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Physical activity and myocardial infarction risk: insights from the global burden of disease study 1990–2021 and Mendelian randomization analysis

Yujie Guo^{1†}, Xianghu Zhao^{2,3†}, Wenyan Xu^{1†}, Changli Cheng⁴, Lan Lei⁵, Meiqi Zhou^{1*} and Yikang He^{6*}

Abstract

Introduction Ischemic heart disease (IHD), particularly myocardial infarction (MI), ranks as a leading cause of death globally. While studies have associated physical activity (PA) with a decreased risk of MI, the extent of the global IHD burden attributable to LPA and the impact of PA on MI remain uncertain.

Methods This study accessed data from the Global Burden of Disease (GBD) 2021 and employed Mendelian randomization (MR) to evaluate these relationships. We analyzed the global age-standardized death rate (ASDR) for IHD attributable to LPA from 1990 to 2021. Additionally, we utilized the MR analysis to assess the relationship between PA and MI, using relevant data from GWAS databases. Within this framework, PA is defined based on the types of PA in the last 4 weeks, including other exercises such as swimming, cycling, keep fit, and bowling.

Results From 1990 to 2021, the global ASDR for IHD attributable to LPA exhibited an upward trend (estimated annual percentage change [EAPC] = 0.70, 95% CI: 0.61 to 0.79). The MR analysis revealed an inverse association between PA and MI (IVW method: OR = 0.17, 95% CI: 0.04 to 0.68, $P = 0.01$). However, significant heterogeneity was observed among the instrumental variables (Cochran's $Q = 18.25$, $P = 0.01$), indicating potential instability in the effect estimates.

Conclusions This study highlights that LPA contributes significantly to the global burden of IHD, with an increasing trend in related mortality from 1990 to 2021. From a genetic perspective, MR analysis indicates that PA reduce the risk of MI, though further research using larger sample sizes and more robust genetic tools is required to definitively establish this relationship. Globally, promoting PA is essential for reducing the burden of disease and enhancing cardiovascular health.

[†]Yujie Guo, Xianghu Zhao and Wenyan Xu contributed equally to this work.

*Yikang He is the primary corresponding author.

*Correspondence:

Meiqi Zhou
meiqizhou1963@126.com
Yikang He
hantanger162@126.com

Full list of author information is available at the end of the article



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Keywords Low physical activity, Myocardial infarction, Global burden of disease, Mendelian randomization

What is already known on this topic?

Ischemic heart disease, particularly myocardial infarction, is a leading cause of mortality globally. Low physical activity has been identified as a significant modifiable risk factor for ischemic heart disease and myocardial infarction, contributing to increased morbidity and mortality rates.

What does this study add?

- This study provides a comprehensive analysis of the global burden of ischemic heart disease attributable to low physical activity from 1990 to 2021, highlighting the increasing trend in mortality rates associated with low physical activity over this period.
- Utilizing Mendelian randomization analysis, this study explores the relationship between physical activity and myocardial infarction, offering genetic evidence that physical activity reduce the risk of myocardial infarction. However, significant heterogeneity in the Mendelian randomization results suggests the need for further validation with larger sample sizes.
- The findings emphasize the importance of promoting physical activity globally to mitigate the burden of ischemic heart disease and improve cardiovascular health, particularly in regions with high low physical activity prevalence.

Introduction

Ischemic heart disease (IHD) is a group of conditions characterized by insufficient blood supply to the heart, typically caused by atherosclerotic narrowing of the coronary arteries [1]. Myocardial infarction (MI), also referred to as a heart attack, is a severe form of IHD. It occurs when blood flow in the coronary arteries is obstructed, leading to ischemic necrosis of the heart muscle and is a major cause of death in acute coronary syndromes [2]. Despite the widespread use of percutaneous coronary intervention and related medications, the long-term recovery and prognosis of MI remain poor, leading to a decline in quality of life and creating a heavy burden on society and families [3]. Therefore, identifying modifiable risk factors for MI can help in early prevention and improve prognosis.

A sedentary lifestyle and low physical activity (LPA) are established modifiable risk factors for IHD [4]. A previous study has indicated that globally, high systolic blood pressure, high low-density lipoprotein cholesterol, and smoking are the three largest contributors to the burden of IHD [5]. However, exercise can not only effectively

control hypertension, hyperlipidemia, and addiction to tobacco but also prevent cardiovascular problems caused by LPA [6–8]. Therefore, understanding the global burden of IHD attributable to LPA is imperative.

Several observational studies have presented evidence for a significant relationship between PA and conditions such as high blood pressure and abdominal aortic calcification [9–11]. Importantly, recent meta-analyses indicated that increased levels of PA are considerably related to a reduced risk of cardiovascular problems [12, 13]. However, these observational studies are influenced by the potential confounders. A recent community-based randomized controlled trial (RCT) has demonstrated that PA plays a positive role in the prevention of adverse cardiovascular events in both the short and medium terms [14]. While RCTs have investigated the impact of PA and sedentary behaviors on cardiovascular risk, the findings remain ambiguous [15]. Given the limited duration of intervention studies, evidence concerning the potential long-term side effects may remain unattainable, which can also result in biases in the results [16].

Mendelian randomization (MR) is a powerful epidemiological method that follows Mendel's independent laws of inheritance [17]. It utilizes genetic variations and single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to evaluate the association of risk factors in complex diseases. Consequently, MR can address the shortcomings of observational studies, including confounding biases. Although previous MR studies have explored the relationship between PA and MI, the types of PA examined in these studies are not entirely consistent with the exercise types used in our study [18–21]. Specifically, the PA types investigated in existing MR studies generally include moderate-intensity PA, vigorous PA, and moderate-to-vigorous PA. While these studies have provided valuable insights, they have not specifically focused on the PA types we are exploring, such as swimming, cycling, keep fit, and bowling. These exercise types may have unique physiological effects on cardiovascular health.

Therefore, our study first utilized data from the Global Burden of Disease (GBD) 2021 to analyze the impact of LPA on the burden of IHD, providing a macroscopic view of this global health issue. This analysis emphasized the significant contribution of LPA to IHD and highlighted the necessity for further research into these associations. Subsequently, we employed a two-sample MR analysis to explore the effect of PA on MI from a genetic perspective, revealing the potential relationship between PA and MI. These two analyses, presented as parallel components, offer distinct insights from both macroscopic

and microscopic viewpoints. It is important to note that the results of these analyses are not intended to interpret each other, but rather provide independent perspectives on understanding this complex relationship.

