Original Article

JER

https://doi.org/10.12965/jer.2550080.040

Journal of Exercise Rehabilitation 2025;21(2):102-111

Physical activity, sedentary behavior, and metabolic syndrome in adults with arthritis: cross-sectional and Mendelian randomization analysis

Dehua Gong[1,2], Seung-Soo Baek[1,2,*]

[1]Major in Sport & Health Care, College of Culture and Arts, Sangmyung University, Seoul, Korea
[2]Exercise Rehabilitation Research Institute, Sangmyung University, Seoul, Korea

This study examined the relationship between moderate-to-vigorous physical activity (MVPA), sedentary behavior (SB), and metabolic syndrome, employing both cross-sectional and Mendelian randomization methods to enhance causal inference. The cross-sectional analysis included adults aged 20 years and older with arthritis (n=4,227) from the National Health and Nutrition Examination Survey and assessed the associations between MVPA, SB, and metabolic syndrome. Mendelian randomization analysis used genome-wide association studies to validate causal relationships, employing instrumental variables selected from single nucleotide polymorphisms linked to accelerometer-based physical activity (fraction of time with accelerations >425 milli-gravities) and SB. The primary Mendelian randomization methods included inverse variance weighting and Bayesian Weighted Mendelian Randomization. Sensitivity analyses, including Mendelian Randomization-Egger intercept test, the weighted median method, and Mendelian Randomization Pleiotropy RESidual Sum and Outlier, were conducted to ensure result robustness. Cross-sectional analysis revealed a significant association between higher levels of MVPA and reduced SB with a lower prevalence of metabolic syndrome. Participants in the high MVPA/low SB group demonstrated lower odds of metabolic syndrome (odds ratio [OR], 0.40; 95% confidence interval [CI], 0.29–0.56), hypertension (OR, 0.55; 95% CI, 0.40–0.75), fasting glucose (OR, 0.52; 95% CI, 0.35–0.77), and waist circumference (OR, 0.34; 95% CI, 0.22–0.54). Mendelian randomization analysis confirmed a causal relationship, showing that physical activity decreases risk factors for metabolic syndrome, while SB exacerbates them. This study emphasizes the critical roles of regular physical activity and reduced SB in mitigating the risk of metabolic syndrome, especially among older adults with arthritis.

Keywords: Metabolic syndrome, Sedentary behavior, Arthritis, Physical activity, Mendelian randomization

INTRODUCTION

The global prevalence of metabolic syndrome has significantly increased in recent years (Shin et al., 2013). Metabolic syndrome is characterized by central obesity and insulin resistance, both of which have a bidirectional association with chronic inflammation (Ju et al., 2017). In the general adult population, metabolic syndrome prevalence ranges from 20% to 34%, whereas in individuals aged 65 years and older, it can reach up to 50% (Li et al., 2023; Shin et al., 2013). Notably, metabolic syndrome prevalence is even higher among individuals with arthritis. In osteoarthritis patients, metabolic syndrome prevalence reaches 59%, approximately 5.26 times that of the general population (Puenpatom and Victor, 2009).

Arthritis is a chronic condition characterized by inflammation and pain in the joints. Individuals with arthritis typically exhibit increased sedentary behavior (SB) due to joint pain and inflammation (Dominick et al., 2004; Duca et al., 2022). This behavior significantly elevates their risk of developing metabolic syndrome (Saunders et al., 2013). Recent studies indicate that approximately 40% of arthritis patients do not meet recommended exercise guidelines. Furthermore, about 30% are completely inactive (Huckleby et al., 2021). SB substantially increases metabolic syndrome risk

*Corresponding author: Seung-Soo Baek https://orcid.org/0000-0002-1340-2098
Major in Sport & Health Care, College of Culture and Arts, Sangmyung University, 20 Hongjimun 2-gil, Jongro-gu, Seoul 03016, Korea
Email: ssoop@smu.ac.kr
Received: February 2, 2025 / Revised: March 17, 2025 / Accepted: March 23, 2025

by elevating blood pressure, waist circumference, triglyceride levels, and reducing insulin sensitivity (Saunders et al., 2013). Additionally, SB promotes abdominal fat accumulation, a core feature of metabolic syndrome (Saunders et al., 2013). Arthritis, characterized by joint inflammation and pain, becomes increasingly prevalent with age. Its pathological features are closely associated with decreased physical activity and increased SB. Older adults with arthritis often experience reduced mobility, leading to higher SB, which significantly increases their risk of developing metabolic syndrome (Dunlop et al., 2011). With advancing age, arthritis patients face even greater risks of metabolic syndrome, highlighting the urgent need for targeted interventions.

In response, the U.S. Department of Health and Human Services recommends that middle-aged and older adults with arthritis engage in regular physical activity (Dunlop et al., 2011). Increasing physical activity and reducing SB are effective strategies to reduce the risk of metabolic syndrome (Greer et al., 2015; Healy et al., 2008). Substituting sedentary time with moderate-to-vigorous physical activity (MVPA) significantly improves cardiovascular metabolic markers such as triglyceride levels, body mass index (BMI), and high-density lipoprotein cholesterol (HDL-C) (Hamer et al., 2014). For instance, resistance training lowers cardiovascular risk and improves quality of life in patients with rheumatoid arthritis (Baillet et al., 2012). A cross-sectional study using objective physical activity measurements reported that increased daily physical activity is linked to a lower prevalence of metabolic syndrome among osteoarthritis patients (Liu et al., 2015).

