	655 (52.8%)	1315 (57.4%)	1102 (55.8%)	
Widowed	1015 (12.0%)	518 (17.5%)	166 (13.4%)	223 (9.74%)	108 (5.47%)	
Divorced	1109 (13.1%)	391 (13.2%)	179 (14.4%)	280 (12.2%)	259 (13.1%)	
Separated	315 (3.72%)	115 (3.89%)	43 (3.46%)	73 (3.19%)	84 (4.25%)	
Never married	929 (11.0%)	272 (9.20%)	129 (10.4%)	259 (11.3%)	269 (13.6%)	
Living with partner	493 (5.83%)	132 (4.47%)	69 (5.56%)	139 (6.07%)	153 (7.75%)	
PIR						< 0.001
<1.35	3060 (36.2%)	1181 (40.0%)	451 (36.3%)	733 (32.0%)	695 (35.2%)	
1.35-3.00	2772 (32.8%)	1036 (35.1%)	372 (30.0%)	707 (30.9%)	657 (33.3%)	
≥3.00	2628 (31.1%)	738 (25.0%)	418 (33.7%)	849 (37.1%)	623 (31.5%)	
BMI						0.057
Under 25	714 (8.44%)	251 (8.49%)	114 (9.19%)	203 (8.87%)	146 (7.39%)	
25-30.0	2548 (30.1%)	883 (29.9%)	370 (29.8%)	731 (31.9%)	564 (28.6%)	
30.0 and over	5198 (61.4%)	1821 (61.6%)	757 (61.0%)	1355 (59.2%)	1265 (64.1%)	
Smoking						< 0.001
Continued						

	Summary descriptives table by groups of 'PA_group'					
	[ALL]	NOPA	LLPA	MLPA	HLPA	
	N=8460	*N*=2955	*N*=1241	*N*=2289	*N*=1975	p.overall
Current smoker	1653 (19.5%)	574 (19.4%)	222 (17.9%)	388 (17.0%)	469 (23.7%)	
Ex-smoker	2465 (29.1%)	877 (29.7%)	341 (27.5%)	680 (29.7%)	567 (28.7%)	
Never smoker	4342 (51.3%)	1504 (50.9%)	678 (54.6%)	1221 (53.3%)	939 (47.5%)	
Drinking						< 0.001
Drinker	6160 (72.8%)	1983 (67.1%)	899 (72.4%)	1712 (74.8%)	1566 (79.3%)	
Non-drinker	2300 (27.2%)	972 (32.9%)	342 (27.6%)	577 (25.2%)	409 (20.7%)	
Health_insurance						< 0.001
Yes	7031 (83.1%)	2535 (85.8%)	1064 (85.7%)	1928 (84.2%)	1504 (76.2%)	
No	1429 (16.9%)	420 (14.2%)	177 (14.3%)	361 (15.8%)	471 (23.8%)	
Energy intake						< 0.001
Adequate	3260 (38.5%)	1050 (35.5%)	489 (39.4%)	918 (40.1%)	803 (40.7%)	
High	1140 (13.5%)	307 (10.4%)	156 (12.6%)	302 (13.2%)	375 (19.0%)	
Low	4060 (48.0%)	1598 (54.1%)	596 (48.0%)	1069 (46.7%)	797 (40.4%)	
HOMA-IR	6.44 (10.4)	6.85 (10.7)	6.04 (7.86)	6.39 (12.3)	6.15 (8.95)	0.045

Table 1. Baseline characteristics of patients with metabolic syndrome by physical activity level, from NHANES (2007–2018).

married, lower income, non-smokers, alcohol consumers, insured, with adequate energy intake and lower HOMA-IR levels (all $P < 0.05$).

Associations of PA with ACM, cause-specific mortality, and premature mortality

Throughout the follow-up period, 1,147 all-cause deaths, 321 cardiovascular deaths, 274 cancer deaths, and 441 premature deaths were recorded. Kaplan-Meier survival curves demonstrated that MetS patients in the LLPA, MLPA, and HLPA groups had lower ACM, CVD mortality, cancer mortality, and premature mortality rates compared to the NOPA group, with the HLPA group exhibiting the lowest rates ($P < 0.001$) (Fig. 2). The log-rank test was employed to evaluate differences between the PA groups.

Multivariable Cox regression analyses revealed that higher PA levels were associated with progressively greater reductions in ACM, cause-specific mortality, and premature mortality compared to the NOPA group. For ACM, the LLPA, MLPA, and HLPA groups showed risk reductions of 39% (HR = 0.61, 95% CI: 0.51–0.73), 44% (HR = 0.56, 95% CI: 0.48–0.66), and 57% (HR = 0.43, 95% CI: 0.35–0.52), respectively. For CVD mortality, risk reductions were 49% (HR = 0.51, 95% CI: 0.36–0.71), 51% (HR = 0.49, 95% CI: 0.37–0.64), and 52% (HR = 0.48, 95% CI: 0.35–0.66) for the LLPA, MLPA, and HLPA groups, respectively. For cancer mortality, only the HLPA group showed a significant 50% risk reduction (HR = 0.50, 95% CI: 0.34–0.74), while the LLPA (HR = 0.71, 95% CI: 0.49–1.03) and MLPA (HR = 0.84, 95% CI: 0.61–1.16) groups showed non-significant reductions of 29% and 16%, respectively. For premature mortality, risk reductions were 29% (HR = 0.71, 95% CI: 0.51–0.99), 30% (HR = 0.70, 95% CI: 0.53–0.93), and 51% (HR = 0.49, 95% CI: 0.36–0.67) for the LLPA, MLPA, and HLPA groups, respectively (Table 2). These findings indicate that even low levels of PA significantly reduce mortality risks in MetS patients, with greater benefits at higher PA levels.

Nonlinear dose-response relationship between PA and ACM, cause-specific mortality, and premature mortality

Among MetS patients, PA levels exhibited a significant nonlinear dose-response relationship with ACM, CVD mortality, and premature mortality risks ($P < 0.05$). Specifically, the protective effect of PA against ACM, CVD mortality, and premature mortality began to manifest in the LLPA (MET < 10 h/week) group and increased with higher PA levels. Notably, in the HLPA (MET ≥ 50 h/week) group, mortality risks gradually plateaued as PA levels reached higher ranges (Fig. 3).

Subgroup analysis

Subgroup analyses evaluated the associations and interaction effects between PA and risks of ACM, cause-specific mortality, and premature mortality among different subgroups of MetS patients. The results revealed a significant interaction effect of sex on CVD mortality risk (P for interaction = 0.019). Among men, HLPA