Methods

Study design

Figure 1 provides a comprehensive visualization of our research approach. Firstly, we conducted an epidemiological study of the global burden of IHD attributable to LPA using the GBD 2021 (<https://www.healthdata.org/>). Secondly, we performed a two-sample MR study with PA as the exposure and MI as the outcome utilizing the data from the IEU OpenGWAS project (<https://gwas.mrcieu.ac.uk/>). In summary, the purpose of our work was to evaluate the GBD 2021 due to IHD as a result of LPA and the association between PA and MI, in order to highlight the importance of PA interventions. This study utilized data from the GBD 2021 study and publicly available GWAS data, all of which are deidentified and aggregated. Therefore, prospective recruitment of human participants and obtaining informed consent were not required for this study. The data were accessed for research purposes from the GBD 2021 database and publicly available GWAS databases on March 15, 2025.

Definitions

Within the GBD study framework, IHD includes acute events and chronic conditions (angina and asymptomatic IHD). The criteria for acute events consist of both confirmed and probable cases [22]. Angina was clinically identified through the Rose Angina Questionnaire, the assessment of physician, or the use of nitrates to alleviate chest discomfort, and was categorized as stable exertional or definite angina pectoris. Asymptomatic IHD following an acute event was defined by a 28-day survival period post-event. The GBD study avoids electrocardiogram-based estimates of acute events due to limitations in specificity and sensitivity [23]. According to information offered by IHME (Institute for Health Metrics and Evaluation), adults should participate in at least 150 min of moderate-intensity PA, or 75 min of vigorous-intensity PA, or a combination of the corresponding activities, per week. Individuals who are less active than these recommendations may be classified as physically inactive [24].

In the IEU OpenGWAS project, we selected the dataset characterized by the types of PA in last 4 weeks: Other exercises (e.g.: swimming, cycling, keep fit, bowling) to be defined as PA. MI, including fatal and nonfatal ST-segment elevation MI and non-ST-segment elevation MI, was the primary outcome of the observational analyses, and data were obtained from the relevant hospital admissions and death registries [25].

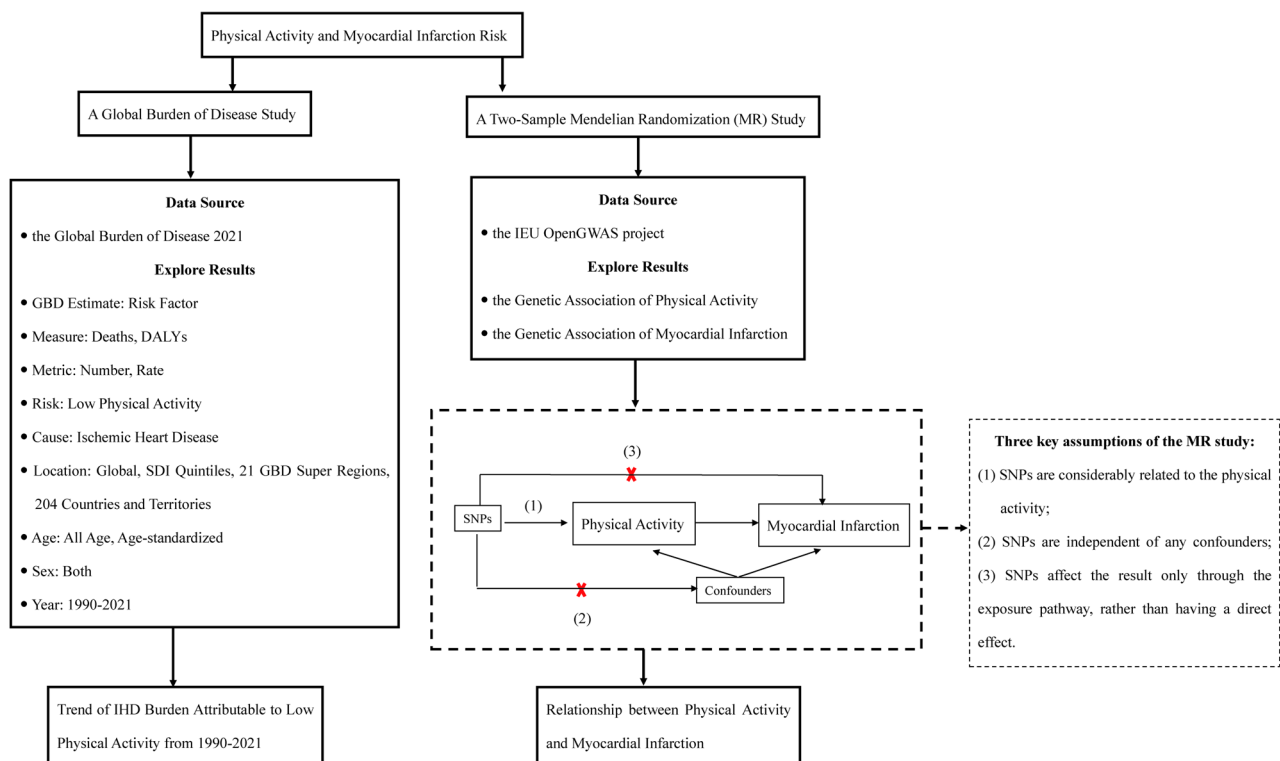


Fig. 1 Study design. GBD, global burden of disease; DALYs, disability-adjusted life years; SDI, socio-demographic index; SNPs, single nucleotide polymorphisms

Data sources

In GBD 2021, we collected the data utilizing the Global Health Data Exchange query tool [Available at: <https://vizhub.healthdata.org/gbd-results>]. The data included the number of deaths and disability-adjusted life years (DALYs), the rate of deaths and DALYs among all ages from 1990 to 2021. The 204 countries and territories are further divided into 21 GBD super regions and, based on geographical contiguity, 5 socio-demographic index (SDI) regions categorized as low, low-middle, middle, middle-high, and high. The SDI, serving as a comprehensive measure of developmental progress, shows a robust association with health outcomes [26]. The SDI is determined by the geometric average of various indices, including the distribution of income lagged per capita, average years of education for those aged 15 and older, and the fertility rate for those under 25 years of age. The SDI value of 0 represents the lowest theoretical developmental level in relation to health outcomes, while the SDI of 1 shows the highest possible level [26].