Although numerous studies have examined the relationship between metabolic syndrome, physical activity, and SB, most are observational, making it difficult to rule out reverse causation. For example, severe arthritis or long-term complications of metabolic syndrome, such as joint stress caused by obesity, may limit mobility. This limitation can inflate observed associations between arthritis and SB. To address this limitation, we incorporated a two-sample Mendelian randomization approach in addition to cross-sectional analysis to strengthen causal inference (Burgess et al., 2015; Hemani et al., 2017). This study used a cross-sectional design to investigate the associations of MVPA and SB with metabolic syndrome and its core components (blood pressure, triglycerides, HDL-C, blood glucose, and waist circumference) among arthritis patients. A stratified analysis was conducted to further explore whether these associations vary across different age groups. Additionally, genome-wide association study (GWAS) data were used to perform a two-sample Mendelian randomization analysis. Genetic instrumental variables were applied to infer causal relationships of physical activity and SB with metabolic syndrome core components.

MATERIALS AND METHODS

Study design

This study utilized cross-sectional analysis and Mendelian randomization to examine the association between physical activity, SB, and metabolic syndrome. The cross-sectional analysis was based on National Health and Nutrition examination survey (NHANES) 2015–2020 data, while Mendelian randomization utilized GWAS with accelerometer-measured physical activity and SB to strengthen causal inference. This study adopted a two-sample Mendelian randomization, strictly follows three basic assumptions when selecting instrumental variables, include: (a) Strong correlation between instrumental variables and the exposure under investigation; (b) Independence of instrumental variables from any known or unknown confounding factors; (c) Sole influence of instrumental variables on outcomes through risk factors without involvement in any other direct causal pathway. Both NHANES and GWAS datasets received ethical approval, and informed consent was obtained from all participants.

Participants

This study analyzed data from NHANES (2015–2020), which included 4,232 adults aged 20 years and older diagnosed with arthritis. While the primary analysis covered the entire population, age-stratified analyses were prespecified to account for known pathophysiological differences in metabolic regulation across the lifespan and to explore potential age-related effects. The final sample included 4,227 participants after excluding individuals with invalid physical activity or SB data and those without an arthritis diagnosis. Arthritis diagnoses were self-reported and confirmed by asking participants, "Has a doctor or other health professional ever diagnosed you with arthritis?" Participants who responded "Yes" were subsequently asked, "What type of arthritis do you have?" Response options included osteoarthritis/degenerative arthritis, rheumatoid arthritis, psoriatic arthritis, other unspecified types, unknown types, and "Prefer not to answer. The NHANES survey comprised three main components: an in-home interview conducted by trained interviewers, a physical examination at a mobile examination center, and laboratory testing.

Metabolic syndrome

Metabolic syndrome was diagnosed based on the criteria defined

by the National Cholesterol Education Program Adult Treatment Panel III. Participants were classified as having metabolic syndrome if they fulfilled at least three of the five defined criteria (Liu et al., 2015).

Physical activity and sedentary time

MVPA was assessed using the Global Physical Activity Questionnaire, which evaluates both work and leisure activities. According to World Health Organization (WHO) standards, participants were categorized as high MVPA (≥30 minutes of moderate activity on 5 or more days per week, ≥20 minutes of vigorous activity on 3 or more days per week, or achieving ≥600 MET-min/wk) or low MVPA (Bull et al., 2020). SB was categorized based on participants' self-reported daily sedentary time. Considering the characteristics of arthritis patients, the median sedentary time was defined as 5 hours per day. Participants were grouped into high SB (>5 hr/day) and low SB (≤5 hr/day) categories accordingly. Participants were further divided into four groups based on the combination of physical activity and SB: low MVPA/high SB, high MVPA/high SB, low MVPA/low SB, and high MVPA/low SB (Choi et al., 2021).

Covariates

Covariates included age, gender, race, marital status, education level, and BMI. BMI was categorized based on WHO standards as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) (Weir and Jan, 2025).

Selection of instrumental variables

Instrumental variables were identified from single nucleotide polymorphisms (SNPs) significantly associated with physical activity and SB, applying a unified significance threshold ($P < 1 \times 10^{-5}$) (1000 Genomes Project Consortium et al., 2010). SNPs were pruned to reduce linkage disequilibrium, and the Steiger test was used to confirm the causal direction (Hemani et al., 2017). Only SNPs with F-statistics>10 were retained, calculated as $F = R^2 (n-k-1)/k(1-R^2)$, to ensure instrumental variable strength (Burgess et al., 2011). A weighting analysis was conducted to account for instrumental variable strength and maintain statistical power.

Data sources

GWAS summary statistics were obtained from the National Human Genome Research Institute-European Bioinformatics Institute genome-wide association studies Catalog (Buniello et al., 2019). The dataset included accelerometer-measured physical activity from 90,667 individuals of European ancestry (GCST006079); SB data from 526,725 individuals of European ancestry (GCST90104339); HDL-C data from 1,320,016 individuals of European ancestry (GCST90239652); waist circumference data from 407,661 individuals of British ancestry (GCST90014020); and triglyceride data from the Within-Family GWAS Consortium, including 78,700 individuals of European ancestry (ieu-b-4850). Hypertension data were obtained from the FinnGen Consortium R11, comprising 137,312 cases and 316,345 controls. Blood glucose data were obtained from the FinnGen Consortium R7, comprising 1,641 cases and 297,969 controls (FinnGen Consortium, 2023).