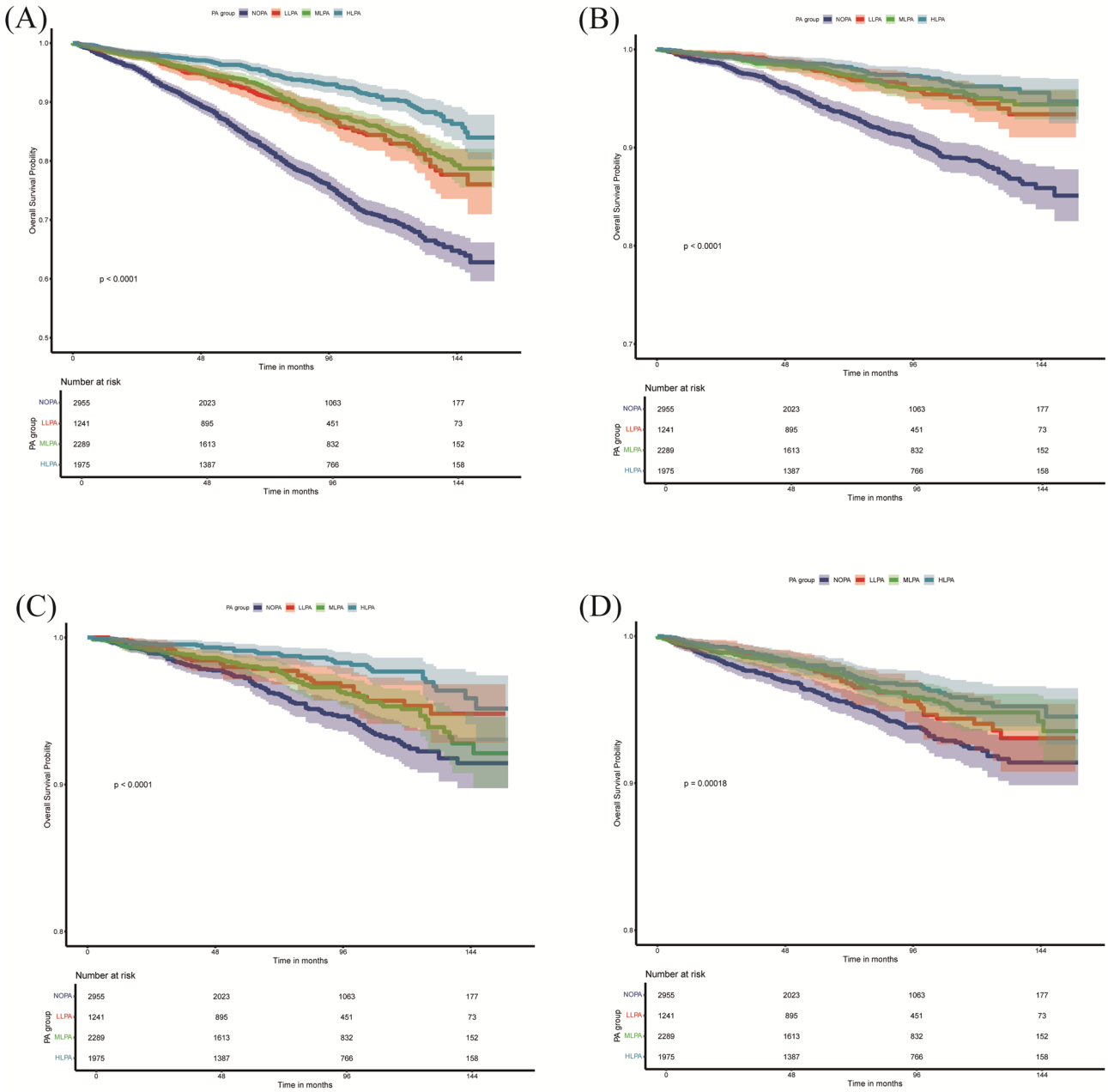

Fig. 2. The Kaplan-Meier curve illustrates the survival rates and the number of individuals (%) with varying levels of physical activity among adults with metabolic syndrome. (A) all-cause mortality; (B) cardiovascular disease (CVD) mortality; (C) cancer mortality; (D) premature mortality.

decreased CVD mortality risk (HR = 0.39, 95% CI: 0.25–0.61). In contrast, among women in the HLPA group, the reduction in mortality risk (HR = 0.68, 95% CI: 0.42–1.11) did not reach statistical significance. Additionally, insurance status significantly modified the association between PA and risks of ACM ($P = 0.009$) and cancer mortality ($P = 0.008$). For premature mortality risk, a statistically significant interaction was observed between PA and marital status ($P = 0.014$). Tables 3, 4, 5 and 6.

Association between PA and HOMA-IR, and HOMA-IR's relationship with ACM, cause-specific mortality, and premature mortality

Table 7 shows linear regression results indicating a significant inverse relationship between PA and HOMA-IR. After adjusting for all covariates, each one standard deviation (SD) increase in PA was associated with a 0.24-unit reduction in HOMA-IR (β = -0.24, 95% CI: -0.30 to -0.18). Table 7 presents the results of the Cox regression model examining the relationship between HOMA-IR and ACM, cause-specific mortality, and premature mortality. After multivariable adjustment, each one-unit increase in HOMA-IR was associated with a 1% increase in the risk of ACM, CVD mortality, cancer mortality, and premature mortality (HR = 1.01, $P < 0.001$).

Type of PA	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause mortality						
NOPA	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
LLPA	0.51 (0.43, 0.62)	< 0.001	0.60 (0.50, 0.72)	< 0.001	0.61 (0.51, 0.73)	< 0.001
MLPA	0.47 (0.40, 0.54)	< 0.001	0.55 (0.48, 0.65)	< 0.001	0.56 (0.48, 0.66)	< 0.001
HLPA	0.30 (0.24, 0.36)	< 0.001	0.42 (0.34, 0.51)	< 0.001	0.43 (0.35, 0.52)	< 0.001
CVD mortality						
NOPA	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
LLPA	0.42 (0.30, 0.59)	< 0.001	0.50 (0.36, 0.70)	< 0.001	0.51 (0.36, 0.71)	< 0.001
MLPA	0.39 (0.30, 0.52)	< 0.001	0.48 (0.36, 0.63)	< 0.001	0.49 (0.37, 0.64)	< 0.001
HLPA	0.31 (0.22, 0.42)	< 0.001	0.46 (0.33, 0.64)	< 0.001	0.48 (0.35, 0.66)	< 0.001
Cancer mortality						
NOPA	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
LLPA	0.62 (0.43, 0.90)	0.012	0.70 (0.48, 1.01)	0.059	0.71 (0.48, 1.03)	0.069
MLPA	0.72 (0.54, 0.96)	0.024	0.81 (0.61, 1.09)	0.161	0.84 (0.63, 1.13)	0.259
HLPA	0.37 (0.25, 0.54)	< 0.001	0.49 (0.33, 0.72)	< 0.001	0.50 (0.34, 0.74)	0.001
Premature mortality						
NOPA	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
LLPA	0.71 (0.51, 0.99)	0.045	0.68 (0.49, 0.96)	0.026	0.71 (0.51, 0.99)	0.043
MLPA	0.64 (0.49, 0.85)	0.002	0.68 (0.51, 0.90)	0.007	0.70 (0.53, 0.93)	0.014
HLPA	0.55 (0.40, 0.74)	< 0.001	0.48 (0.35, 0.65)	< 0.001	0.49 (0.36, 0.67)	< 0.001

Table 2. Hazard ratios and 95% confidence intervals for the effects of different levels of physical activity on all-cause mortality, cardiovascular disease (CVD) mortality, cancer mortality and premature mortality in American adult metabolic syndrome patients. Model 1: Unadjusted model; Model 2: Adjusted for age, sex, race, BMI, education level, marital status and PIR; Model 3: Further adjusted for smoking status, drinking status, energy intake and health insurance status based on Model 2.

Mediation analysis of HOMA-IR in the relationship between PA and ACM, cause-specific mortality, and premature mortality

We conducted causal mediation analyses to evaluate whether HOMA-IR mediated the associations between PA and ACM, cause-specific mortality, and premature mortality. The results demonstrated that HOMA-IR played a significant mediating role in the relationship between PA and ACM (22.1%, $P=0.022$), CVD mortality (16.7%, $P=0.002$), and cancer mortality (15.7%, $P=0.030$). Additionally, HOMA-IR exhibited a borderline significant mediating effect between PA and premature mortality (mediation proportion: 10.1%, $P=0.058$) (Fig. 4).

Sensitivity analyses

To further explore the differential effects of various types of PA on mortality risk, we conducted sensitivity analyses for recreational, work-related, and transport-related PA[35]. Although the strength and statistical significance of the associations varied slightly across PA types, the overall trends remained consistent with the main analyses, indicating the robustness of our findings. For recreational PA, LLPA, MLPA, and HLPA were all significantly associated with reduced risks of ACM, CVD mortality, and premature mortality (all $p<0.05$), with stronger protective effects observed compared to the main analysis. However, the associations with cancer mortality did not reach statistical significance (Table S1). For work-related PA, all PA levels were significantly associated with lower ACM risk ($p<0.05$). Specifically, HLPA was inversely associated with cancer mortality, while LLPA and MLPA showed significant protective effects primarily against CVD mortality ($p<0.05$). Notably, only HLPA significantly reduced the risk of premature mortality (Table S2). Regarding transport-related PA, LLPA and MLPA were significantly associated with reduced risks of ACM and CVD mortality, while HLPA showed a significant association only with lower ACM risk. No significant associations were observed between transport-related PA and cancer mortality or premature mortality (Table S3).