In MR study, we selected the data from the publicly accessible GWAS databases in the IEU OpenGWAS project [Available at: <https://opengwas.io/>]. The GWAS involved a total of 460,376 samples for PA and 461,823 samples for MI all from European populations and the MRC-IEU consortium. Detailed information regarding the data sources for both the exposure (PA) and the outcome (MI) is provided in Supplementary Table S1. The IVs used in this work were selected derived from three key assumptions of MR studies (Fig. 1). Firstly, SNPs with significant associations ($P < 5 \times 10^{-8}$) were derived from the pooled data of the GWAS for all phenotypes. Next, the SNPs were filtered utilizing the “clump_data” function in R software, with a threshold of $r^2 < 0.001$ and a genetic distance of 10,000 kb, to meet the first assumption of MR. Additionally, a query was performed in the PhenoScanner database (<https://www.phenoscaner.medschl.cam.ac.uk>) to confirm that the involved SNPs were not related to established confounding factors (Supplementary Table S5) [27]. Secondly, the SNPs recognized as IVs were consistent with those in the GWAS database for the outcome phenotype to build genetic relationships. The overview statistics for SNP-phenotype and SNP-outcome associations were adjusted for consistency of effect sizes, and SNPs with palindromic properties were removed from the analysis. Thirdly, F-statistics (> 10) were adopted to assess the reliability of the IVs and minimize the effects of weak instrumental bias (Supplementary Table S4) [28].

Statistical analysis of the GBD study

The IHD data in the GBD 2021 were estimated by models, which included the data on vital registration, case reports, routine surveillance, prevalence surveys, and

literature. During the process of model estimation, methods included weighting, sample external validity prediction, and covariate adjustment, which were used to calibrate the model accuracy. In addition, to ensure reasonableness, the uncertainty interval (UI) of each estimate value was calculated [23]. The detailed methodology to estimate the numbers and rates from the GBD 2021 has been explained in previous studies and indicated in the “Methods” section in the Supplemental Information [23, 29].

In our work, we analyzed the burden of IHD attributable to LPA by all age, both sex, 5 SDI quintiles, 21 GBD super regions, and 204 countries and territories. To quantify the trends, we calculated the age-standardized death rate (ASDR), the age-standardized DALYs rate, the estimated annual percentage change (EAPC) in death, and EAPC in DALYs. Analyzing the age-standardized rate (per 100,000 population) can provide a better knowledge of the burden of IHD as well as additional evaluation of the efficiency of its prevention and therapy. The age-standardized rate was computed by aggregating the products of the age-specific rates (a_i) and the corresponding number of cases (or weight; w_i) of the selected reference standard population in the same age group (i), and subsequently dividing this sum by the total number (or weight) of the standard population ($ASR = \frac{\sum_{i=1}^A a_i w_i}{\sum_{i=1}^A w_i}$

$\times 100\ 000$). The GBD world population was utilized as the age standard population in the GBD analysis. EAPC is a statistical measure utilized to quantify the rate at which a specific metric is changing over time [30]. In this work, a linear regression model was matched to the natural logarithm of the age group-specific rate: $y = \alpha + \beta x + \varepsilon$, where $y = \ln$ (age group-specific rate) and $x = \text{year}$. $EAPC = 100 \times (e\beta)$, its 95% confidence interval (CI) was also sourced from this model. Negative values of EAPC and its upper 95% CI show a downward trend of the rate during the observation period, whereas positive values indicate an upward trend. However, it should be noted that the linear regression model used to estimate the EAPC assumes a constant rate of change over time, which may not fully capture the complexities of disease burden dynamics over the 31-year period. The model was chosen for its simplicity and interpretability, providing a clear trend estimate that serves as a useful starting point for preliminary analysis. All analyses and figures were performed using R software, version 4.3.1.

Statistical analysis of the MR study

MR is a study design that utilizes genetic IVs to explore and assess causal relationships between an exposure variable and an outcome. In our work, we employed MR to

examine the causal relationship between the exposure and the result variable. We commenced the analysis by calculating the Wald ratio for each IV, which involved dividing the outcome statistics by the corresponding exposure statistics. This step yielded preliminary estimates of the associations between the exposures and the outcomes for each SNP. Then, we utilized the inverse variance weighted (IVW) method to assess the overall association between the exposures and the outcomes. The IVW analysis assigned weights to the Wald ratio of every SNP based on its IVs, taking into account the variability and precision of each IV estimate. Depending on the results of Cochran's Q test for heterogeneity among IV estimates, we selected random-effects or fixed-effects models for the IVW analysis. When the Q test indicated significant heterogeneity ($P < 0.05$), random-effects models were used to account for the variability. On the other hand, when the significance level was not achieved, fixed-effects models were employed to establish consistent effect sizes across the various studies. In addition to the IVW analysis, we employed several supplementary approaches to enhance the robustness of our outcomes. These included the MR-Egger, simple mode, and weighted median, weighted mode methods. These approaches offered additional insights and alternative estimates of the causal association, further strengthening the validity of our results. By employing these various MR analysis methods, we obtained comprehensive and robust results that helped evaluate the causal association between the exposure variable and the outcome of interest. Finally, we calculated the statistical power of our MR analysis using an online tool [Available at: <https://shiny.cnsngénomics.com/mRnd/>]. We assumed an odds ratio (OR) of 0.17. For the outcome GWAS, we utilized a 1:1 case-control ratio, meaning the number of cases (n_{cases}) and controls (n_{controls}) were equal, with each group set at 230,911.5. Furthermore, we presumed that the IVs accounted for 10% of the variance, which is a standard assumption in similar analyses. With these parameters, the calculated statistical power was 85%, ensuring that our study had sufficient capability to detect causal effects. The MR analysis was conducted in accordance with STROBE-MR checklist.

The results from the MR analysis were reported as estimated values, specifically ORs for binary variables. These estimated values were linked with 95% CIs, providing a measure of the precision and uncertainty associated with the estimates. Throughout the analysis, the estimated values, including ORs and CIs, were consistently reported to ensure accuracy and reliability in presenting the findings. The statistical analysis and figures were conducted utilizing the “Two-sample MR” package in software R, version 4.3.1.