Two-sample Mendelian randomization

This study utilized a two-sample Mendelian randomization approach to investigate the causal relationship between MVPA and the components of metabolic syndrome. The primary methods included the inverse variance weighted (IVW) approach and Bayesian Weighted Mendelian Randomization. IVW estimates the overall effect by weighting and aggregating each SNP's effect on exposure and outcome. In contrast, the Bayesian method provides more robust and flexible estimates by incorporating prior knowledge and accounting for data uncertainty (Burgess et al., 2011; Burgess et al., 2013; Zhao et al., 2020).

Sensitivity analysis

To ensure the robustness of the results, multiple sensitivity analyses were conducted. The Mendelian Randomization-Egger intercept test was used to correct for horizontal pleiotropy, while the weighted median method was applied in cases with a higher proportion of invalid SNPs (Bowden et al., 2015; Bowden et al., 2016). The Robust Adjusted Profile Score was employed to enhance robustness in the presence of weak instrumental variables and pleiotropy (Yu et al., 2023). Leave-one-out analysis was performed to evaluate the influence of each SNP on the results (Mainali et al., 2024). Mendelian Randomization Pleiotropy RESidual Sum and Outlier and Radial Mendelian Randomization were used to detect and correct pleiotropy, while Cochran's Q statistic was applied to evaluate heterogeneity in SNP effects (Bowden et al., 2018; Burgess et al., 2015; Verbanck et al., 2018).

Statistical analysis

NHANES data were weighted to ensure the representativeness of the population (Liu et al., 2015). Descriptive statistics and chi-

 https://doi.org/10.12965/jer.2550080.040

square tests were performed to compare the metabolic syndrome and nonmetabolic syndrome groups. Binary logistic regression was applied to adjust for covariates, and the results were stratified by age group. Mendelian randomization analyses were conducted in R 4.4.1 using the TwoSampleMR, MendelianRandomization, and RadialMR packages. The analyses included IVW, Mendelian Randomization-Egger intercept test, and Radial Mendelian randomization methods for robustness checks. Statistical significance was defined as $P < 0.05$.

RESULTS

Characteristics of participants with arthritis

This study included 4,227 participants, with 74.61% diagnosed with metabolic syndrome and 25.39% without a diagnosis of metabolic syndrome (Table 1).

Association between moderate-to-vigorous physical activity, SB, and prevalence of metabolic syndrome in adults with arthritis

Table 2 presents the associations between MVPA, SB, and metabolic syndrome components in arthritis patients. Table 2 presents the associations between MVPA, SB, and individual components of metabolic syndrome in arthritis patients. Adjusted analyses (Model 2) showed that the high MVPA/low SB group had significantly lower risks of metabolic syndrome (OR, 0.40; 95% CI, 0.29–0.56; $P < 0.001$), hypertension (OR, 0.55; 95% CI, 0.40–0.75; $P < 0.001$), and elevated fasting glucose (OR, 0.52; 95% CI, 0.35–0.77; $P < 0.001$). For waist circumference, significant reductions in risk were observed in both the high MVPA/low SB group (OR, 0.34; 95% CI; 0.22–0.54, $P < 0.001$) and the high MVPA/high SB group (OR, 0.34; 95% CI, 0.19–0.60; $P < 0.001$).

In contrast, the low MVPA/low SB group showed no significant associations with blood pressure or triglyceride levels. Notably, no statistically significant associations were found between MVPA/SB groups and HDL-C levels in any model. However, triglyceride levels showed borderline significance in the high MVPA/high SB group (OR, 0.71; 95% CI, 0.54–0.92; $P < 0.05$).

Stratified associations between moderate-to vigorous physical activity, SB, and metabolic syndrome in different age groups

Stratified analysis revealed notable differences in the effects of MVPA and SB on metabolic syndrome risk across age groups (Fig. 1). Among participants aged 60 years and older, the high MVPA/low SB group showed the largest reduction in metabolic syndrome risk (OR, 0.38; 95% CI, 0.24–0.59; $P < 0.001$), followed by the high MVPA/ high SB group (OR, 0.51; 95% CI, 0.34–0.77; $P < 0.005$). In the 40–59 age group, both the high MVPA/high SB group (OR, 0.38; 95% CI, 0.22–0.67; $P < 0.001$) and the low MVPA/low SB group (OR, 0.48; 95% CI, 0.24–0.96; $P < 0.05$) showed a significant reduction in metabolic syndrome risk.

Table 1. Characteristics of arthritis patients (n = 4,227)

Variable	Nonmetabolic syndrome (25.39%)	Metabolic syndrome (74.61%)	*P*-value
Age (yr)			0.000
20–39	38.73%	61.27%	
40–59	28.34%	71.66%	
≥ 60	21.49%	78.51%	
Gender			0.441
Male	26.41%	73.59%	
Female	24.72%	75.28%	
Race/Hispanic			0.171
Mexican American	22.54%	77.46%	
Other Hispanic	28.33%	71.67%	
Non-Hispanic White	25.71%	74.29%	
Non-Hispanic Black	22.59%	77.41%	
Non-Hispanic Asian	33.84%	66.16%	
Other race-including multiracial	21.64%	78.36%	
Marital status			0.377
Married/living with partner	24.76%	75.24%	
Other	26.76%	73.24%	
Education level			0.001
Without university education	21.01%	78.99%	
With university education	28.23%	71.77%	
BMI			0.000
Underweight	59.35%	40.65%	
Normal weight	60.54%	39.46%	
Overweight	30.47%	69.53%	
Obese	9.96%	90.04%	
MVPA			0.000
Low MVPA	15.68%	84.32%	
High MVPA	29.91%	70.09%	
SB			0.000
Low SB (< 5 hr)	32.23%	67.77%	
High SB (≥ 5 hr)	21.74%	78.26%	

All analyses were conducted using weighted data to account for the complex survey design. Data are expressed as number (%) with rows summing to 100%. Chi-squared tests were used for categorical comparisons.
BMI, body mass index; MVPA, moderate-to-vigorous physical activity; SB, sedentary behavior.

