

Association of Physical Activity with Asthma and Chronic Obstructive Pulmonary Disease and Mediation of Frailty: Mendelian Randomization Analyses

Nanxin Chen¹, Xuejie Si², Jun Wang², Wenjing Chen²

¹First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, 250014, People's Republic of China;

²Department of Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, 250001, People's Republic of China

Correspondence: Wenjing Chen, Department of Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, 250000, People's Republic of China, Email cl3969155126@163.com

Background: The existence of an association between physical activity (PA) and asthma and chronic obstructive pulmonary disease (COPD) has been confirmed in observational studies. Therefore, it is necessary to reveal whether there is a risk-effect relationship between physical activity and asthma and COPD through Mendelian randomization (MR) analysis.

Materials and Methods: Univariate Mendelian randomization (UVMR) analyses were performed to examine the associations between moderate to vigorous physical activity (MVPA), vigorous physical activity (VPA), accelerometer-assessed physical activity (AA), and strenuous exercise or other exercise (SSOE) with asthma and COPD. The methods of analysis were dominated by Inverse Variance-Weighted (IVW), Weighted median (WM), and MR-Egger methods. In addition, multivariate Mendelian randomization (MVMR) analyses were performed to correct the effects of four types of physical activity on asthma and COPD. Finally, potential mediating effect relationships were identified through mediation analyses.

Results: The results of Univariate Mendelian randomization analysis showed that SSOE could reduce the risk of asthma and COPD (asthma: $OR=0.15$, 95% $CI=0.04-0.58$, $P=0.006$; COPD: $OR=0.05$, 95% $CI=0.01-0.33$, $P=0.002$). The results of the Multivariate Mendelian randomization analysis showed that SSOE was still able to reduce the risk of asthma and COPD after adjusting for the effects of different types of physical activity (asthma: 95% $CI=-2.77--0.31$, $P=0.014$; COPD: 95% $CI=-4.00--0.50$, $P=0.012$). Mediation analyses showed that frailty intervened in the causal relationship between physical activity and asthma and chronic obstructive pulmonary disease.

Conclusion: SSOE is a protective factor for asthma and COPD in the European population, while frailty plays a mediating role.

Keywords: asthma, chronic obstructive pulmonary disease, multivariate Mendelian randomization, mediation analyses, physical activity, univariate Mendelian randomization

Introduction

The 1997 and 2007 guidelines for the management of asthma suggest that asthma is a chronic inflammatory disease of the respiratory tract, while the inflammatory response recurs in a combination of cells, including mast cells, eosinophils, and T lymphocytes.^{1,2} Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease, mainly consisting of chronic bronchitis and emphysema, in which persistent airflow limitation and dyspnea are seen in clinical.³ According to studies, COPD has become the leading cause of death in the world today, second only to cardiovascular disease and stroke, placing a heavy burden on the healthcare system and society.⁴

It is well known that physical activity forms an important part of health, it promotes the body's metabolism and appears in numerous medical prescriptions. At the same time, there are numerous studies showing the anti-inflammatory

effects of physical activity. Some studies have pointed out that during physical activity, interleukin 6 can be produced by contracting muscles and released into the circulation in response to energy demands.⁵ Therefore, they believe that interleukin 6 plays a major role in the physical activity anti-inflammatory process.⁵ In another experiment with obese mice that lacked exercise, they found that inflammatory macrophages in the mice produced inflammatory cytokines and caused cell necrosis after infiltrating adipose tissue.^{6,7} Follow-up results after the exercise intervention showed that these pathologic changes could be prevented.^{6,7} Interestingly, in addition to the well-known aerobic exercise, resistance exercise also reduces the inflammatory response, which is accomplished by lowering C-reactive protein and increasing adiponectin levels.⁸

It is worth noting that the relationship between physical activity and asthma and COPD has also received a lot of attention because of the inflammatory response. This is because asthma and COPD, as chronic respiratory diseases in which there is an inflammatory response, means that it is logical to reduce the level of inflammation in asthma and COPD through physical activity. There was a randomized controlled trial of the effect of exercise training on the frequency of acute exacerbations in patients with COPD conducted by researchers, and their results support the conclusion that an exercise program reduces the number of acute exacerbations in COPD.⁹ This seems to imply that the intervention of exercise training is one of the protective factors in reducing the number of acute COPD episodes.⁹ There is also a large body of literature that suggests that normal physical activity is one way to control asthma and that the benefits of being physically active during a non-acute asthma attack far outweigh the risks for asthmatics.¹⁰⁻¹²

It is alarming that asthma and chronic obstructive pulmonary disease (COPD) have become globally prevalent chronic respiratory diseases, and their incidence has risen rapidly over the past few decades, posing a huge challenge to clinicians and seriously affecting people's physical and mental health.^{4,13,14} Therefore, it is of great interest to explore whether there is a causal relationship between physical activity and the genetics of asthma and COPD, and to clarify health guidelines. In addition, frailty is defined as a state of clinical vulnerability resulting from increasing age and declining function and reserve of physiological systems, and the frailty index is commonly utilized to assess the state of frailty of the body.^{15,16} It has been suggested that frailty is strongly associated with an increased risk of asthma and COPD, and can serve as a marker of adverse health outcomes.¹⁷⁻¹⁹ Therefore, it is of interest to explore whether the frailty index is a potential mediating mechanism through mediation analysis.