Discussion

In this prospective cohort study conducted among U.S. adults, we found that LLPA, MLPA, and HLPA significantly reduced the risks of ACM, CVD mortality, and premature mortality in patients with MetS. Moreover, the protective effects strengthened with increasing PA levels. Notably, even LLPA substantially reduced these mortality risks. However, a significant reduction in cancer mortality was observed exclusively in the HLPA group. Additionally, insulin resistance significantly mediated the associations between PA and ACM, CVD mortality, and cancer mortality.

Our findings are consistent with previous evidence indicating that PA significantly reduces ACM, cause-specific mortality, and premature mortality in MetS patients. A large cohort study involving 88,140 U.S. adults demonstrated that even low levels of PA (10–59 min per week) significantly lowered ACM and CVD mortality

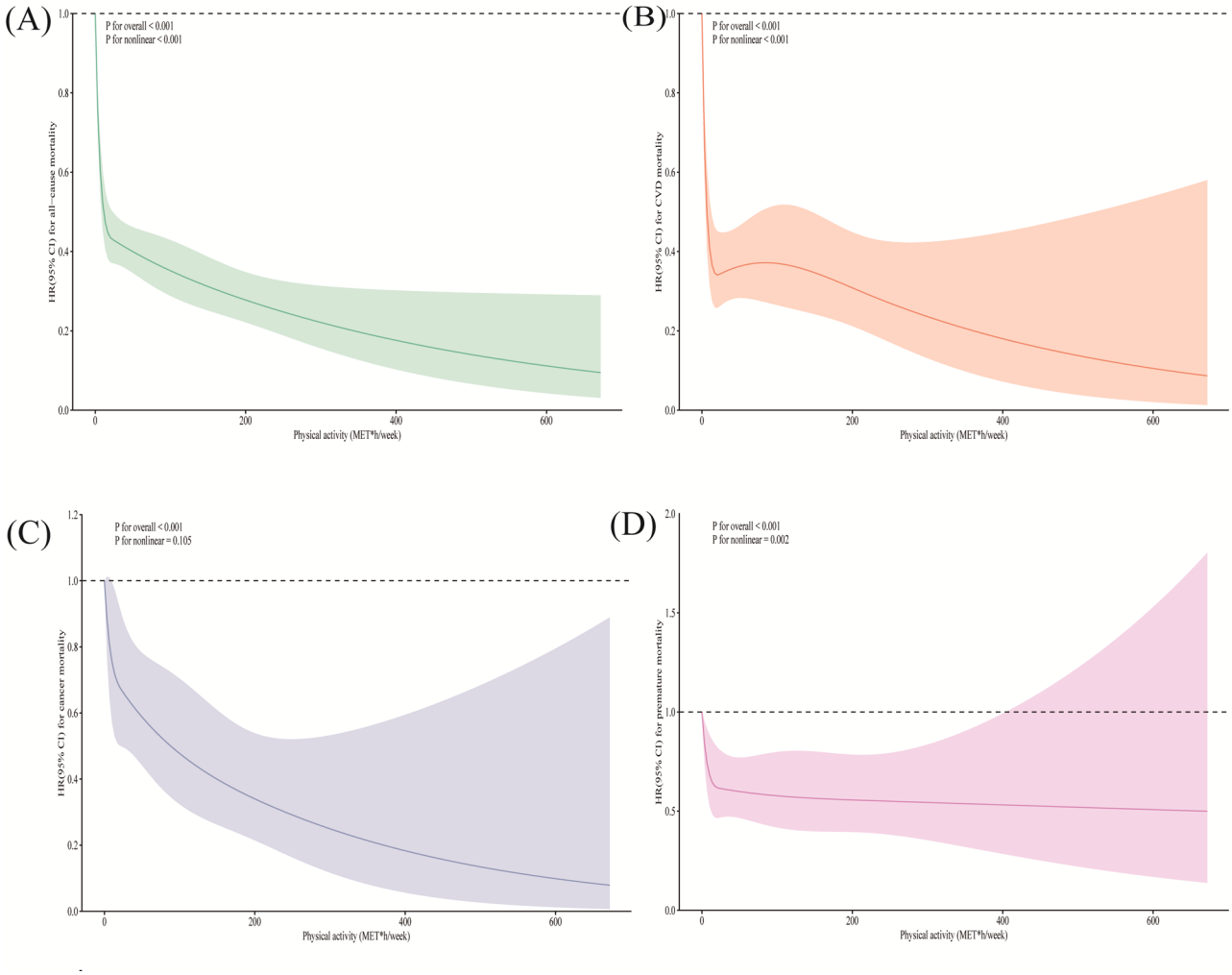

Fig. 3. Dose-response relationship between physical activity (PA) level and various mortality risks. (A) all-cause mortality; (B) cardiovascular disease (CVD) mortality; (C) cancer mortality; (D) premature mortality.

Associations	Model 1		Model 2		Model 3	
	β/HR (95% CI)	*P* value	β/HR (95% CI)	*P* value	β/HR (95% CI)	*P* value
PA on HOMAIR, β (95% CI)						
PA	− 0.34 (− 0.38, − 0.30)	< 0.001	− 0.30 (− 0.35, − 0.25)	< 0.001	− 0.24 (− 0.30, − 0.18)	< 0.001
HOMAIR on mortality, HR (95% CI)						
All-cause mortality	1.01 (1.00, 1.01)	< 0.001	1.01 (1.00, 1.01)	< 0.001	1.01 (1.00, 1.02)	< 0.001
CVD mortality	1.01 (1.00, 1.02)	< 0.001	1.01 (1.00, 1.02)	< 0.001	1.01 (1.00, 1.02)	< 0.001
Cancer mortality	1.01 (1.00, 1.01)	< 0.001	1.01 (1.00, 1.01)	< 0.001	1.01 (1.00, 1.01)	< 0.001
Premature mortality	1.01 (1.01, 1.02)	< 0.001	1.01 (1.01, 1.02)	< 0.001	1.01 (1.01, 1.02)	< 0.001

Table 3. Subgroup analysis of the association between physical activity and all-cause mortality. Model 1: Unadjusted model; Model 2: Adjusted for age, sex, race, BMI, education level, marital status and PIR; Model 3: Further adjusted for smoking status, drinking status, energy intake and health insurance status based on Model 2.

risks, with protective effects progressively increasing at higher PA levels[36]. Additionally, a meta-analysis of 94 cohorts reported that higher PA levels were associated with significant reductions in ACM, cause-specific mortality, and premature mortality in the general population, with the greatest benefits observed between 0 and 8.75 MET-hours/week[37]. Furthermore, a cohort study involving 1.44 million participants found that higher leisure-time PA significantly reduced the risk of 13 different types of cancer[38].