Table 2. Association between moderate-to-vigorous physical activity, sedentary behavior, and prevalence of metabolic syndrome in adults with arthritis (n = 4,227)

Variable	Low MVPA/high SB	High MVPA/high SB	*P*-value	Low MVPA/low SB	*P*-value	High MVPA/low SB	*P*-value
Metabolic syndrome							
Model 1	Refence	0.42 (0.31–0.57)	0.000	0.50 (0.34-0.75)	0.001	0.29 (0.21-0.40)	0.000
Model 2	Refence	0.47 (0.34-0.64)	0.000	0.57 (0.38-0.87)	0.009	0.40 (0.29-0.56)	0.000
Blood pressure							
Model 1	Refence	0.51 (0.39-0.68)	0.000	0.81 (0.54-1.21)	0.306	0.40 (0.30-0.54)	0.000
Model 2	Refence	0.64 (0.47-0.86)	0.003	0.76 (0.50-1.15)	0.190	0.55 (0.40-0.75)	0.000
HDL-C							
Model 1	Refence	0.82 (0.63-1.06)	0.135	1.08 (0.76-1.55)	0.667	0.75 (0.57-0.99)	0.043
Model 2	Refence	1.18 (0.80-1.75)	0.127	1.18 (0.80-1.75)	0.395	0.83 (0.61-1.11)	0.210
Triglycerides							
Model 1	Refence	0.72 (0.56-0.93)	0.011	0.73 (0.51-1.03)	0.072	0.72 (0.55-0.95)	0.022
Model 2	Refence	0.71 (0.54-0.92)	0.011	0.79 (0.55-1.13)	0.197	0.77 (0.58-1.02)	0.066
Fasting glucose							
Model 1	Refence	0.52 (0.32-0.86)	0.010	0.52 (0.37-0.74)	0.000	0.44 (0.30-0.64)	0.000
Model 2	Refence	0.54 (0.38-0.79)	0.001	0.53 (0.32-0.89)	0.016	0.52 (0.35-0.77)	0.001
Waist circumference							
Model 1	Refence	0.52 (0.38–0.71)	0.000	0.37 (0.25–0.54)	0.000	0.27 (0.20–0.37)	0.000
Model 2	Refence	0.67 (0.43–1.04)	0.072	0.34 (0.19–0.60)	0.000	0.34 (0.22–0.54)	0.000

All analyses were conducted using weighted data to account for the complex survey design. Model 1 represents unadjusted analyses, while model 2 accounts for confounders including age, gender, race/ethnicity, marital status, education level, body mass index.
HDL-C, high-density lipoprotein cholesterol; MVPA, moderate-to-vigorous physical activity; SB, sedentary behavior.

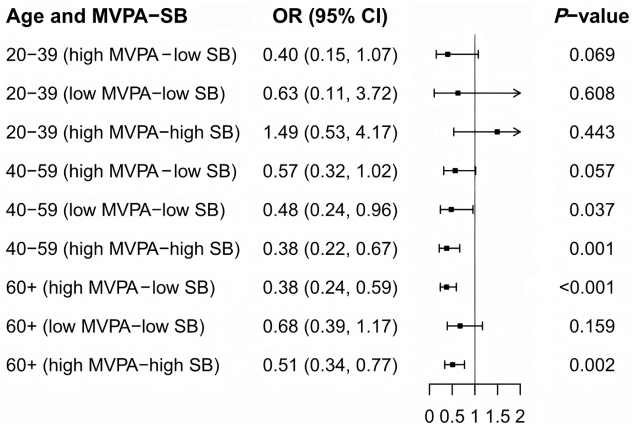

Fig. 1. Stratified associations between moderate-to-vigorous physical activity, sedentary behavior, and metabolic syndrome in different age groups. MVPA, moderate-to-vigorous physical activity; SB, sedentary behavior; OR, odds ratio; 95% CI, 95% confidence interval.

Two-sample Mendelian randomization analysis of physical activity and SB on metabolic syndrome risk factors

Sensitivity analyses from the two-sample Mendelian randomization showed no evidence of horizontal pleiotropy. The Radial Mendelian randomization analysis identified and excluded outlier SNPs, with all F-statistics exceeding 10 (Table 3).

The two-sample Mendelian randomization analysis demonstrated significant differences in the effects of physical activity and SB on metabolic syndrome risk factors (Figs. 2 and 3). IVW analysis demonstrated that PA significantly reduced blood pressure (OR, 0.87; 95% CI, 0.80-0.94; $P = 9.91e-04$), triglyceride levels ($\beta = -0.13$; 95% CI, -0.21 to -0.05; $P = 1.67e-03$), and waist circumference ($\beta = -0.13$; 95% CI, -0.21 to -0.05; $P = 1.67e-03$). However, no significant effect was observed on fasting glucose. Conversely, SB was associated with significant increases in blood pressure (OR, 1.17; 95% CI, 1.13–1.21; $P = 1.38e-21$), triglyceride levels ($\beta = 0.06$; 95% CI, 0.02–0.09; $P = 8.42e-04$), and waist circumference ($\beta = 0.14$; 95% CI, 0.13–0.15; $P = 9.68e-100$), with no significant effect on fasting glucose.