Materials and Methods

Ethical approval was not required for this study, because the genome-wide association studies (GWAS) data used are publicly available.

Study Design and Data Source

The Mendelian randomization (MR) method is a research method for inferring causality that has been recently developed by introducing the tools and theories of genetics. It is worth mentioning that the process of genetic variation is completely randomized during pregnancy, which is why the MR method is able to simulate a randomized controlled trial.²⁰ In addition, MR analyses need to satisfy three major assumptions as a basis, and then IVs that can substitute for SNPs are utilized to assess the relationship between exposure and outcome potential causal effects, an approach that takes advantage of the principle that genes are not susceptible to external confounders and reverse causation.²¹⁻²³ Therefore, we designed Univariate Mendelian randomization (UVMR) analyses to reveal whether there is a risk-effect relationship between physical activity and asthma and COPD based on the fulfillment of three main hypotheses: (1) the correlation hypothesis, in which IVs are strongly associated with exposure factors; (2) the independence hypothesis, in which IVs are not associated with confounders; and (3) the exclusivity hypothesis, in which IVs can only influence outcome factors through exposure factors. The design of this UVMR study was completed under the guidance of the MR study guidelines, and an overview of the study design can be seen in [Figure 1](#).²⁴ Multivariate Mendelian randomization (MVMR) study design was similar to the UVMR, details of which can be seen in [Figure 2](#). In addition, potential mediators were explored through mediation analyses, the research design of which can be seen in [Figure 3](#).

We studied four types of physical activity: (1) self-reported moderate to vigorous physical activity (MVPA); (2) self-reported vigorous physical activity (VPA); (3) self-reported strenuous exercise or other exercise (SSOE); and

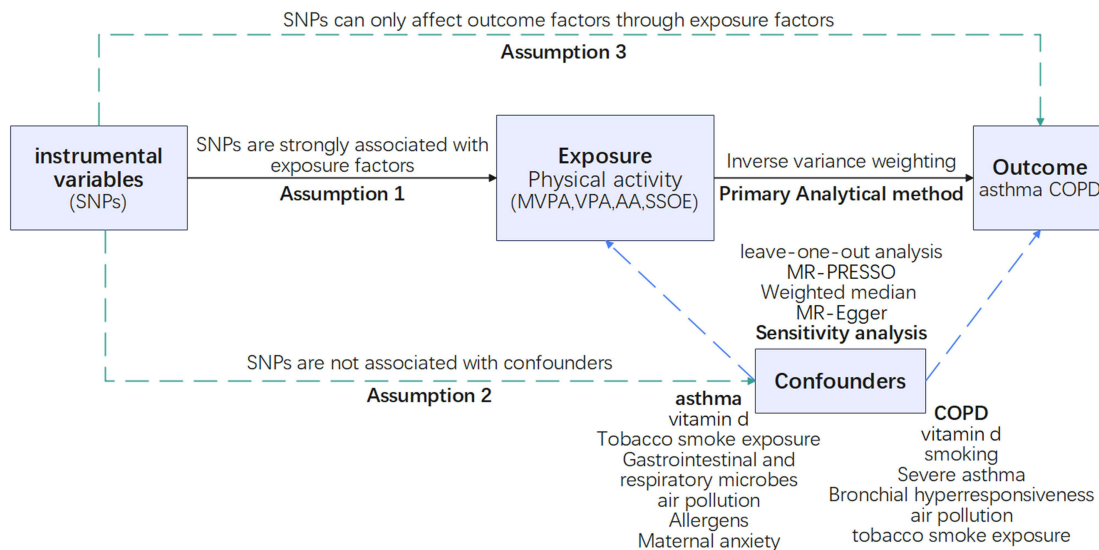


Figure 1 Overview of two-sample Mendelian randomization study design. Instrumental variables: Used to infer exposure and outcome causation; Exposure: exposure factors, including the four types of physical activity: MVPA (self-reported moderate to vigorous physical activity), VPA (self-reported vigorous physical activity), AA (accelerometer-assessed physical activity), SSOE (self-reported strenuous exercise or other exercise); Outcome: Outcome factors, including asthma and COPD (chronic obstructive pulmonary disease); Assumptions 1, 2 and 3: Basic principles of Mendelian randomization analysis; Primary Analytical method: The most important analytical method for assessing the causality of exposure outcomes, the inverse variance weighting method; Sensitivity analysis: This includes leave-one-out analysis, MR-PRESSO test, Weighted median method and MR-Egger method. Confounders, asthma and COPD: Confounders associated with asthma and COPD.