All-cause mortality					
PA levels	HR (95%CI)				P for interaction
	NOPA	LLPA	MLPA	HLPA	
Gender					0.066
Men	REF	0.6 (0.46–0.77)	0.56 (0.45–0.69)	0.39 (0.30, 0.50)	
Women	REF	0.6 (0.46–0.78)	0.55 (0.43–0.69)	0.48 (0.35, 0.66)	
Age_group	REF				0.065
20–44	REF	0.67 (0.2–2.26)	1.01 (0.40, 2.57)	0.45 (0.18, 1.16)	
45–64	REF	0.67 (0.47–0.96)	0.67 (0.49, 0.91)	0.45 (0.32, 0.64)	
≥ 65	REF	0.59 (0.47–0.73)	0.51 (0.43, 0.62)	0.39 (0.31, 0.51)	
Race	REF				0.791
Mexican American	REF	0.72 (0.38–1.34)	0.75 (0.43, 1.30)	0.49 (0.25, 1.00)	
Other Hispanic	REF	0.66 (0.35–1.24)	0.77 (0.45, 1.31)	0.47 (0.23, 0.98)	
Non-Hispanic White	REF	0.54 (0.42–0.7)	0.54 (0.44, 0.65)	0.40 (0.31, 0.51)	
Non-Hispanic Black	REF	0.71 (0.48–1.06)	0.49 (0.32, 0.74)	0.38 (0.23, 0.62)	
OtherRace-Including Multi-Racial	REF	0.58 (0.17–1.98)	0.42 (0.19, 0.91)	0.27 (0.08, 0.88)	
Education_level	REF				0.683
< High school	REF	0.75 (0.56, 1.03)	0.58 (0.44, 0.77)	0.49 (0.35, 0.69)	
High school graduate	REF	0.52 (0.36, 0.76)	0.59 (0.44, 0.79)	0.45 (0.30, 0.65)	
Some college	REF	0.59 (0.41, 0.85)	0.56 (0.41, 0.76)	0.33 (0.22, 0.50)	
College graduate or above	REF	0.47 (0.27, 0.82)	0.44 (0.28, 0.70)	0.32 (0.18, 0.58)	
Marital_status	REF				0.131
Married	REF	0.41 (0.30, 0.57)	0.60 (0.48, 0.75)	0.39 (0.29, 0.51)	
Widowed	REF	0.72 (0.51, 1.00)	0.47 (0.34, 0.65)	0.60 (0.38, 0.93)	
Divorced	REF	0.75 (0.46, 1.21)	0.63 (0.42, 0.95)	0.34 (0.20, 0.59)	
Separated	REF	0.45 (0.12, 1.53)	0.20 (0.04, 1.02)	0.06 (0.01, 0.39)	
Never married	REF	1.33 (0.66, 2.66)	0.63 (0.33, 1.22)	0.35 (0.14, 0.85)	
Living with partner	REF	3.80 (0.73, 19.72)	1.28 (0.37, 4.44)	0.76 (0.20, 2.85)	
PIR_group	REF				0.955
< 1.35	REF	0.75 (0.57, 0.98)	0.52 (0.40, 0.67)	0.41 (0.30, 0.57)	
1.35–3.00	REF	0.46 (0.33, 0.64)	0.59 (0.45, 0.75)	0.41 (0.30, 0.57)	
≥ 3.00	REF	0.65 (0.43, 1.00)	0.57 (0.41, 0.78)	0.42 (0.28, 0.64)	
BMI_group	REF				0.969
Under 25	REF	0.34 (0.02, 0.59)	0.36 (0.24, 0.55)	0.37 (0.23, 0.59)	
25–30.0	REF	0.82 (0.60, 1.12)	0.67 (0.51, 0.87)	0.43 (0.30, 0.61)	
30.0 and over	REF	0.57 (0.44, 0.73)	0.55 (0.44, 0.68)	0.42 (0.32, 0.55)	
Smoking	REF				0.119
Current smoker	REF	0.67 (0.44, 1.03)	0.74 (0.52, 1.06)	0.45 (0.30, 0.69)	
Ex-smoker	REF	0.57 (0.42, 0.77)	0.58 (0.46, 0.74)	0.36 (0.26, 0.49)	
Continued					

All-cause mortality					
PA levels	HR (95%CI)				P for interaction
	NOPA	LLPA	MLPA	HLPA	
Never smoker	REF	0.65 (0.49, 0.86)	0.49 (0.38, 0.63)	0.47 (0.34, 0.65)	
Drinking	REF				0.947
Drinker	REF	0.63 (0.50, 0.78)	0.60 (0.50, 0.73)	0.44 (0.35, 0.56)	
Non-drinker	REF	0.59 (0.42, 0.82)	0.45 (0.33, 0.60)	0.36 (0.24, 0.54)	
Health_insurance	REF				0.009
Yes	REF	0.60 (0.49, 0.72)	0.54 (0.46, 0.63)	0.39 (0.32, 0.48)	
No	REF	0.64 (0.31, 1.32)	0.78 (0.43, 1.41)	0.70 (0.40, 1.24)	
Energy intake	REF				0.47
Adequate	REF	0.51 (0.36, 0.73)	0.50 (0.38, 0.65)	0.34 (0.24, 0.48)	
High	REF	049 (0.24, 0.99)	0.41 (0.22, 0.77)	0.48 (0.25, 0.93)	
Low	REF	0.65 (0.52, 0.82)	0.62 (0.51, 0.76)	0.46 (0.36, 0.61)	

Table 4. Subgroup analysis of the association between physical activity and cardiovascular disease mortality.

Consistent with our results, two large-scale cohort studies involving Korean MetS patients reported that PA had significant protective effects against ACM, and these effects increased as PA levels rose[12,13]. In contrast, a Swedish study found that moderate or high-intensity PA among MetS patients showed inverse associations with ACM and CVD mortality compared to sedentary individuals, but these associations did not reach statistical significance after multivariable adjustments[11]. This discrepancy might result from smaller sample sizes or fewer covariates in their Cox regression models. To our knowledge, the current study is the first prospective cohort study conducted specifically among U.S. MetS patients to systematically evaluate the associations between different PA levels and risks of ACM, cause-specific mortality, and premature mortality, providing crucial evidence supporting PA as an effective intervention to reduce mortality risks in this population.

Given that cancer and CVD are the leading causes of mortality among MetS patients in this study, this section explores the mechanisms by which PA mitigates these risks. For CVD mortality, PA confers protective effects through several pathways. First, it improves cardiovascular health by reducing insulin resistance and regulating lipid and liver metabolism[23,39]. Second, PA enhances endothelial function, lowers blood pressure, promotes vasodilation, and increases vascular elasticity[40]. Additionally, elevated insulin resistance and myostatin levels in MetS patients contribute to skeletal muscle loss[41]. PA counteracts this by improving muscle mass, enhancing muscle function, and boosting antioxidant capacity in inflammatory conditions like MetS[42,43], thus improving metabolic health. Moreover, PA's anti-inflammatory and antioxidant effects reduce endothelial damage, enhance vascular function, and lower arterial stiffness risk[44]. Regarding cancer mortality, while the LLPA and MLPA groups showed a trend toward reduced risk, the results were inconclusive, likely due to small effect sizes leading to confidence intervals that included the null value. In contrast, the HLPA group exhibited a significant risk reduction, likely due to its ability to reverse the pro-tumorigenic environment in MetS through multiple mechanisms. First, HLPA enhances immune surveillance by mobilizing natural killer (NK) cells, $CD8^+$ T cells, and B lymphocytes via catecholamine and myokine (e.g., IL-6, irisin) signaling, improving tumor cell clearance[45,46]. Second, MetS is characterized by chronic low-grade inflammation with elevated pro-inflammatory cytokines (e.g., IL-6, TNF-α, CRP), which promote tumor initiation and metastasis[47]. HLPA reduces these cytokines, increases anti-inflammatory factors (e.g., IL-10, TGF-β), and inhibits tumor-associated macrophage (TAM) polarization toward the pro-tumor M2 phenotype[48,49]. Third, HLPA improves insulin resistance, suppressing the PI3K-Akt-mTOR pathway, which is overactivated in MetS-related hyperinsulinemia and drives cancer cell proliferation[50,51]. Fourth, HLPA, often including resistance training, reduces visceral fat, increases muscle mass, normalizes adipokine profiles, and limits tumor-promoting adipose tissue signaling[52,53]. Fifth, HLPA induces epigenetic changes, such as DNA methylation and miRNA (e.g., miR-21) regulation, suppressing oncogene expression[54]. Sixth, HLPA lowers circulating estrogen and IGF-1 levels, reducing the risk of hormone-dependent cancers (e.g., breast, prostate)[55,56]. Finally, HLPA improves the tumor microenvironment by decreasing VEGF and HIF-1α expression, inhibiting angiogenesis and tumor hypoxia[57].