DISCUSSION

This study combines cross-sectional analysis and Mendelian randomization to systematically evaluate the impact of MVPA and SB on the risk of metabolic syndrome among arthritis patients aged 20 years and older in the United States. The findings indicate that a combination of high MVPA and low SB significantly reduces the risk of metabolic syndrome and its key components, such as hypertension, waist circumference, and triglycerides. In patients aged 60 and older, those with high MVPA and low SB exhibited

https://doi.org/10.12965/jer.2550080.040

Table 3. Two-sample Mendelian randomization estimates for the causal effects of physical activity and sedentary behavior on metabolic syndrome risk factors (F-statistics reported)

Exposure	Outcome	IVW *P*-value	MR-Egger *P*-value	MR-PRESSO causal estimate (95% CI)	MR-PRESSO *P*-value	F-statistics (mean)	No. of SNPs
Physical activity	Blood pressure	5.86e-01	6.67e-01	0.87 (0.80–0.94)	1.45e-03	17.10	45
Physical activity	High-density lipoprotein levels	3.01e-01	2.57e-01	0.02 (-0.02 to 0.05)	3.12e-01	17.52	23
Physical activity	Triglycerides	5.16e-01	4.72e-01	-0.13 (-0.20 to -0.05)	2.81e-03	17.19	41
Physical activity	Fasting glucose	9.49e-01	9.53e-01	0.68 (0.44–1.07)	1.00e-01	16.88	47
Physical activity	Waist circumference	3.54e-01	4.60e-01	0.34 (0.22–0.46)	2.40e-06	15.20	37
Sedentary behavior	Blood pressure	4.45e-01	4.74e-01	1.17 (1.13–1.21)	1.02e-18	96.19	263
Sedentary behavior	High-density lipoprotein levels	1.87e-01	2.32e-01	-0.08 (-0.10 to -0.06)	2.99e-16	90.96	100
Sedentary behavior	Triglycerides	9.73e-01	9.72e-01	0.06 (0.03–0.09)	2.95e-04	96.23	218
Sedentary behavior	Fasting glucose	9.51e-01	9.50e-01	1.06 (0.88–1.26)	5.45e-01	97.75	296
Sedentary behavior	Waist circumference	1.00e+00	1.00e+00	-0.11 (-0.15 to -0.08)	5.25e-09	94.09	203

IVW, inverse variance weighted; MR-Egger, Mendelian Randomization-Egger; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; OR, odds ratio; CI, confidence interval; F-statistics, mean F-statistic value of instrumental variables; SNP, single nucleotide polymorphism.

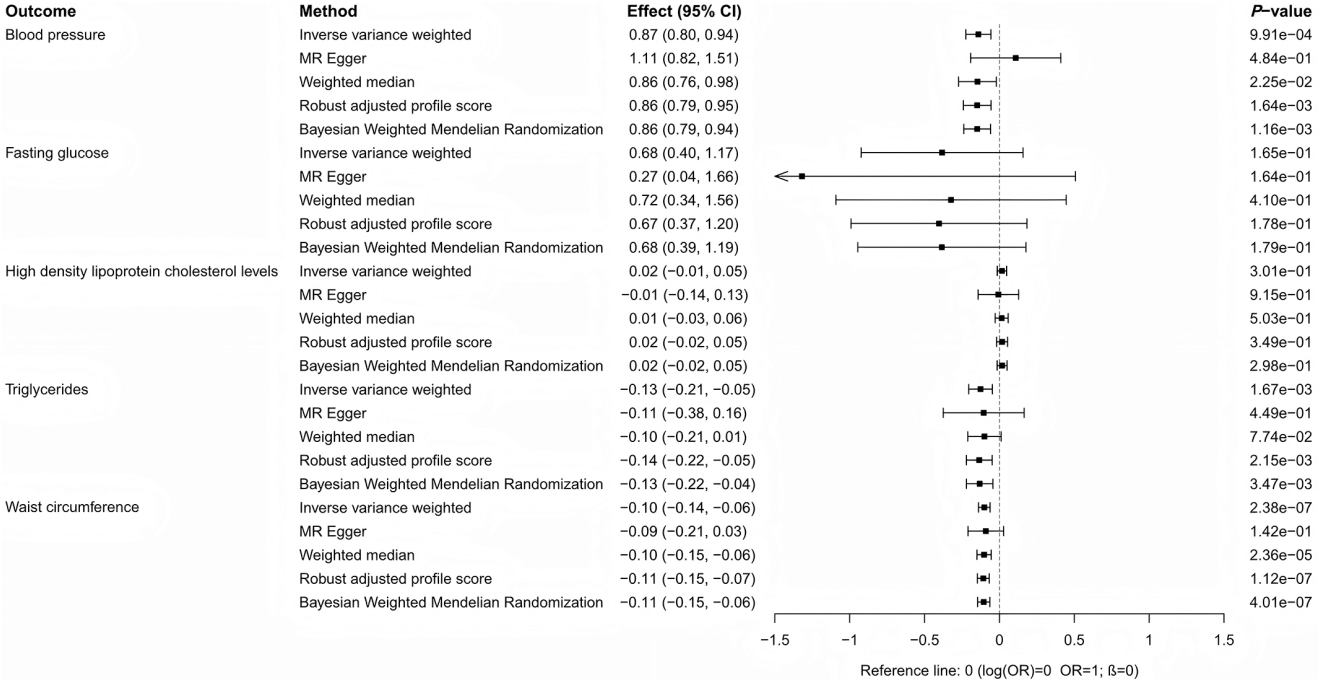

Fig. 2. Two-sample Mendelian randomization analysis of physical activity on metabolic syndrome risk factors. Odds ratios (ORs) for hypertension and fasting glucose are presented on a logarithmic scale, with confidence intervals calculated based on log (OR). MR Egger, Mendelian Randomization-Egger; CI, confidence interval.

a 62% lower risk of metabolic syndrome (OR, 0.38; 95% CI, 0.24–0.59), a reduction significantly greater than that observed in the 40–59 and 18–39 age groups. Furthermore, the results suggest that reducing SB alone, even at low physical activity levels, can effectively lower the risk of metabolic syndrome. The Mendelian randomization analysis enhances causal inference by addressing confounding factors and reverse causality, thereby further supporting the cross-sectional findings (Burgess et al., 2015; Hemani et al., 2017).