Evaluation of horizontal Pleiotropy and heterogeneity in MR study

In the background of the IVW analysis, it is essential to assess the possible impacts of pleiotropy on causal inferences and research outcomes [31]. To evaluate the appropriateness of the chosen SNPs as IVs, we conducted tests for pleiotropy using the “Two-sample MR” package. This test helps determine whether significant pleiotropy is evident ($P > 0.05$) and informs us about the suitability of utilizing the IVs in the analysis. Additionally, we used Cochran's Q test as a statistical tool to assess the degree of heterogeneity or inconsistency among the selected IVs. A random-effects model is the default or conservative choice when heterogeneity is present, not that it is only used after a significant Q test, while fixed-effects are used otherwise. This helps to address potential variability in the causal estimates due to differences among the IVs. By performing these assessments for pleiotropy and heterogeneity, we confirm the robustness of our results and the validity of the IVW analysis approach.

Sensitivity analysis in MR study

To ensure the robustness and validity of the causal association estimate obtained from MR analysis, we conducted several sensitivity analyses. Firstly, we used the MR-Egger intercept approach to assess the presence of pleiotropy among the selected SNPs. The MR-Egger intercept tests for the potential bias caused by horizontal pleiotropy. When the intercept term showed statistical significance ($P < 0.05$), it would indicate the potential presence of pleiotropic effects, suggesting that the IVs might have additional direct effects on the outcome. Conversely, if the intercept term was not statistically significant ($P > 0.05$), it would suggest no indications of horizontal pleiotropy among the IVs. Secondly, we utilized the MR pleiotropy residual sum as a tool to identify and correct any data anomalies that could affect the reliability of the estimates. This approach helps to address any potential bias arising from pleiotropy by adjusting the MR estimates. Additionally, we conducted a “leave-one-out” analysis, where every individual SNP was sequentially excluded from the analysis to assess its impact on the overall estimates. This method helps to appraise the robustness and stability of the outcomes by examining the influence of individual SNP on the results. By conducting these sensitivity analyses, we aimed to confirm the validity and robustness of the MR causal association estimate by assessing potential pleiotropy, addressing data anomalies, and evaluating the influence of individual SNPs on the results.

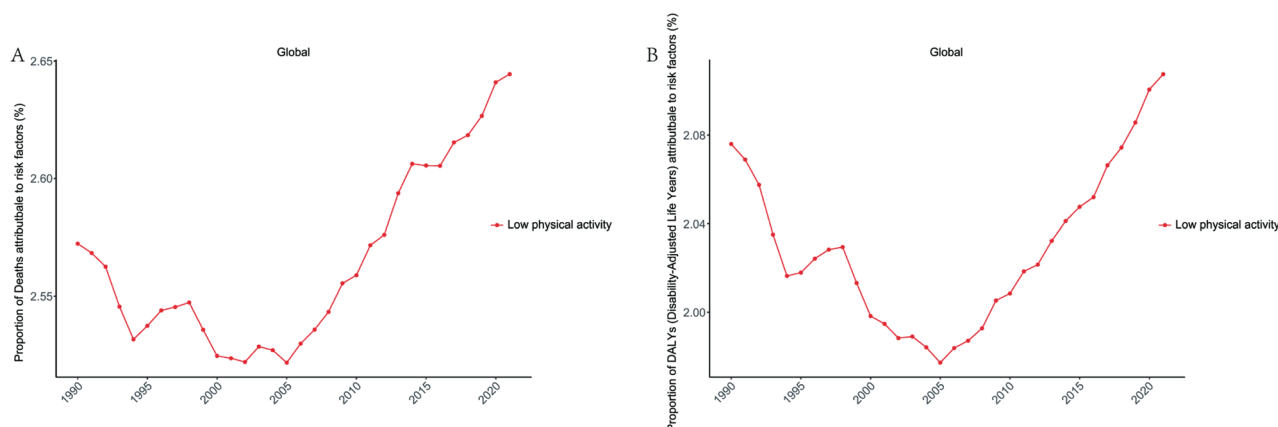


Fig. 2 Global trends in ASDR **A** and age-standardized DALYs rate **B** for IHD attributable to LPA from 1990 to 2021. ASDR, age-standardized death rate; DALYs, disability-adjusted life years; IHD, ischemic heart disease; LPA, low physical activity

Table 1 ASDR, age-standardized dalys rate, and EAPCs of IHD attributable to LPA from 1990 to 2021 in global and SDI quintiles. (N, 95 UI%)

	ASDR		EAPC	Age-standardized DALYs rate		EAPC
	1990	2021	1990–2021	1990	2021	1990–2021
Global SDI quintiles	4.09(1.78,6.56)	2.88(1.28,4.59)	0.70(0.61,0.79)	64.51(28.78,101.42)	46.63(21.15,73.38)	0.44(0.34,0.54)
Low SDI	1.98(0.82,3.14)	1.90(0.79,3.13)	0.03(−0.15,0.21)	36.16(15.55,56.12)	32.83(14.30,52.29)	−0.34(−0.50, −0.18)
Low-middle SDI	3.60(1.52,5.55)	3.68(1.61,5.89)	1.49(1.39,1.59)	68.84(30.52,104.96)	65.79(29.64,103.15)	0.98(0.88,1.08)
Middle SDI	3.62(1.55,5.79)	3.56(1.59,5.66)	2.60(2.53,2.68)	61.61(27.35,96.59)	57.71(26.11,90.69)	1.97(1.89,2.05)
High-middle SDI	4.69(2.00,7.47)	3.52(1.53,5.88)	1.44(1.34,1.53)	66.73(29.36,102.20)	49.51(21.54,80.04)	0.99(0.89,1.09)
High SDI	4.10(1.73,6.79)	1.40(0.58,2.27)	−1.72(−1.88,−1.56)	61.50(26.52,97.76)	21.77(9.40,34.53)	−2.01(−2.22,−1.79)

ASDR age-standardized death rate, DALYs disability-adjusted life-years, EAPC estimated annual percentage change, IHD ischemic heart disease, LPA low physical activity, SDI sociodemographic index

Results

Global trends in IHD attributable to LPA

In 2021, the global ASDR for IHD attributable to LPA was 2.88 (95% UI: 1.28 to 4.59) and the age-standardized DALYs rate was 46.63 (95% UI: 21.15 to 73.38). From 1990 to 2021, both the global ASDR (EAPC=0.70, 95% CI: 0.61 to 0.79) and the age-standardized DALYs rate (EAPC=0.44, 95% CI: 0.34 to 0.54) increased (Fig. 2; Table 1).