RCS analyses revealed significant nonlinear dose-response relationships between PA and risks of ACM, CVD mortality, and premature mortality in patients with MetS. RCS curves showed a sharp decline in HRs for ACM, CVD mortality, and premature mortality at LLPA to MLPA, indicating that even minimal PA significantly reduces mortality risks in MetS patients. As PA levels increased, mortality risks continued to decline but plateaued at HLPA, suggesting that further increases in PA yield minimal additional benefits. In contrast, the nonlinear relationship between PA and cancer mortality was not significant, with only the HLPA group showing a significant risk reduction. These findings are consistent with prior studies. Wen et al. analyzed data from 416,175 participants

Cardiovascular mortality					
PA levels	HR (95%CI)				P for interaction
	NOPA	LLPA	MLPA	HLPA	
Gender					0.019
Men	REF	0.48 (0.30, 0.76)	0.50 (0.35, 0.72)	0.39 (0.25, 0.61)	
Women	REF	0.49 (0.30, 0.80)	0.45 (0.29, 0.71)	0.68 (0.42, 1.11)	
Age_group					0.308
20-44	REF	0.40 (0.06, 2.91)	0.95 (0.26, 3.48)	0.05 (0.00, 0.45)	
45-64	REF	0.53 (0.25, 1.12)	0.61 (0.33, 1.12)	0.55 (0.29, 1.03)	
≥65	REF	0.49 (0.33, 0.73)	0.43 (0.31, 0.59)	0.50 (0.34, 0.75)	
Race					0.982
Mexican American	REF	0.35 (0.08, 1.64)	0.80 (0.29, 2.16)	1.19 (0.36, 3.90)	
Other Hispanic	REF	0.33 (0.09, 1.212)	0.64 (0.26, 1.61)	0.20 (0.04, 0.93)	
Non-Hispanic White	REF	0.50 (0.32, 0.80)	0.45 (0.31, 0.64)	0.49 (0.33, 0.75)	
Non-Hispanic Black	REF	0.54 (0.28, 1.07)	0.40 (0.19, 0.82)	0.47 (0.23, 0.98)	
OtherRace-Including Multi-Racial	REF	0.74 (0.14, 3.94)	0.34 (0.06.1.80)	0.13 (0.01, 2.32)	
Education_level					0.711
< High school	REF	0.55 (0.30, 1.01)	0.63 (0.39, 1.00)	0.71 (0.42, 1.20)	
High school graduate	REF	0.56 (0.31, 1.03)	0.44 (0.25, 0.77)	0.52 (0.27, 0.98)	
Some college	REF	0.37 (0.18, 0.77)	0.50 (0.29, 0.86)	0.30 (0.15, 0.63)	
College graduate or above	REF	0.35 (0.12, 0.99)	0.29 (0.12, 0.67)	0.32 (0.12, 0.83)	
Marital_status					0.496
Married	REF	0.30 (0.16, 0.57)	0.52 (0.35, 0.79)	0.42 (0.26, 0.68)	
Widowed	REF	0.58 (0.33, 1.02)	0.36 (0.21, 0.64)	0.83 (0.45, 1.53)	
Divorced	REF	0.39 (0.13, 1.21)	0.69 (0.32, 1.46)	0.30 (0.11, 0.87)	
Separated	REF	0.05 (0.01, 0.26)	0.00 (0.00, 0.00)	0.11 (0.01, 1.27)	
Never married	REF	1.27 (0.43, 3.73)	0.39 (0.12, 1.26)	0.21 (0.05, 0.95)	
Living with partner	REF	0.18 (0.03, 1.21)	1.09 (0.22, 5.53)	0.00 (0.00, 0.00)	
PIR_group					0.938
<1.35	REF	0.59 (0.36, 0.98)	0.38 (0.23, 0.62)	0.50 (0.29, 0.86)	
1.35-3.00	REF	0.35 (0.19, 0.64)	0.50 (0.32, 0.78)	0.44 (0.26, 0.76)	
≥3.00	REF	0.65 (0.3, 1.41)	0.53 (0.30, 0.92)	0.53 (0.27, 1.06)	
BMI_group					0.562
Under 25	REF	0.25 (0.09, 0.71)	0.34 (0.16, 0.73)	0.37 (0.16, 0.87)	
25-30.0	REF	0.83 (0.48, 1.45)	0.68 (0.42, 1.10)	0.50 (0.27, 0.94)	
30.0 and over	REF	0.38 (0.23, 0.62)	0.43 (0.29, 0.64)	0.50 (0.32, 0.78)	
Smoking					0.091
Current smoker	REF	0.42 (0.17, 1.00)	0.54 (0.27, 1.08)	0.46 (0.22, 0.93)	
Ex-smoker	REF	0.28 (0.14, 0.56)	0.47 (0.30, 0.74)	0.32 (0.18, 0.60)	
Continued					

Cardiovascular mortality					
PA levels	HR (95%CI)				P for interaction
	NOPA	LLPA	MLPA	HLPA	
Never smoker	REF	0.74 (0.47, 1.15)	0.45 (0.30, 0.70)	0.66 (0.41, 1.07)	
Drinking					0.940
Drinker	REF	0.46 (0.30, 0.70)	0.47 (0.33, 0.66)	0.51 (0.35, 0.75)	
Non-drinker	REF	0.61 (0.35, 1.07)	0.48 (0.29, 0.78)	0.41 (0.21, 0.78)	
Health_insurance					0.709
Yes	REF	0.48 (0.33, 0.68)	0.44 (0.33, 0.59)	0.50 (0.35, 0.70)	
No	REF	0.78 (0.18, 3.38)	1.71 (0.55, 5.30)	0.32 (0.08, 1.24)	
Energy intake					0.36
Adequate	REF	0.54 (0.29, 1.00)	0.35 (0.21, 0.60)	0.33 (0.17, 0.61)	
High	REF	0.29 (0.07, 1.27)	0.21 (0.05, 0.90)	0.43 (0.12, 1.48)	
Low	REF	0.47 (0.30, 0.73)	0.59 (0.42, 0.83)	0.58 (0.38, 0.88)	

Table 5. Subgroup analysis of the association between physical activity and cancer mortality.

and found that 90 min of moderate-intensity PA per week (equivalent to 6–7.5 MET-hours/week) significantly reduced ACM risk, with further reductions at higher PA levels[58]. Similarly, Garcia et al.'s dose-response meta-analysis reported significant inverse associations between PA and ACM, CVD mortality, cancer mortality, and premature mortality, with the steepest risk reduction at 0–8.75 MET-hours/week and a plateau thereafter[37]. Jeong et al. also identified a significant nonlinear dose-response relationship between leisure-time PA and ACM, noting substantial risk reductions at 0–8 MET-hours/week and diminishing returns beyond 16 MET-hours/week[59]. Additionally, Ekelund et al.'s systematic review and meta-analysis, using accelerometer-based measures, confirmed a nonlinear relationship, emphasizing that low PA levels significantly reduce ACM risk in the general population, with only modest additional benefits at higher levels[60]. These nonlinear dose-response relationships have important clinical implications for MetS management. The pronounced risk reduction at LLPA aligns with the US Physical Activity Guidelines, recommending 150–300 min of moderate-intensity PA per week[61]. However, the plateau at HLPA suggests limited additional benefits beyond a certain threshold, highlighting the need for personalized PA prescriptions to optimize health outcomes without promoting excessive exercise.

Subgroup analysis indicated that the impact of PA on CVD mortality risk among patients with MetS varied by gender. Although both genders experienced similar benefits from LLPA and MLPA, men exhibited greater reductions in CVD mortality risk compared to women in the HLPA group. This observation aligns with Barengo et al., who found that men engaging in high levels of leisure-time PA achieved greater reductions in CVD mortality than women[62]. Similarly, Moholdt et al. demonstrated that long-term, high-intensity PA provided more significant protection against CVD mortality in men[63]. Chen et al. further observed gender differences in PA frequency requirements for MetS risk reduction, noting that women needed more frequent PA (more than four times per week) compared to men (at least twice per week) to achieve similar benefits[64]. These gender differences may be explained by several physiological factors. Men typically have higher basal metabolic rates[65], greater fat oxidation rates, higher total energy expenditure, and increased post-exercise oxygen consumption compared to women[66]. Additionally, premenopausal women have inherently lower CVD incidence compared to men, but their risk significantly increases post-menopause due to declining estrogen levels and rising androgen levels[67,68]. Moreover, evidence suggests that baseline MetS and changes in MetS status during follow-up exert stronger effects on CVD and coronary heart disease risks in women compared to men. Women may thus be more vulnerable to elevated CVD mortality associated with metabolic abnormalities such as hypertension and hyperglycemia[69]. These physiological and metabolic factors potentially diminish the protective effect of HLPA against CVD mortality risk in women. Consequently, these findings highlight the necessity of incorporating gender-specific considerations into PA intervention designs for MetS patients to optimize cardiovascular health outcomes.