Our study demonstrated that individuals in the high MVPA and low SB group experienced a significant reduction in metabolic syndrome risk, likely due to the metabolic benefits of MVPA. MVPA lowers metabolic syndrome risk through various mechanisms, including improving insulin sensitivity, regulating lipid metabolism, and enhancing cardiovascular function (Pattyn et al., 2013; Thyfault and Bergouignan, 2020). Regular moderate phys-

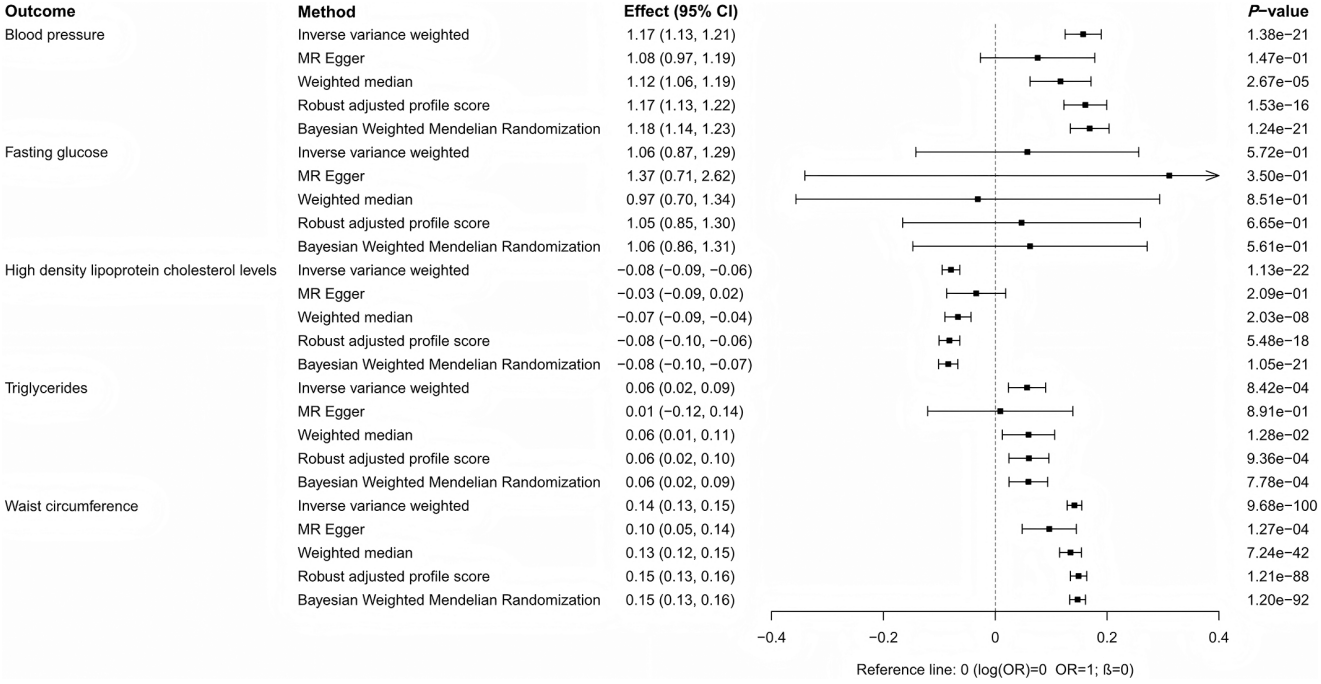

Fig. 3. Two-sample Mendelian randomization analysis of sedentary behavior on metabolic syndrome risk factors. Odds ratios (ORs) for hypertension and fasting glucose are presented on a logarithmic scale, with confidence intervals calculated based on log (OR). MR Egger, Mendelian Randomization-Egger; CI, confidence interval.

ical activity alleviates hyperglycemia and central obesity by enhancing glucose uptake in skeletal muscles and reducing insulin resistance (Chomiuk et al., 2024). Furthermore, MVPA promotes lipolysis, lowers triglycerides and low-density lipoprotein cholesterol, and increases HDL-C (Chomiuk et al., 2024; Hamer et al., 2014). Additionally, physical activity helps regulate blood pressure by promoting vasodilation, improving endothelial function, and reducing sympathetic nervous system activity, collectively lowering cardiovascular disease risk (Chomiuk et al., 2024; Pattyn et al., 2013). Meanwhile, reducing SB independently decreases metabolic syndrome risk by increasing energy metabolism and improving metabolic flexibility (Thyfault and Bergouignan, 2020). SB suppresses energy metabolism and fat oxidation, thereby increasing the risks of central obesity and hypertension. Reducing SB reverses these adverse effects and significantly improves metabolic health (Julian et al., 2021; Hamer et al., 2014). These findings align with WHO recommendations, suggesting that individuals who cannot avoid prolonged sedentary periods should increase physical activity to mitigate adverse health effects (Bull et al., 2020). Even among arthritis patients with low physical activity levels, reducing SB notably improved metabolic health.