Global trends in IHD attributable to LPA by SDI

In 2021, the age-standardized death rate and age-standardized DALYs rate were highest in low-middle SDI regions (ASDR=3.68, 95% UI: 1.61 to 5.89; DALYs rate=65.79, 95% UI: 29.64 to 103.15) and lowest in high SDI regions (ASDR=1.40, 95% UI: 0.58 to 2.27; DALYs rate=21.77, 95% UI: 9.40 to 34.53) (Table 1). From 1990 to 2021, middle SDI regions saw the most significant increases in ASDR and DALYs rate, with EAPCs of 2.60 (95% CI: 2.53 to 2.68) and 1.97 (95% CI: 1.89 to 2.05), respectively. Conversely, high SDI regions experienced the most pronounced declines, with EAPCs of −1.72 (95% CI: −1.88 to −1.56) and −2.01 (95% CI: −2.22 to −1.79), respectively (Fig. 3; Table 1).

Regional trends in IHD attributable to LPA

In 2021, the highest ASDR and age-standardized DALYs rate were observed in North Africa and the Middle East (ASDR=6.99, 95% UI: 3.09–11.10; DALYs rate=125.43, 95% UI: 57.53–196.35). In contrast, Eastern Sub-Saharan Africa had the lowest ASDR (0.46, 95% UI: 0.19–0.78), and Southern Latin America had the lowest DALYs rate (7.77, 95% UI: 3.13–13.53) (Supplementary Table S2).

From 1990 to 2021, East Asia experienced the most significant increases in ASDR and DALYs rate, with EAPCs of 4.75 (95% CI: 4.52–4.98) and 3.83 (95% CI: 3.64–4.02), respectively. Conversely, Australasia saw the most pronounced declines, with EAPCs of −2.48 (95% CI: −2.59–−2.37) and −3.02 (95% CI: −3.13–−2.91), respectively (Supplementary Table S2).

National trends in IHD attributable to LPA

In 2021, Sudan had the highest ASDR and age-standardized DALYs rate (ASDR=18.10, 95% UI: 7.94–32.14; DALYs rate=435.90, 95% UI: 189.04–752.70), while Tanzania had the lowest (ASDR=0.17, 95% UI: 0.06–0.36; DALYs rate=3.13, 95% UI: 1.16–6.28) (Fig. 4A/C, Supplementary Table S2).

From 1990 to 2021, Albania experienced the most significant increases in ASDR and DALYs rate, with EAPCs

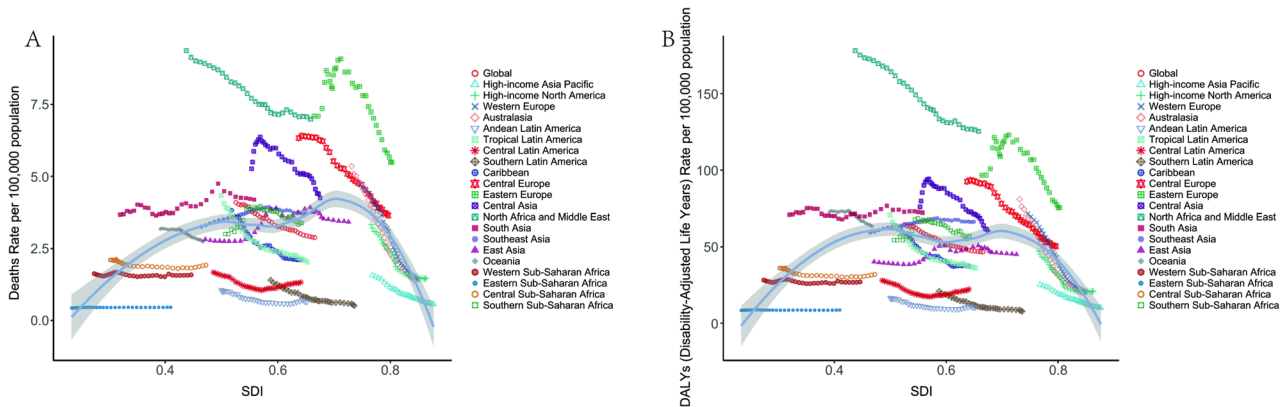


Fig. 3 Trends in ASDR **A** and age-standardized DALYs rate **B** for IHD attributable to LPA by SDI from 1990 to 2021. ASDR, age-standardized death rate; DALYs, disability-adjusted life years; IHD, ischemic heart disease; LPA, low physical activity; SDI, socio-demographic index

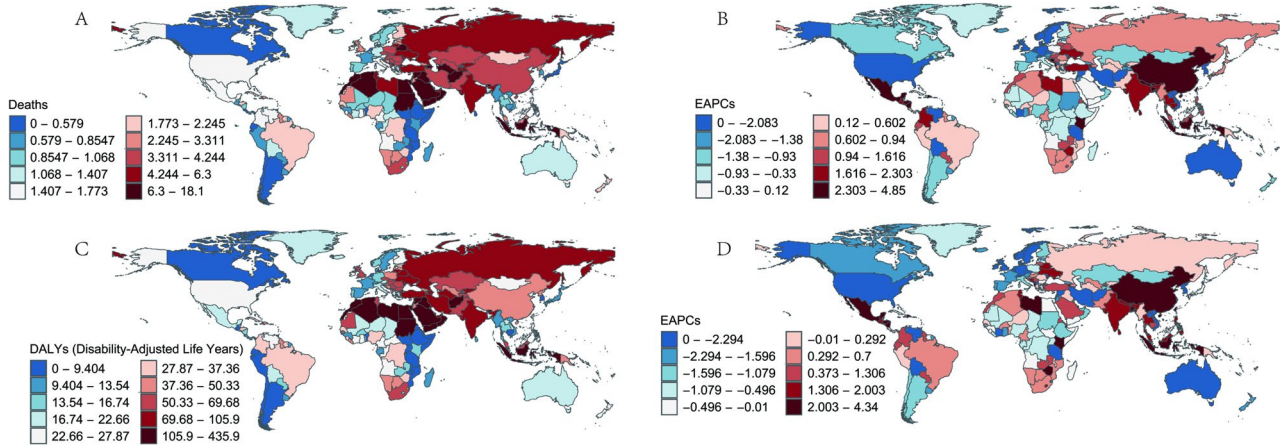


Fig. 4 National trends in ASDR **A** and age-standardized DALYs rate **B** for IHD attributable to LPA from 1990 to 2021. ASDR, age-standardized death rate; DALYs, disability-adjusted life years; IHD, ischemic heart disease; LPA, low physical activity