This study evaluated insulin resistance in patients with MetS using HOMA-IR, revealing a significant independent inverse association between PA and HOMA-IR. Consistent with previous research, these findings underscore the pivotal role of PA in enhancing insulin sensitivity[22,23]. This may be ascribed to the subsequent mechanisms. First, PA can enhance the translocation and expression of GLUT4, facilitating glucose uptake by skeletal muscles and reducing blood glucose levels[70]. Moreover, PA promotes fatty acid oxidation, mitigates the accumulation of lipid metabolites, and optimizes the cellular metabolic environment, thereby enhancing insulin action[71]. PA also reduces hepatic fat content and improves liver insulin sensitivity[72]. Additionally, PA activates the AMP-activated protein kinase (AMPK) signaling pathway, which modulates energy metabolism and promotes glucose uptake by skeletal muscles, thereby improving insulin sensitivity[73].

Cancer mortality					
PA levels	HR(95%CI)				P for interaction
	NOPA	LLPA	MLPA	HLPA	
Gender					0.158
Men	REF	0.85 (0.51, 1.43)	0.94 (0.62, 1.41)	0.54 (0.33, 0.88)	
Women	REF	0.59 (0.33, 1.05)	0.7 (0.44, 1.1)	0.41 (0.19, 0.85)	
Age_group					0.547
20–44	REF	0.03 (0.00.Inf)	12.32 (0.22, Inf)	0.00 (0.00, Inf)	
45–64	REF	0.73 (0.35, 1.52)	0.88 (0.51, 1.55)	0.54 (0.28, 1.05)	
≥ 65	REF	0.74 (0.47, 1.15)	0.82 (0.57, 1.18)	0.50 (0.30, 0.83)	
Race					0.456
Mexican American	REF	0.22 (0.02, 1.95)	0.72 (0.24, 2.13)	0.42 (0.11, 1.66)	
Other Hispanic	REF	1.74 (0.38, 7.84)	2.05 (0.7, 6.03)	1.26 (0.34, 4.63)	
Non-Hispanic White	REF	0.85 (0.53, 1.37)	0.82 (0.56, 1.2)	0.52 (0.32, 0.87)	
Non-Hispanic Black	REF	0.51 (0.20, 1.29)	0.64 (0.3, 1.33)	0.20 (0.06, 0.69)	
OtherRace-Including Multi-Racial	REF	Inf (0.26, Inf)	0.43 (0.08, 2.37)	0.34 (0.01, 16.87)	
Education_level					0.513
< High school	REF	1.14 (0.61, 2.13)	0.68 (0.37, 1.26)	0.61 (0.29, 1.28)	
High school graduate	REF	0.63 (0.29, 1.34)	0.78 (0.45, 1.35)	0.40 (0.18, 0.89)	
Some college	REF	0.54 (0.23, 1.25)	1.06 (0.61, 1.86)	0.53 (0.25, 1.13)	
College graduate or above	REF	0.88 (0.32, 2.42)	0.68 (0.3, 1.54)	0.40 (0.13, 1.22)	
Marital_status					0.063
Married	REF	0.70 (0.40, 1.23)	1.07 (0.71, 1.61)	0.66 (0.40, 1.11)	
Widowed	REF	0.58 (0.25, 1.35)	0.72 (0.38, 1.38)	0.33 (0.10, 1.13)	
Divorced	REF	0.74 (0.27, 1.97)	0.73 (0.32, 1.67)	0.31 (0.09, 1.01)	
Separated	REF	6.93 (0.00, Inf)	0.00 (0.00, Inf)	0.00 (0.00, Inf)	
Never married	REF	2.86 (0.53, 15.46)	0.45 (0.10, 2.04)	0.65 (0.11, 3.8)	
Living with partner	REF	0.00 (0.00, Inf)	0.37(0.07, 2.07)	3.12(0.52, 18.81)	
PIR_group					0.214
<1.35	REF	0.92 (0.55, 1.56)	0.45 (0.26, 0.80)	0.36 (0.17, 0.74)	
1.35–3.00	REF	0.54 (0.25, 1.18)	1.35 (0.83, 2.2)	0.87 (00.47, 1.61)	
≥ 3.00	REF	0.72 (0.31, 1.67)	0.95 (0.53, 1.69)	0.30 (0.12, 0.75)	
BMI_group					0.97
Under 25	REF	0.20 (0.04, 1.01)	0.64 (0.27, 1.5)	0.25 (0.08, 0.74)	
25–30.0	REF	1.10 (0.60, 2.00)	0.91 (0.55, 1.51)	0.48 (0.23, 1.00)	
30.0 and over	REF	0.66 (0.38, 1.13)	0.83 (0.54, 1.27)	0.57 (0.33, 0.98)	
Smoking					0.963
Current smoker	REF	0.56 (0.24, 1.28)	0.69 (0.36, 1.34)	0.45 (0.20, 1.00)	
Ex-smoker	REF	0.86 (0.48.1.54)	0.94 (0.59, 1.49)	0.43 (0.23, 0.80)	
Continued					

Cancer mortality					
PA levels	HR(95%CI)				P for interaction
	NOPA	LLPA	MLPA	HLPA	
Never smoker	REF	0.69 (0.35, 1.37)	0.81 (0.49, 1.35)	0.61 (0.30, 1.25)	
Drinking					0.695
Drinker	REF	0.77 (0.50, 1.18)	0.9 (0.64, 1.27)	0.49 (0.31, 0.78)	
Non-drinker	REF	0.60 (0.26, 1.36)	0.61 (0.32, 1.16)	0.55 (0.24, 1.29)	
Health_insurance					0.008
Yes	REF	0.72 (0.49, 1.06)	0.85 (0.63, 1.16)	0.42 (0.27, 0.66)	
No	REF	0.47 (0.07, 3.06)	0.58 (0.13, 2.56)	1.71 (0.57, 5.07)	
Energy intake					0.6
Adequate	REF	0.47 (0.22, 1.01)	0.86 (0.53, 1.38)	0.45 (0.24, 0.86)	
High	REF	0.27 (0.05, 1.56)	0.46 (0.16, 1.29)	0.15 (0.03, 0.73)	
Low	REF	0.95 (0.60, 1.51)	0.87 (0.58, 1.31)	0.64 (0.37, 1.11)	

Table 6. Subgroup analysis of the association between physical activity and premature mortality.

Previous studies have demonstrated that increased insulin resistance is associated with higher risks of ACM, CVD mortality, and cancer mortality in adults[25,26].This is consistent with our findings indicating that HOMA-IR is positively associated with ACM, cause-specific mortality, and premature mortality in MetS patients. Given that insulin resistance is a core component of MetS, understanding its mediating role in mortality risks is crucial. Insulin resistance improves mortality risks through multiple interconnected mechanisms. As a systemic disorder, it affects various organs and physiological systems, including skeletal muscles, kidneys, the cardiovascular system, liver, and immune response[74]. This broad impact contributes to premature aging and numerous health complications, thereby increasing risks of ACM and premature mortality. In the context of CVD, insulin resistance serves as a key mediator. It is closely associated with the development of atherogenic dyslipidemia, characterized by elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and increased small, dense low-density lipoprotein (LDL) particles[75]. These lipid abnormalities significantly contribute to atherosclerosis and cardiovascular disease. Additionally, insulin resistance impairs endothelial function by reducing nitric oxide production, leading to vascular inflammation and accelerated atherosclerotic plaque formation[76,77]. Collectively, these metabolic and vascular disturbances increase CVD risk in insulin-resistant individuals. Regarding cancer mortality, insulin resistance also emerges as an important mediator. Hyperinsulinemia, a hallmark of insulin resistance, stimulates cancer cell growth and survival. Insulin and insulin-like growth factor 1 (IGF-1) share common signaling pathways, notably the PI3K-Akt-mTOR pathway, which is dysregulated in various cancers and promotes cell proliferation, survival, and migration[78–80]. Furthermore, insulin resistance is associated with chronic inflammation and oxidative stress, both of which contribute to a pro-tumorigenic microenvironment[81,82]. Therefore, in MetS patients—characterized inherently by insulin resistance—this condition critically mediates the relationship between metabolic dysfunction and elevated CVD and cancer mortality risks. Targeting insulin resistance through lifestyle modifications and pharmacological interventions is thus essential for reducing these mortality risks.