Although our study includes arthritis patients across all age groups, stratified analysis indicates that increased physical activity and reduced SB have a greater impact on older adults, especially those aged 60 and above. This effect may result from greater metabolic dysfunction and diminished metabolic flexibility in older adults (Amorim et al., 2022). Aging leads to a decline in basal metabolic rate, mitochondrial function, and lipid oxidation efficiency (Amorim et al., 2022; Frisard and Ravussin, 2006). Reducing SB, such as standing or engaging in low-intensity activities, may enhance metabolic flexibility by activating nutrient-sensing pathways like adenosine monophosphate-activated protein kinase, leading to greater health benefits (Andersson et al., 2020). Furthermore, MVPA can further reduce metabolic risk in older arthritis patients by alleviating chronic low-grade inflammation (Bartlett et al., 2018). Therefore, older adults with arthritis should be prioritized for metabolic health interventions.

The findings of this study are consistent with previous literature and confirm the causal effects of physical activity and SB on metabolic syndrome through Mendelian randomization analysis. For example, physical activity lowers triglyceride levels by enhancing insulin sensitivity and regulating lipid metabolism, whereas SB elevates the risk of central obesity and hypertension (Hamer et al., 2014; Thyfault and Bergouignan, 2020). However, the study identified inconsistencies in the effects of physical activity and SB on fasting glucose and HDL-C levels. While cross-sectional analysis indicated a significant association between physical activity and fasting glucose, Mendelian randomization analysis failed to confirm

https://doi.org/10.12965/jer.2550080.040

a causal relationship. This discrepancy may stem from the complex interaction of genetic and environmental factors, such as insulin sensitivity, diet, and circadian rhythms, influencing fasting glucose levels (Zhao et al., 2020). Furthermore, Mendelian randomization analysis demonstrated that high SB significantly reduces HDL-C levels, highlighting the detrimental effects of SB on lipid metabolism.

This study integrated cross-sectional analysis and Mendelian randomization to systematically investigate the influence of physical activity and SB on metabolic syndrome. Each approach employed distinct physical activity measurement methods to leverage unique strengths and address specific limitations. The cross-sectional analysis used WHO-recommended criteria for MVPA, which are well-suited for large-scale population studies. These criteria effectively captured real-world activity patterns and their associations with health outcomes. In contrast, the Mendelian randomization analysis utilized accelerometer-based objective measurements of average activity intensity to overcome recall bias and inaccuracies in self-reported data. This method offered precise insights into the long-term causal effects of habitual activity on metabolic syndrome. Integrating these complementary methods facilitated a robust evaluation of observational associations and causal inferences. However, this study has certain limitations. The cross-sectional design inherently cannot capture dynamic changes over time, restricting its ability to infer long-term effects. Additionally, the limited explanatory power of instrumental variables in the Mendelian randomization analysis may compromise the precision of effect estimates. Future research should employ longitudinal designs to explore the long-term effects of physical activity and SB on metabolic syndrome and its components, with the aim of refining targeted health interventions.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

The author acknowledges the participants and investigators of the FinnGen Study (https://finngen.gitbook.io/documentation/) for their invaluable contributions and thanks the CDC for making the NHANES data publicly available (http://www.cdc.gov/nchs/nhanes.htm). This study was funded by Sangmyung University's 2024 intramural research grant.

REFERENCES

1000 Genomes Project Consortium; Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. A map of human genome variation from population-scale sequencing. Nature 2010;467:1061-1073.

Amorim JA, Coppotelli G, Rolo AP, Palmeira CM, Ross JM, Sinclair DA. Mitochondrial and metabolic dysfunction in ageing and age-related diseases. Nat Rev Endocrinol 2022;18:243-258.

Andersson SEM, Lange E, Kucharski D, Svedlund S, Önnheim K, Bergquist M, Josefsson E, Lord JM, Mårtensson IL, Mannerkorpi K, Gjertsson I. Moderate- to high intensity aerobic and resistance exercise reduces peripheral blood regulatory cell populations in older adults with rheumatoid arthritis. Immun Ageing 2020;17:12.

Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. Rheumatology (Oxford) 2012;51:519-527.

Bartlett DB, Willis LH, Slentz CA, Hoselton A, Kelly L, Huebner JL, Kraus VB, Moss J, Muehlbauer MJ, Spielmann G, Kraus WE, Lord JM, Huffman KM. Ten weeks of high-intensity interval walk training is associated with reduced disease activity and improved innate immune function in older adults with rheumatoid arthritis: a pilot study. Arthritis Res Ther 2018;20:127.

Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44:512-525.

Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40:304-314.

Bowden J, Spiller W, Del Greco M F, Sheehan N, Thompson J, Minelli C, Davey Smith G. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the Radial plot and Radial regression. Int J Epidemiol 2018;47:1264-1278.

Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, Dempsey PC, DiPietro L, Ekelund U, Firth J, Friedenreich CM, Garcia L, Gichu M, Jago R, Katzmarzyk PT, Lambert E, Leitzmann M, Milton K, Ortega FB, Ranasinghe C, Stamatakis E, Tiedemann A, Troiano RP, van der Ploeg HP, Wari V, Willumsen JF. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451-1462.