Table 2 MR outcomes for the association between PA and MI

Methods	Number of SNPs, <i>N</i>	MR analysis		
		OR	95% CI	<i>P</i> -value
MR-Egger	10	330.42	0.01 to 18477100.00	0.33
Weighted median	10	0.23	0.06 to 0.99	0.05
IVW	10	0.17	0.04 to 0.68	0.01
Simple mode	10	0.19	0.01 to 2.91	0.27
Weighted mode	10	0.15	0.01 to 2.38	0.21

PA physical activity, MI myocardial infarction, IVW inverse variance weight, MR Mendelian randomization, SNP single nucleotide polymorphism

of 4.85 (95% CI: 4.55–5.16) and 4.34 (95% CI: 4.05–4.62), respectively. Conversely, Denmark had the most pronounced declines, with EAPCs of −5.00 (95% CI: −5.20–−4.80) and −5.23 (95% CI: −5.45–−5.01), respectively (Fig. 4B/D, Supplementary Table S2).

Association of PA on MI

The MR analysis revealed a negative relationship between PA and MI, with an IVW OR of 0.17 (95% CI: 0.04 to

0.68, *P*=0.01). Other methods yielded varied results: MR-Egger OR 330.42 (95% CI: 0.01 to 18477100.00, *P*=0.33), weighted median OR 0.23 (95% CI: 0.06 to 0.99, *P*=0.05), simple mode OR 0.19 (95% CI: 0.01 to 2.91, *P*=0.27), and weighted mode OR 0.15 (95% CI: 0.01 to 2.38, *P*=0.21) (Table 2).

Sensitivity analysis of MR analysis

The MR-Egger intercept analysis did not show significant evidence of directional pleiotropy (*P*=0.21). However, given the limited number of IVs (*N*=10), the statistical power of the test is relatively low, and the non-significant result is inconclusive. We are unable to reject the null hypothesis of no pleiotropy (Supplementary Table S3). Additionally, a random-effects model was used in the IVW analysis to account for heterogeneity (IVW: Cochran’s *Q*=18.25, *P*=0.01) (Supplementary Table S3).

The scatter plot (Fig. 5A) and forest plot (Fig. 5B) describing the relationship of PA on MI were consistent with the reported results, showing similar patterns. The “leave-one-out” sensitivity analyses (Fig. 5C) indicated

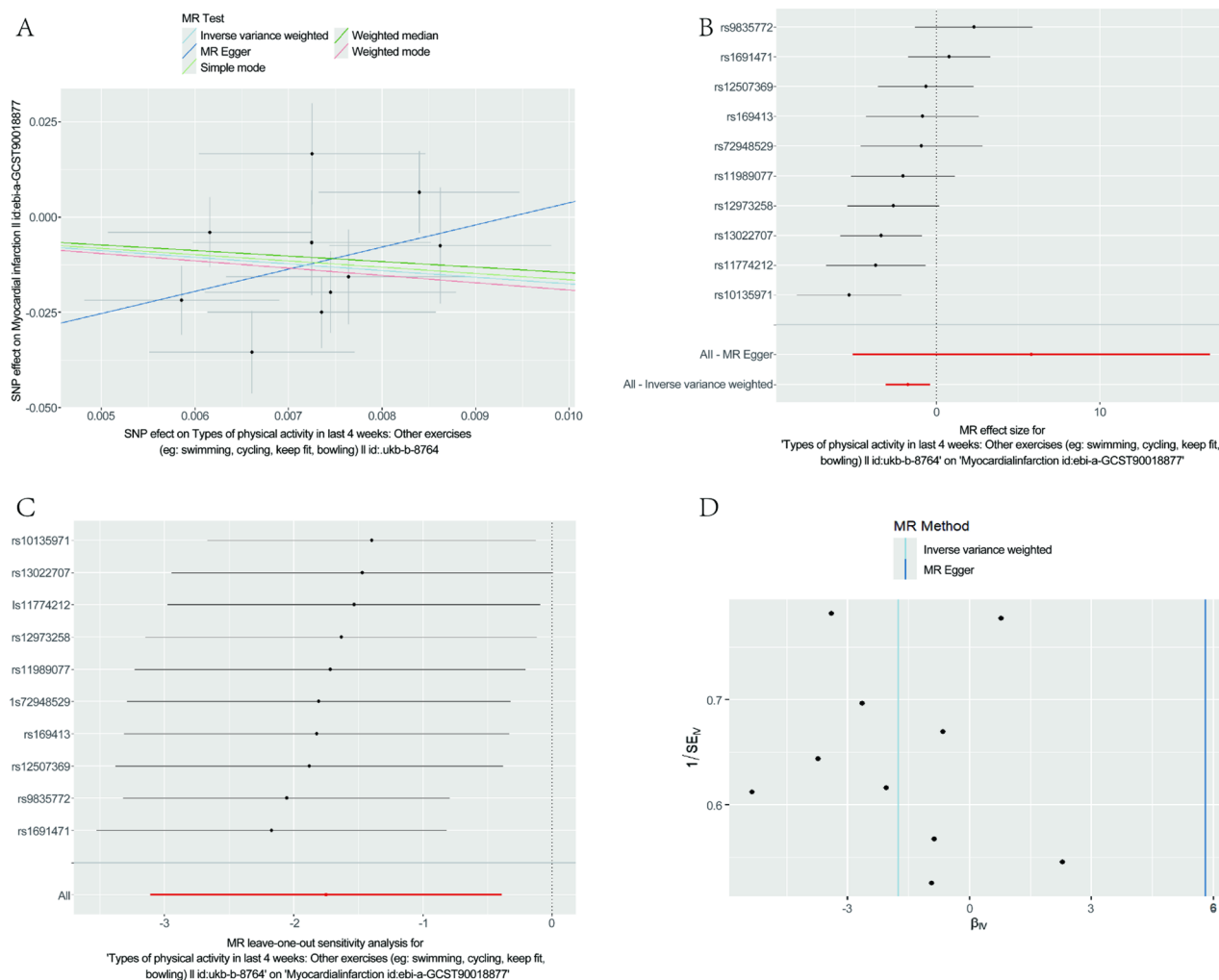


Fig. 5 Sensitivity analysis of MR analysis. **A** The scatter plot; **B** The forest plot; **C** The “leave-one-out” sensitivity analysis; **D** The funnel plot. MR, Mendelian randomization