Building upon the aforementioned results, we conducted further analyses to explore the mediating role of HOMA-IR in the relationships between PA and ACM, cause-specific mortality, and premature mortality among patients with MetS. Notably, HOMA-IR significantly mediated the inverse associations of PA with ACM, CVD mortality, and cancer mortality, accounting for 22.1%, 16.7%, and 15.7% of the associations, respectively. These findings indicate that HOMA-IR is a critical mechanism through which PA influences mortality outcomes in this population.

Based on these findings, we recommend PA as a pivotal intervention to reduce various mortality risks among MetS patients. Existing evidence demonstrates that even LLPA significantly lowers the risks of ACM, CVD mortality, and premature mortality, while MLPA and HLPA provide further protective benefits. It is noteworthy that a significant reduction in cancer mortality was observed exclusively in the HLPA group. From a public health perspective, sedentary individuals with MetS should be prioritized and encouraged to progressively increase their PA levels by setting achievable goals. For instance, engaging in just 10 min of moderate-intensity activity daily (e.g., brisk walking) is a practical and effective starting point. This recommendation is supported by our findings, as 10 min of moderate-intensity PA per day (approximately 3.5 METs) translates to roughly 4.08 MET-hours per week, falling within the LLPA range and associated with significant mortality risk reductions. This aligns with the current U.S. Physical Activity Guidelines, which recommend 150–300 min of moderate-intensity or 75–150 min of vigorous-intensity aerobic activity weekly, emphasizing that "some PA is better than none"[61]. For MetS patients diagnosed with cancer, HLPA should be conducted under professional supervision to ensure

Premature mortality					
PA levels	HR (95%CI)				P for interaction
	NOPA	LLPA	MLPA	HLPA	
Gender					0.127
Men	REF	0.59 (0.36, 0.98)	0.82 (0.55, 1.21)	0.41 (0.27, 0.63)	
Women	REF	0.84 (0.53, 1.33)	0.60 (0.39, 0.92)	0.64 (0.39, 1.04)	
Age_group	REF				0.564
20–44	REF	0.67 (0.20, 2.26)	1.01 (0.40, 2.57)	0.45 (0.18, 1.16)	
45–64	REF	0.71 (0.49, 1.03)	0.68 (0.49, 0.94)	0.45 (0.31, 0.65)	
≥ 65	REF	0.58 (0.17, 2.02)	0.86 (0.34, 2.17)	0.54 (0.18, 1.63)	
Race	REF				0.722
Mexican American	REF	0.78 (0.27, 2.23)	1.40 (0.62, 3.15)	0.40 (0.14, 1.20)	
Other Hispanic	REF	0.25 (0.06, 1.11)	0.35 (0.10, 1.32)	0.37 (0.10, 1.31)	
Non-Hispanic White	REF	0.66 (0.39, 1.12)	0.67 (0.44, 1.03)	0.47 (0.30, 0.75)	
Non-Hispanic Black	REF	0.78 (0.45, 1.37)	0.59 (0.33, 1.04)	0.49 (0.26, 0.91)	
OtherRace-Including Multi-Racial	REF	0.00 (0.00, Inf)	1.20 (0.20, 7.12)	0.00 (0.00, 0.01)	
Education_level	REF				0.662
< High school	REF	0.95 (0.54, 1.68)	0.81 (0.49, 1.34)	0.49 (0.28, 0.89)	
High school graduate	REF	0.47 (0.22, 1.02)	0.65 (0.36, 1.18)	0.50 (0.27.0.90)	
Some college	REF	0.74 (0.40, 1.36)	0.65 (0.39, 1.08)	0.45 (0.25, 0.81)	
College graduate or above	REF	0.64 (0.24, 1.74)	0.76 (0.28, 2.03)	0.24 (0.07, 0.88)	
Marital_status	REF				0.014
Married	REF	0.53 (0.30, 0.96)	0.92 (0.61, 1.39)	0.47 (0.29, 0.78)	
Widowed	REF	1.52 (0.45, 5.11)	1.35 (0.36, 2.09)	4.70 (1.34, 16.55)	
Divorced	REF	0.50 (0.23, 1.08)	0.61 (0.33, 1.15)	0.28 (0.13, 0.61)	
Separated	REF	0.62 (0.13, 2.91)	0.04 (0.00, 0.70)	0.08 (0.01, 1.04)	
Never married	REF	1.18 (0.48, 2.91)	0.55 (0.22, 1.33)	0.37 (0.14, 0.98)	
Living with partner	REF	1.52 (0.13, 17.67)	1.34 (0.23, 7.70)	2.47 (0.45, 13.57)	
PIR_group	REF				0.378
<1.35	REF	0.68 (0.43, 1.09)	0.74 (0.50, 1.09)	0.41 (0.26, 0.66)	
1.35–3.00	REF	0.97 (0.55, 1.73)	0.68 (0.39, 1.21)	0.63 (0.36, 1.11)	
≥ 3.00	REF	0.51 (0.18, 1.44)	0.69 (0.36, 1.33)	0.45 (0.21, 0.97)	
BMI_group	REF				0.569
Under 25	REF	0.22 (0.06, 0.83)	1.04 (0.40, 2.73)	0.62 (0.25, 1.53)	
25–30.0	REF	0.84 (0.41, 1.73)	0.94 (0.52, 1.68)	0.56 (0.28, 1.12)	
30.0 and over	REF	0.71 (0.47, 1.07)	0.61 (0.42, 0.88)	0.41 (0.27, 0.62)	
Smoking	REF				0.740
Current smoker	REF	0.69 (0.39, 1.23)	0.83 (0.53, 1.30)	0.46 (0.28, 0.75)	
Ex-smoker	REF	0.53 (0.27, 1.06)	0.71 (0.42, 1.21)	0.51 (0.28, 0.94)	
Continued					

Premature mortality					
PA levels	HR (95%CI)				P for interaction
	NOPA	LLPA	MLPA	HLPA	
Never smoker	REF	0.87 (0.49, 1.52)	0.59 (0.34, 1.02)	0.48 (0.25, 0.90)	
Drinking	REF				0.092
Drinker	REF	0.78 (0.53, 1.15)	0.74 (0.53, 1.02)	0.48 (0.33, 0.70)	
Non-drinker	REF	0.51 (0.24, 1.07)	0.61 (0.33, 1.13)	0.50 (0.26, 0.96)	
Health_insurance	REF				0.194
Yes	REF	0.7 (0.48, 1.02)	0.67 (0.49.0.93)	0.42 (0.29, 0.62)	
No	REF	0.66 (0.29, 1.50)	0.74 (0.38, 1.45)	0.61 (0.32, 1.15)	
Energy intake	REF				0.908
Adequate	REF	0.41 (0.21, 0.83)	0.73 (0.47, 1.14)	0.45 (0.27, 0.74)	
High	REF	0.45 (0.18, 1.10)	0.66 (0.30, 1.48)	0.40 (0.18, 0.91)	
Low	REF	0.99 (0.63, 1.55)	0.71 (0.46, 1.11)	0.49 (0.29, 0.82)	

Table 7. Survey-weighted association between weighted physical activity and the homeostasis model of insulin resistance (HOMA-IR), as well as the association of HOMA-IR with all-cause mortality, cardiovascular disease (CVD) mortality, cancer mortality, and premature mortality.