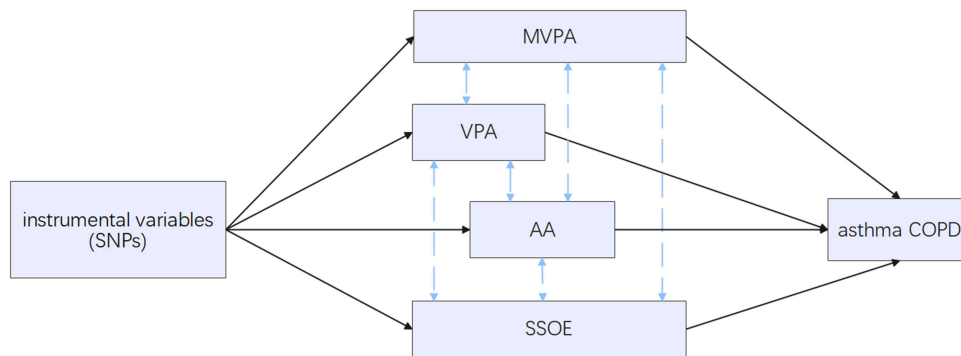


Figure 2 Overview of Multivariate Mendelian randomization study design.

Abbreviations: MVPA, Self-reported moderate to vigorous physical activity; VPA, Self-reported vigorous physical activity; AA, Accelerometer-assessed physical activity; SSOE, Self-reported strenuous exercise or other exercise; COPD, Chronic obstructive pulmonary disease; SNPs, Instrumental variables.

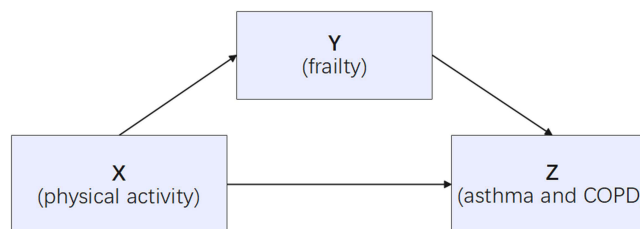


Figure 3 Overview of mediated Mendelian randomization study design..

Abbreviation: COPD, Chronic obstructive pulmonary disease.

(4) accelerometer-assessed physical activity(AA), for which GWAS data were obtained from a published article in the UK Biobank.²⁵ In this case, self-reported physical activity levels based on a touch-screen questionnaire were measured similarly to the International Physical Activity Questionnaire (IPAQ),²⁶ and physical activity based on accelerometer assessment was measured by wearing an Axirate AX3 wrist-mounted accelerometer.²⁷ The GWAS

data for asthma and COPD were obtained from the IEU OpenGWAS project, available at <https://gwas.mrcieu.ac.uk/>, and detailed information is provided in [Supplementary Table 1](#).

Selection of Instrumental Variables

In UVMR analyses, the selection of IVs is based on three conditions: (1) IVs are strongly correlated with exposure factors (genome-wide threshold of significant level is $P < 5 \times 10^{-8}$); (2) chain imbalance is excluded ($r^2 = 0.001$, window size = 10,000 kb); and (3) palindromic structures are excluded. Meanwhile, Also, the selection of IVs in the MVMR analysis is similar and all meaningful IVs are pooled together.

Vitamin D, Tobacco Smoke Exposure, Gastrointestinal and Respiratory Microorganisms, Air Pollution, Allergens, and Maternal Anxiety Included as Confounding Factors for Asthma.²⁸ Vitamin D, Smoking, Severe Asthma, Bronchial Hyperresponsiveness, Air Pollution, and Tobacco Smoke Exposure Included as Confounders of COPD.^{29,30} To ensure hypotheses 2 and 3, IVs associated with confounders and outcomes were excluded by searching the PhenoScanner V2 database ($P < 5 \times 10^{-8}$). In addition, the F-statistic was calculated by the formula β^2/se^2 to assess the strength of individual SNPs, and F-statistics < 10 were considered weak IVs, and it was also eliminated.^{31,32} Details of the IVs can be found in [Supplementary Table 2](#).