that the general estimates were not disproportionately affected by any single SNP, further strengthening the robustness of the findings. Additionally, the funnel plot (Fig. 5D) did not indicate horizontal pleiotropy, supporting the validity of the MR analysis. Supplementary Table S4 and Table S5 provide a comprehensive list of the chosen SNPs involved or uninvolved in the MR analysis for replication, ensuring transparency in the methodology and replication process.

Discussion

We conducted a multi-stage analysis to comprehensively evaluate the global burden of IHD attributable to LPA and utilized MR analysis to explore the association between PA and MI. In an epidemiological study from GBD 2021 data, ASDR and age-standardized DALYs rate for IHD attributable to LPA showed an increasing trend globally. In this two-sample MR analysis, we provide evidence for a potential role of PA in the incidence of MI.

Despite previous MR studies having investigated the relationship between PA and MI [18–21], our work uniquely focuses on specific types of PA (e.g., swimming, cycling, keep fit, bowling) and provides a detailed examination of their relationship with the risk of MI. This specific focus on PA complements existing literature and offers new insights into the potential protective effects of these activities against MI. As parallel components, these two analyses provide unique insights from macro- and micro-level perspectives, respectively. Importantly, their results are not intended to be mutually explanatory but rather to furnish independent perspectives for understanding this complex relationship.

The increasing global burden of IHD attributable to LPA is consistent with previous GBD study findings [32, 33], emphasizing the significant influence of LPA on global health. Studies have also uncovered substantial regional differences in the burden of IHD due to LPA, with the highest burden in middle SDI areas and the

lowest in high SDI areas [33]. This is consistent with the findings of our study, indicating that middle SDI regions encounter significant health challenges during their economic development, characterized by the prevalence of unhealthy lifestyles and insufficient health awareness. Conversely, high SDI regions, characterized by more advanced public health policies and health promotion measures, have exhibited a downward trend. It is important to highlight that while the results of our study correspond with other GBD studies in terms of overall trends, our specific analyses reveal differences. Previous research has largely concentrated on the general burden of cardiovascular problems, while our study specifically targets IHD. This approach enables us to more precisely evaluate the particular influence of LPA on IHD and offers a scientific foundation for focused interventions. Moreover, our work further refines the observation that the increase in IHD burden is particularly prominent in middle SDI regions, suggesting that these areas should be given special attention when formulating public health policies.

From both physiological and demographic perspectives, the differences in disease burden across SDI regions are primarily the result of a combination of economic, educational, healthcare, and lifestyle factors. High SDI regions typically boast higher income levels, better education, and lower fertility rates, all of which contribute to heightened health awareness and the widespread adoption of healthy lifestyles [34]. Residents in these regions are more likely to engage in regular exercise, and the well-developed healthcare systems can offer effective prevention and treatment measures, thereby alleviating the burden of IHD. Middle SDI regions, with their relatively lower levels of economic development, face greater economic pressures among residents, who tend to have less health awareness and adopt less healthy lifestyles [35]. The healthcare systems in these regions are also less comprehensive, leading to an increased burden of IHD. Residents may choose unhealthy lifestyles due to economic limitations, such as sedentary behavior and a diet high in salt and fat, which can further worsen the burden of cardiovascular health [36]. In low SDI regions, residents have lower income and education levels and less knowledge about healthy lifestyles [37]. The limited availability of healthcare resources and delayed medical intervention imply that, despite a potentially lower absolute burden of IHD, these regions face greater health challenges [38]. Countries in low SDI regions might be deficient in fundamental medical infrastructure and professional medical personnel, leading to inadequate timely medical care for individuals with IHD, thereby exacerbating disease severity and mortality.

Significant disparities in the IHD burden attributable to LPA are also observed across the 21 GBD super regions, potentially attributable to varying levels of economic

development and geo-cultural distinctions. Eastern Sub-Saharan Africa and Southern Latin America have a lower burden of IHD due to better healthcare and hygiene policies, whereas regions such as North Africa and Middle East face a higher risk of IHD due to limited resources and worse healthcare [39]. Among the 204 countries and regions, Sudan had the highest levels of ASDR and age-standardized DALYs rate, while Tanzania had the lowest. This is associated with the level of economic development, the coverage and efficacy of the healthcare system, and the lifestyle of the respective countries. Sudan faces more severe health challenges and socioeconomic problems, whereas Tanzania has a lower burden of IHD due to healthier lifestyle habits and lower heart failure risk factors [40].

During the COVID-19 pandemic, significant reductions in daily activity levels due to closures and social isolation measures have contributed to the trend in IHD burden [41–43]. Therefore, innovative strategies to promote daily activity in a variety of surroundings and constrained conditions are necessary. Specifically, alternatives such as home-based exercise and virtual fitness programs become particularly important to reduce the adverse effects of sedentary behavior on cardiovascular health and to maintain the overall health of the population [44, 45].

While previous studies have broadly focused on cardiovascular problems, our research specifically targets IHD, providing a more detailed analysis of this particular condition. This targeted approach enables us to delve deeper into the epidemiological trends and potential interventions for IHD. However, it is important to note that GBD analyses are inherently descriptive and correlational, and cannot directly prove causality. Our study design also cannot derive direct causal links from descriptive trends. Therefore, although our study reveals an association between LPA and the burden of IHD, these associations do not necessarily imply causality.

Moreover, our work employs MR to explore the relationship between PA and MI, thereby offering new insights into modifiable risk factors for MI. Although numerous MR studies have examined the relationship between PA and MI, the PA methods used in this work (including other exercises in the past four weeks, such as swimming, cycling, keep fit, and bowling) differ from those used in other studies, which makes our research somewhat innovative.