Buniello A, MacArthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C, McMahon A, Morales J, Mountjoy E, Sollis E, Suveges D, Vrousgou O, Whetzel PL, Amode R, Guillen JA, Riat HS, Trevanion SJ, Hall P, Junkins H, Flicek P, Burdett T, Hindorff LA, Cunningham F, Parkinson H. The NHGRI-EBI GWAS Catalog of published genome-wide associ-

ation studies, targeted arrays and summary statistics 2019. Nucleic Acids Res 2019;47:D1005-D1012.

Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013;37:658-665.

Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG; EPIC-InterAct Consortium. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol 2015;30:543-552.

Burgess S, Thompson SG; CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol 2011;40:755-764.

Choi JI, Cho YH, Kim YJ, Lee SY, Lee JG, Yi YH, Tak YJ, Hwang HR, Lee SH, Park EJ, Lee YI, Ra YJ, Lee SJ. The relationship of sitting time and physical activity on the quality of life in elderly people. Int J Environ Res Public Health 2021;18:1459.

Chomiuk T, Niezgoda N, Mamcarz A, Śliż D. Physical activity in metabolic syndrome. Front Physiol 2024;15:1365761.

Dominick KL, Ahern FM, Gold CH, Heller DA. Health-related quality of life among older adults with arthritis. Health Qual Life Outcomes 2004;2:5.

Duca LM, Helmick CG, Barbour KE, Murphy LB, Guglielmo D, Odom EL, Boring MA, Croft JB. State-specific prevalence of inactivity, self-rated health status, and severe joint pain among adults with arthritis - United States, 2019. Prev Chronic Dis 2022;19:E23.

Dunlop DD, Song J, Semanik PA, Sharma L, Chang RW. Physical activity levels and functional performance in the osteoarthritis initiative: a graded relationship. Arthritis Rheum 2011;63:127-136.

FinnGen Consortium. FinnGen: R11 release: summary statistics for genome-wide association studies in Finland [Internet]. Helsinki: FinnGen; c2023 [cited 2025 Mar 13]. Available from: https://www.finngen.fi/en.

Frisard M, Ravussin E. Energy metabolism and oxidative stress: impact on the metabolic syndrome and the aging process. Endocrine 2006;29:27-32.

Greer AE, Sui X, Maslow AL, Greer BK, Blair SN. The effects of sedentary behavior on metabolic syndrome independent of physical activity and cardiorespiratory fitness. J Phys Act Health 2015;12:68-73.

Hamer M, Stamatakis E, Steptoe A. Effects of substituting sedentary time with physical activity on metabolic risk. Med Sci Sports Exerc 2014;46:1946-1950.

Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, Owen N. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care 2008;31:369-371.

Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet 2017;13:e1007081.

Huckleby J, Williams F, Ramos R, Nápoles AM. The effects of race/ethnicity and physician recommendation for physical activity on physical activity levels and arthritis symptoms among adults with arthritis. BMC Public Health 2021;21:1564.

Ju SY, Lee JY, Kim DH. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-analysis of prospective cohort studies. Medicine (Baltimore) 2017;96:e8491.

Julian V, Ciba I, Olsson R, Dahlbom M, Furthner D, Gomahr J, Maruszczak K, Morwald K, Pixner T, Schneider A, Pereira B, Duclos M, Weghuber D, Thivel D, Bergsten P, Forslund A. Association between metabolic syndrome diagnosis and the physical activity-sedentary profile of adolescents with obesity: a complementary analysis of the beta-JUDO study. Nutrients 2021;14:60.

Li W, Qiu X, Ma H, Geng Q. Incidence and long-term specific mortality trends of metabolic syndrome in the United States. Front Endocrinol (Lausanne) 2023;13:1029736.

Liu SH, Waring ME, Eaton CB, Lapane KL. Association of objectively measured physical activity and metabolic syndrome among US adults with osteoarthritis. Arthritis Care Res (Hoboken) 2015;67:1371-1378.

Mainali N, Balasubramaniam M, Johnson J, Ayyadevara S, Shmookler Reis RJ. Leave-one-out-analysis (LOOA): web-based tool to predict influential proteins and interactions in aggregate-crosslinking proteomic data. Bioinformation 2024;20:4-10.

Pattyn N, Cornelissen VA, Eshghi SR, Vanhees L. The effect of exercise on the cardiovascular risk factors constituting the metabolic syndrome: a meta-analysis of controlled trials. Sports Med 2013;43:121-133.

Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med 2009;121:9-20.

Saunders TJ, Tremblay MS, Després JP, Bouchard C, Tremblay A, Chaput JP. Sedentary behaviour, visceral fat accumulation and cardiometabolic risk in adults: a 6-year longitudinal study from the Quebec Family Study. PLoS One 2013;8:e54225.

Shin JA, Lee JH, Lim SY, Ha HS, Kwon HS, Park YM, Lee WC, Kang MI, Yim HW, Yoon KH, Son HY. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. J Diabetes Investig 2013;4:334-343.

Thyfault JP, Bergouignan A. Exercise and metabolic health: beyond skeletal muscle. Diabetologia 2020;63:1464-1474.

Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian random-

 https://doi.org/10.12965/jer.2550080.040

ization between complex traits and diseases. Nat Genet 2018;50:693-698.

Weir CB, Jan A. BMI classification percentile and cut-off points. 2023 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.

Yu K, Chen XF, Guo J, Wang S, Huang XT, Guo Y, Dong SS, Yang TL. Assessment of bidirectional relationships between brain imaging-derived phenotypes and stroke: a Mendelian randomization study. BMC Med 2023;21:271.

Zhao J, Ming J, Hu X, Chen G, Liu J, Yang C. Bayesian weighted Mendelian randomization for causal inference based on summary statistics. Bioinformatics 2020;36:1501-1508.