Statistical and Sensitivity Analyses

When all SNPs are valid, IVW models provide the most effective results for the relationship between the risk effect of exposure on outcome.³³ Therefore, the current study used IVW as the primary method to assess the risk relationship between physical activity and asthma and COPD. It is worth mentioning that if there was heterogeneity in the IVW model, both a p-value < 0.05 for the Cochran's Q test, we chose the random-effects IVW model for our analyses, otherwise we chose the fixed-effects IVW model.³⁴ At the same time, we compared the results of IVW, WM, and MR-Egger methods, and the results are more convincing if the three models have the same direction of effect sizes. Collinearity analyses were first performed before MVMR analyses to adjust for the type of physical activity incorporated into the exposure.

In the present study, the presence of heterogeneity depended on the p-value of Cochran's Q test, with a p-value > 0.05 indicating the absence of heterogeneity. To check for horizontal pleiotropy, we chose the MR-Egger intercept test, which has an intercept term that responds to horizontal pleiotropy effects.³⁵ If the MR-Egger intercept p-value is > 0.05 , then there is no horizontal multiplicity. Also, when the intercept term is equal to zero, the MR-Egger method estimates will be equal to the IVW estimates.³⁵ Of interest, we performed the MR-PRESSO test, which tests for horizontal pleiotropy while excluding potential outliers.³⁶ Finally, the results of the statistical analyses were analyzed by the leave-one-out method to test their stability. All analyses were performed using the "TwoSampleMR" package (version 0.5.7), the "MR-PRESSO" package (version 1.0), and the "Mendelian Randomization" package (version 0.9.0) in R software (version 4.3.2).

Results

Instrumental Variable

[Supplementary Table 2](#) describes the details of the instrumental variable selection. For UVMR analysis, 39 SNPs (MVPA-18, VPA-6, AA-6, SSOE-9) were finally selected for MR analysis instead of IVs, details can be found in [Supplementary Table 2A–D](#). In the MVMR analysis, 21 SNPs were eventually pooled for MR analysis, details can be found in [Supplementary Table 2E](#). When mediation analyses were conducted, 12 SNPs in the SSOE-frailty index model met the screening conditions; 9 SNPs in the frailty index-asthma model met the screening conditions; and 10 SNPs were screened to meet the instrumental variable conditions in the frailty index-COPD model, details can be found in [Supplementary Table 2F–H](#).

UVMR

The results of UVMR analyses showed that SSOE was a protective factor for asthma and COPD, and was able to reduce the risk of asthma and COPD (asthma: $OR = 0.15, 95\% CI = 0.04–0.58, P = 0.006$; COPD: $OR = 0.05, 95\% CI = 0.01–0.33,$

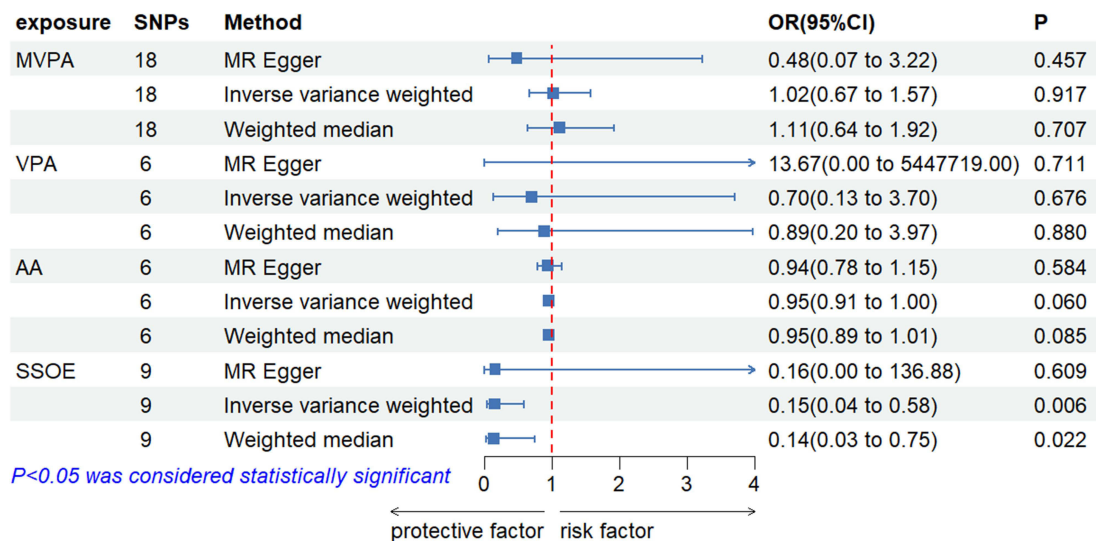


Figure 4 Results of univariate Mendelian randomization analysis for asthma. Exposure: exposure factors, including MVPA (self-reported moderate to vigorous physical activity), VPA (self-reported vigorous physical activity), AA (accelerometer-assessed physical activity), SSOE (self-reported strenuous exercise or other exercise); SNPs: Number of instrumental variables; Method: Methods of analysis; OR(95% CI): odds ratio and 95% confidence interval; (P) statistical p-value; *P*<0.05 was considered statistically significant: Statistically significant thresholds.