Our MR analysis indicates that PA is associated with a reduced risk of MI. This finding is consistent with previous observational studies and RCTs that have demonstrated the benefits of PA in reducing the risk of cardiovascular health. However, it is crucial to recognize that, despite the suggestive nature of the MR results, there are limitations to consider when interpreting these

findings. In our analysis, the IVW method indicates a possible protective effect of PA against MI. However, significant heterogeneity and inconsistency across various MR approaches suggest that the results should be interpreted with caution. These findings suggest that hypothetical inferences might be influenced by factors such as weak instrumental variables and potential pleiotropy. Therefore, the MR estimates in this study are presented only as suggestive results.

Given the limitations of MR and exposure heterogeneity, we hypothesize that PA may enhance cardiovascular health via mechanisms such as improved myocardial function, increased nitric oxide release, and better lipid metabolism [46–51]. However, significant heterogeneity in our analysis highlights the need for further validation of these pathways.

The epidemiological significance of our study lies in its comprehensive evaluation of the global burden of IHD attributable to LPA from 1990 to 2021. Our analysis reveals an increasing trend in the ASDR and DALYs for IHD attributable to LPA, indicating that sedentary lifestyles have become a more pronounced public health issue over this period. This trend is particularly evident in middle SDI regions, which have seen the most significant increases in ASDR and DALYs. These findings underscore the importance of targeting public health interventions towards regions with high LPA prevalence to mitigate the burden of IHD. Furthermore, our MR analysis provides genetic evidence suggesting that PA may reduce the risk of MI, although significant heterogeneity in the MR results highlights the need for further validation with larger sample sizes. Overall, our study highlights the critical role of PA in reducing the global burden of diseases and improving cardiovascular health, emphasizing the necessity for global efforts to promote active lifestyles.

In conclusion, although our MR study provides interesting insights into the potential role of PA in reducing the risk of MI, the results are influenced by the inherent limitations of the MR approach. Therefore, we can only interpret the findings as hypothetical inferences. Future research should aim to address these limitations by using larger sample sizes, more robust genetic instruments, and a combination of MR methods to enhance the reliability of causal inferences. Additionally, clinical trials and other experimental designs also offer complementary evidence to further elucidate the relationship between PA and MI.

Our work offers valuable insights into the global burden of IHD attributable to LPA and the potential relationship between PA and MI. However, it is important to recognize that both the methodology and findings are subject to certain limitations. Firstly, the definition of PA in our study is based on a broad range of activities reported in the past four weeks, including swimming,

cycling, keep fit, and bowling. Although this approach captures a variety of activities, it may not precisely reflect the specific nature and intensity of aerobic exercise, thereby potentially affecting the precision of our hypothetical inferences. Secondly, the heterogeneity observed in the MR analysis suggests variability in estimates across different genetic instrumental variables, which may be related to differences in the strength of these instruments or potential unmeasured confounders. Thirdly, while the MR-Egger intercept analysis did not reveal significant directional pleiotropy, the limited number of instrumental variables constrains the statistical power of this test, making it difficult to entirely rule out the potential impact of pleiotropy on our estimates. Fourthly, the linear regression model used to estimate the EAPC in the GBD study assumes a constant rate of change over time, which may not fully capture the complexities of disease burden dynamics. Lastly, although the data sources and statistical models used in the GBD study have undergone rigorous validation, residual confounding factors may still exist, which could affect the accuracy and reliability of our results. Given these limitations, future research should consider increasing the number of genetic instrumental variables, employing more robust statistical methods, and exploring experimental designs.

Conclusion

Since 1990, the ASDR and disability-adjusted life years rate for IHD attributable to LPA have shown an increasing trend, presenting substantial public health challenges globally. Our MR analysis hypothesizes that PA is associated with a reduced risk of MI. However, given the significant heterogeneity observed in the analysis, these findings should be considered suggestive rather than definitive evidence of a definite relationship. In conclusion, the increasing global trend of IHD attributed to LPA underscores the importance of developing effective public health policies to promote exercise, which is of great significance in preventing diseases and enhancing the health of the global population. As a global non-pharmacological intervention, PA plays a critical role in increasing health awareness and improving clinical prognosis in patients with MI. Through effective public health policy promotion, PA not only improves cardiac function in patients but also serves as a powerful preventive measure against MI, thereby promoting cardiovascular health globally.

Abbreviations

IHD	Ischemic heart disease
MI	Myocardial infarction
LPA	Low physical activity
PA	Physical activity
RCT	Randomized controlled trial
MR	Mendelian randomization
SNPs	Single nucleotide polymorphisms

IVs	Instrumental variables
GBD	Global Burden of Disease
DALYs	Disability-adjusted life years
SDI	Socio-demographic index
UI	Uncertainty interval
ASDR	Age-standardized death rate
EAPC	Estimated annual percentage change
IVW	Inverse variance weighted
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12872-025-05453-6>.

Supplementary material 1.

Supplementary material 2.

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Author's contributions

****Conception and Design:** ** Yikang He. ****Data curation:** ** Xianghu Zhao. ****Formal analysis:** ** Wenyuan Xu. ****Funding acquisition:** ** Yikang He. ****Investigation:** ** Yujie Guo. ****Software:** ** Lan Lei, Changli Cheng. ****Writing – original draft:** ** Xianghu Zhao, Wenyuan Xu. ****Writing–review & editing:** ** Xianghu Zhao, Yikang He, Yujie Guo, Meiqi Zhou.

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Data availability

Corresponding authors can be contacted to request access to the datasets used or analyzed in this study.

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this study as it utilized deidentified and aggregated data from the Global Burden of Disease (GBD) 2021 study and publicly available GWAS databases.

Consent to publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Graduate School, Anhui University of Chinese Medicine, Hefei, Anhui, China

²Department of Rehabilitation Medicine, Zhongda Hospital, Southeast University, Nanjing, Jiangsu, China

³College of Sports Medicine, Wuhan Sports University, Wuhan, Hubei, China

⁴Department of Rehabilitation Medicine, the Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

⁵Department of Rehabilitation Medicine, Nanjing Pukou District Hospital of Traditional Chinese Medicine, Nanjing, China

⁶Department of Rehabilitation Medicine, Children's Hospital of Nanjing Medical University, Nanjing, China

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