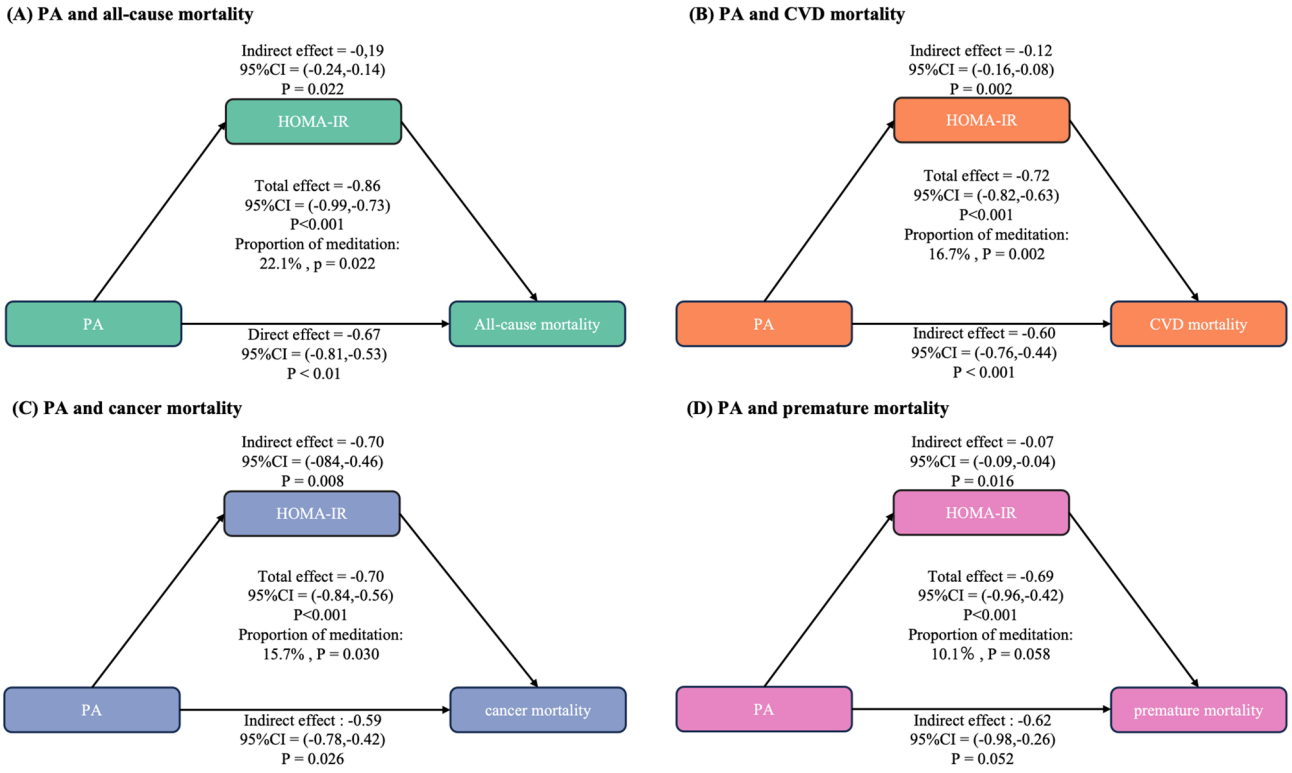

Fig. 4. HOMA-IR mediates the relationship between physical activity and various mortality. (A) PA and all-cause mortality; (B) PA and cardiovascular disease mortality; (C) PA and cancer mortality; (D) PA and premature mortality.

safety and maximize health benefits, particularly when potential complications exist. Future research should further examine the specific impacts of varying PA types, intensities, and frequencies on different mortality risks among MetS patients, with the aim of refining personalized exercise prescriptions and better informing clinical practice and public health policy.

In addition, future research should focus on several critical areas. First, further investigation into how specific PA types, intensities, and frequencies influence different mortality risks among MetS patients is essential for optimizing personalized exercise interventions and informing public health policy. Second, prospective studies incorporating repeated PA assessments are needed to capture dynamic changes in activity levels and to provide a more comprehensive understanding of their long-term health impacts. Third, detailed exploration of the biological mechanisms linking various forms and intensities of PA to improved insulin sensitivity is vital for strengthening causal inference and guiding targeted interventions. Fourth, multinational cohort studies are recommended to enhance the external generalizability of research findings. Lastly, future research should address gender-specific and socioeconomic disparities in PA participation and associated health outcomes, thereby supporting equitable and personalized public health strategies.

Strengths and limitations

Strengths

This study has several notable strengths. First, it utilized the NHANES database, which employs a nationally representative, stratified sampling design, ensuring both extensive sample size and broad generalizability. Second, the prospective study design, rigorous methodology, and extended follow-up period facilitated an in-depth investigation of the relationship between PA and mortality risks in patients with MetS. Third, PA was quantified not only categorically into four distinct levels (NOPA, LLPA, MLPA, and HLPA), but also analyzed continuously, enabling the assessment of nonlinear dose-response relationships between PA and various mortality risks. Fourth, multiple statistical approaches were used to confirm the consistency of the findings, thereby enhancing the reliability of the conclusions. Fifth, mediation analysis demonstrated the role of HOMA-IR in the relationship between PA and mortality risks among MetS patients, further clarifying the underlying mechanisms through which PA exerts its beneficial effects. Sixth, the study further classified PA into recreational, work-related, and transport-related domains for sensitivity analyses. The consistent direction of associations across PA domains with the main analysis findings further confirmed the robustness of the results.

Limitations

Several limitations should also be acknowledged. First, PA and covariates were self-reported, which could introduce recall bias and measurement inaccuracies. Additionally, self-reported socioeconomic and marital statuses may similarly be susceptible to recall bias or misclassification, potentially affecting the observed associations. Second, PA was assessed only at baseline, restricting the ability to capture changes in activity patterns over the average 6.3-year follow-up period, which may influence the strength or direction of associations with mortality outcomes. Third, both PA and HOMA-IR measurements were conducted simultaneously at baseline, limiting our ability to establish a clear temporal sequence required for causal mediation analysis, raising concerns of potential reverse causality or simultaneity bias. Fourth, since the sample is based on a U.S. population, the external validity of the findings may be limited when generalizing to other countries or cultural contexts. Lastly, this study was unable to distinguish specific types of PA, such as aerobic and resistance training, which may have different physiological mechanisms and effects in improving insulin sensitivity and reducing mortality risk. This limitation restricts our ability to further understand how different forms of exercise specifically influence mortality risk among individuals with MetS.

Conclusion

In conclusion, this nationally representative cohort study demonstrates that PA is significantly associated with reduced risks of ACM, CVD mortality, and premature mortality in MetS patients, with even LLPA conferring significant protective effects. However, a significant reduction in cancer mortality was observed exclusively among participants engaging in HLPA. Moreover, insulin resistance was identified as a key mediator, highlighting its importance as a potential therapeutic target in lifestyle interventions. Consequently, our findings strongly support the implementation of achievable and sustainable PA strategies in clinical and public health settings to improve survival outcomes in this high-risk population. Healthcare providers should prioritize encouraging sedentary MetS patients to initiate moderate-intensity activities, such as 10 min of daily brisk walking, and progressively increase their activity levels to further reduce mortality risks.

Data availability

The original findings of this study are provided within the article and its Supplementary Material. Additional questions can be addressed to the corresponding author. All data supporting this research are publicly accessible on the NHANES website (https://www.cdc.gov/nchs/nhanes/). This survey was approved by the National Center for Health Statistics Research Ethics Review Board. Informed consent was obtained from all participants.

Received: 26 March 2025; Accepted: 16 May 2025
Published online: 29 May 2025

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Author contributions

Kedi Gao conceived the initial idea, study's design, and was responsible for data analysis, data statistics and manuscript drafting of the study. Youliang Lin contributed to methodology, supervision, and writing – review & editing.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Competing interests

The authors declare no competing interests.

Ethics statement

This study involving human participants was approved by the Research Ethics Review Board of the National Center for Health Statistics (Protocol #2005-06, #2011-17, and #2018-01), and was conducted in compliance with local legislation and institutional requirements. Informed consent was obtained from all participants prior to their inclusion in the study.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-02921-z.

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