P=0.002). There was no risk-effect relationship between MVPA, VPA, and AA and asthma. There was no risk-effect relationship between VPA and AA and COPD. Details can be found in Figures 4 and 5.

The results of the sensitivity analysis of the univariate model for asthma can be seen in Supplementary Table 3. No evidence of heterogeneity in the IVW model was found in the MR analyses of MVPA, AA, and SSOE, except in the MR analyses of VPA (*P*-IVW = 0.048; *P*-MR-Egger = 0.031). Meanwhile, the MR-Egger method test was used to get the conclusion that there is no horizontal multiplicity in this study. In addition, the absence of horizontal multiplicity as well as the exclusion of three outliers (MVPA: rs429358; AA: rs11012732, rs59499656) in the current study was again demonstrated by the MR-PRESSO test. The results of the leave-one-out method of analysis proved that the protective effect of SSOE on asthma was stable, details of which can be seen in Supplementary Figure 1A. The scatter plot can be seen in the Supplementary Figure 2A.

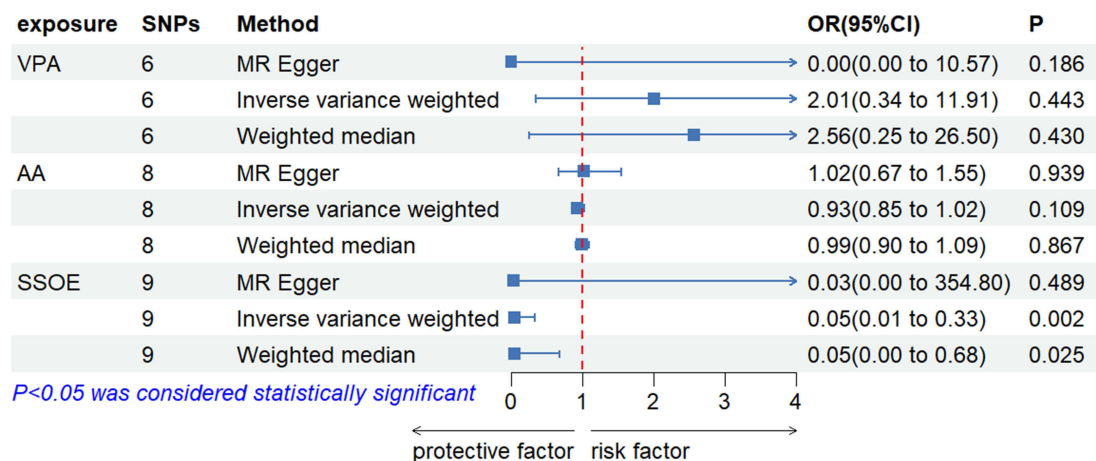


Figure 5 Results of univariate Mendelian randomization analysis for COPD (Chronic obstructive pulmonary disease). Exposure: exposure factors, including VPA (self-reported vigorous physical activity), AA (accelerometer-assessed physical activity), SSOE (self-reported strenuous exercise or other exercise); SNPs: Number of instrumental variables; Method: Methods of analysis; OR(95% CI): odds ratio and 95% confidence interval; (P) statistical p-value; *P*<0.05 was considered statistically significant: Statistically significant thresholds.

Table 1 Results of a Multivariate Mendelian Randomization Analysis of Asthma

PA	Method	SNPs	Beta	95% CI	P
AA	Multivariable IVW	21	-0.016	-0.070, 0.037	0.548
SSOE	Multivariable IVW	21	-1.540	-2.770, -0.311	0.014
AA	Multivariable MR-Egger	21	-0.062	-0.140, 0.015	0.115
SSOE	Multivariable MR-Egger	21	-2.354	-3.921, -0.788	0.003

Abbreviations: PA, physical activity; AA, accelerometer-assessed physical activity; SSOE, self-reported strenuous exercise or other exercise; SNPs, single-nucleotide polymorphisms; IVW, Inverse Variance-Weighted.

Table 2 Results of a Multivariate Mendelian Randomization Analysis of COPD

PA	Method	SNPs	Beta	95% CI	P
AA	Multivariable IVW	21	-0.036	-0.113, 0.040	0.350
SSOE	Multivariable IVW	21	-2.247	-3.998, -0.497	0.012
AA	Multivariable MR-Egger	21	-0.095	-0.207, 0.017	0.095
SSOE	Multivariable MR-Egger	21	-3.290	-5.550, -1.031	0.004

Abbreviations: PA, physical activity; AA, accelerometer-assessed physical activity; SSOE, self-reported strenuous exercise or other exercise; SNPs, single-nucleotide polymorphisms; IVW, Inverse Variance-Weighted.

The results of the sensitivity analysis of the univariate model for COPD can be seen in [Supplementary Table 3](#). Of concern, there was horizontal pleiotropy in the MR analysis of MVPA (P-Intercept=0.048), thus excluding its results from the scope of the current COPD study. In the MR analyses of VPA, AA, and SSOE, no evidence of heterogeneity and the presence of horizontal pleiotropy was found. In addition, the results of the MR-PRESSO test again demonstrated the absence of horizontal pleiotropy as well as the absence of outliers for the three physical activities (VPA, AA, and SSOE) in the COPD study. The results of the leave-one-out method of analysis proved that the protective effect of SSOE on COPD was stable, details of which can be seen in [Supplementary Figure 1B](#). The scatter plot can be seen in the [Supplementary Figure 2B](#).

MVMR

The collinearity analysis performed before the MVMR analysis only supported the inclusion of AA and SSOE in the exposure. The results of the subsequent MVMR analyses continued to show that SSOE is a protective factor for asthma and COPD and reduces the risk of asthma and COPD, details of which can be found in [Tables 1](#) and [2](#), respectively. No evidence was found to support the existence of heterogeneity and horizontal pleiotropy in the sensitivity analyses conducted for asthma and COPD, details of which can be found in [Supplementary Table 4](#).

Mediation Analyses

The results of the mediation analysis can be seen in [Figure 6](#), which suggests that one of the reasons why SSOE can be a protective factor against asthma and COPD is that SSOE can attenuate the symptomatic manifestations of asthma and COPD by lowering frailty. None of the sensitivity analyses found evidence of heterogeneity or horizontal pleiotropy, as shown in [Supplementary Table 5](#). The MR-PRESSO test showed that no outliers were seen in the SSOE-frailty model, the frailty-asthma model, and the frailty-COPD model and again demonstrated that there was no horizontal pleiotropy. It is also worth mentioning that in the results of the first statistical analysis of the SSOE-

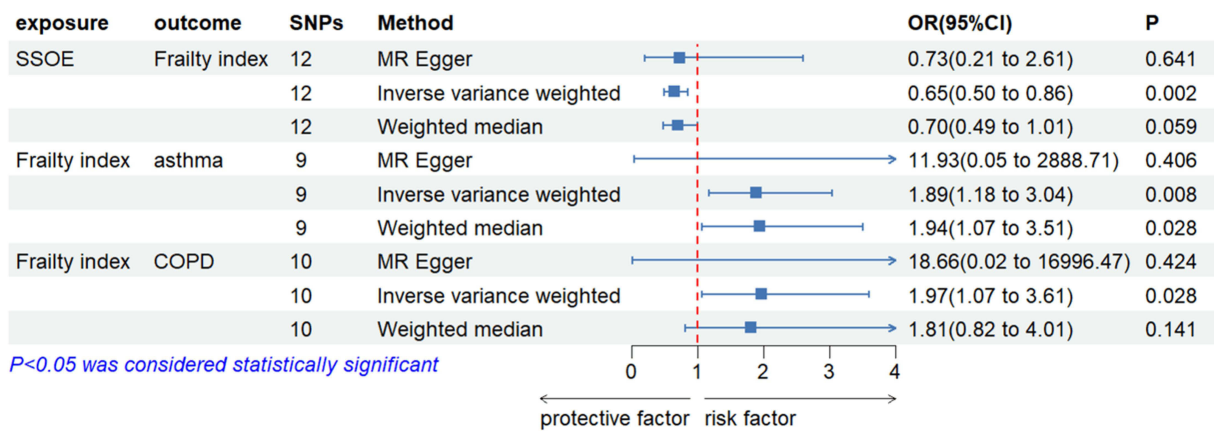


Figure 6 Mediated Mendelian randomization analysis results. Exposure: Exposure factors, including SSOE (self-reported strenuous exercise or other exercise), Frailty index; Outcome: outcome factors, including asthma, COPD (Chronic obstructive pulmonary disease), and frailty index; SNPs: Number of instrumental variables; Method: Methods of analysis; OR(95% CI): odds ratio and 95% confidence interval; (P) statistical p-value; *P*<0.05 was considered statistically significant: Statistically significant thresholds.

frailty model, IVW, MR-Egger, and WM did not have the same direction of effect, while the results of the leave-one-out analysis indicated that there was a change in the driving of the causal effector by the SNP (rs1200154). Therefore, it was removed and re-run for statistical and sensitivity analyses, with a comparison of the scatter plots before and after removal and the results of the leave-one-out method can be seen in [Figures 7 and 8](#). The mediating effect of the asthma model ($\beta_{XY} \cdot \beta_{YZ} = -0.270$, the total effect ($\beta_{XZ} = -1.867$, and the proportion of mediating effect = 14.46%. The mediating effect of the COPD model ($\beta_{XY} \cdot \beta_{YZ} = -0.287$, the total effect ($\beta_{XZ} = -3.055$, and the proportion of intermediaries = 9.39%. The results of the leave-one-out method for frailty-asthma and frailty-COPD can be seen in the [Supplementary Figure 3A and B](#); Scatter plots of frailty-asthma and frailty-COPD can be seen in the [Supplementary Figure 4A and B](#).

Discussion

Our study is based on MR analyses done in European populations and aims to explore whether there is a risk-effect relationship between physical activity and asthma and COPD. The results of the UVMR study support the ability of SSOE to reduce the risk of asthma and COPD. Meanwhile, the MVMR findings equally support the ability of SSOE to reduce the risk of asthma and COPD after adjusting for covariates and the effect of physical activity. Finally, mediation

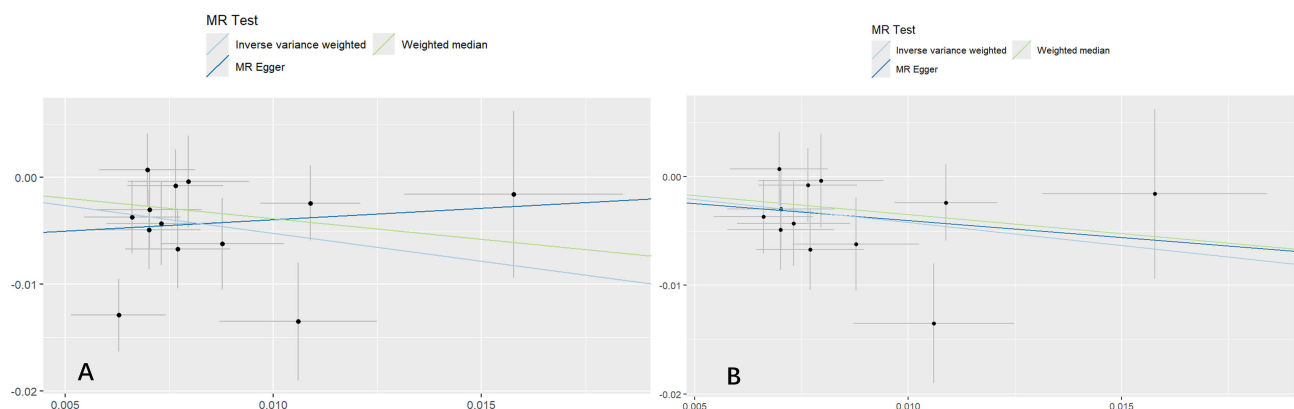


Figure 7 Scatterplot Comparison. (A) Scatterplot results before removing SNP in the SSOE-frailty model; (B) Scatterplot results after removing SNP in the SSOE-frailty mode.

Abbreviations: SSOE, self-reported strenuous exercise or other exercise; SNP, instrumental variable.

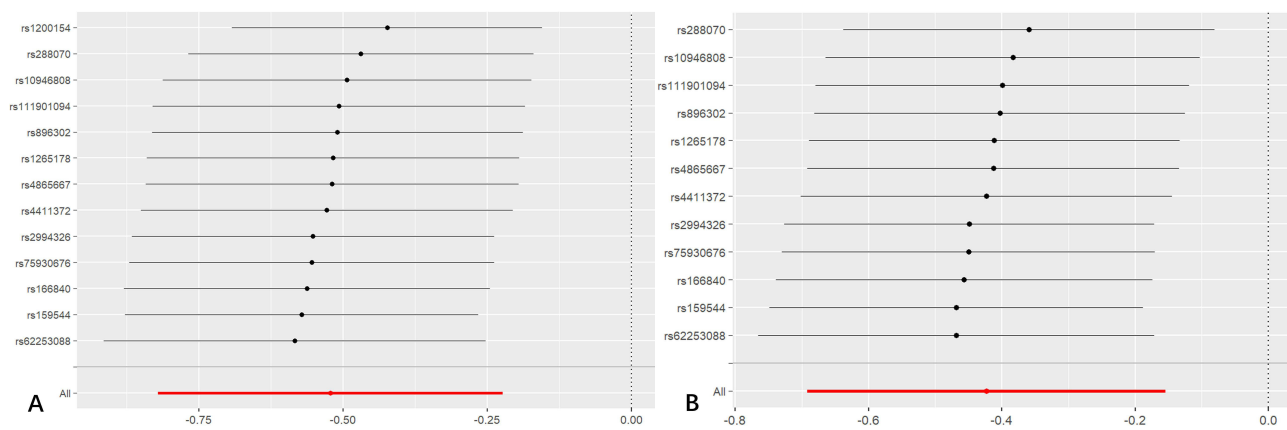


Figure 8 Comparison of the results of the leave-one-out method. **(A)** Results of the leave-one-out method before removing SNP in the SSOE-frailty model; **(B)** Results of the leave-one-out method after removing SNP in the SSOE-frailty model.

Abbreviations: SSOE, self-reported strenuous exercise or other exercise; SNP, instrumental variable.

analyses then suggest that one of the mechanisms by which SSOE mitigates the risk of COPD and asthma is by improving frailty.

Frailty is a syndrome that worsens with age and is intrinsically caused by a decline in the functioning of physiological systems.¹⁵ Prolonged sedentary behavior is a risk factor for frailty, and physical activity plays an important role in improving frailty levels.^{37,38} What is known is that physical activity is one of the healthy habits that boost the body's metabolism. Physical activity can improve frailty levels through mechanisms such as reducing oxidative damage, increasing autophagy, and improving mitochondrial function, which is considered to be one of the main ways to counteract physical frailty.³⁹ There was a randomized clinical trial study that analyzed 1,623 older adults at risk for mobility impairments, and they concluded that a good physical activity program improves frailty.⁴⁰ Another meta-analysis indicated that a low risk of frailty was associated with high levels of physical activity, which seems to coincide with the ability of SSOE to reduce the risk of frailty in the mediation analysis.⁴¹ Obviously, physical activity is beneficial in the improvement of a debilitated condition. Asthma and COPD, as common chronic respiratory diseases, are also inextricably linked to frailty.⁴² There was a cohort study that pointed out that people with asthma are at increased risk of frailty, which means that it is more difficult for people with asthma to achieve health assurance.¹⁸ At the same time, frailty has emerged as an independent risk factor for COPD progression, which means that the importance of frailty indices in COPD patients should be recognized.⁴³

In addition, there may be some positive effects of physical activity on asthma and COPD in the long term. Asthma is known to be an inflammatory disease, so it is logical to treat it with anti-inflammatory therapy to improve asthma symptoms. A randomized controlled trial of an aerobic exercise intervention was done on 58 patients with asthma, and the results of the study found that bronchial hyperresponsiveness and a decrease in serum pro-inflammatory cytokines were strongly associated with aerobic exercise, and thus they support the use of physical activity as an adjunctive therapy.⁴⁴ COPD is an irreversible, slow-progressing lung disease that occurs by unclear mechanisms but generally involves inflammatory and oxidative stress responses.⁴⁵ A study has shown that long-term regular physical activity reduces Th1 cells but has no effect on Th2 cells.⁴⁶ This seems to imply that there is an imbalance in the ratio of Th1 cells to Th2 cells, possibly reducing the inflammatory response. At the same time, other studies have shown that physical activity elevates adrenaline, which in turn reduces Th1 cell expression through both inhibition of antigen-presenting cells and direct T-cell receptor blockade, which also appears to reduce the inflammatory response.⁴⁷

It is worth noting that in clinical practice, numerous asthmatics have self-reported exacerbation or triggering of asthma symptoms after exercise. This is because of the large loss of water in the airways during exercise due to the increase in respiratory rate and depth, which creates a highly osmotic environment to activate various cellular mechanisms capable of releasing mediators, leading to the contraction of the smooth muscles of the airways and the onset of asthma symptoms.⁴⁸ But for a long time, physical activity has also been gaining ground as a logical non-pharmacological

treatment method.⁴⁹ At the same time, there are some negative or inconclusive reports about whether people with asthma should be physically active or not.^{50–52} In addition, physical activity is often stigmatized in the asthmatic population, which leads asthmatics to fear engaging in physical activity and self-abandonment of exercise opportunities, thus making physical activity an obstacle in the path of patient care.⁵³ In fact, the ability of asthmatics to be physically active is highly correlated with their mental fitness and activity habits, not with their respiratory response.^{54,55} Therefore, it is necessary to actively guide asthmatics to develop a correct understanding of physical activity. It is well known that one of the typical symptoms of COPD patients is dyspnea. One study pointed out that severe dyspnea is associated with reduced levels of physical activity.⁵⁶ Patients are afraid to engage in physical activity and will try to alleviate their breathing difficulties by limiting their physical activity, which will undoubtedly lead to a vicious cycle.⁵⁶ At the same time, because patients with chronic diseases experience anxiety and depression 2–3 times more often than patients with non-chronic diseases, the psychological factor again casts a cloud over the patient's ability to perform exercise.⁵⁷ In addition, the fact that some patients may be admitted to the hospital with acute exacerbations due to following the advice of non-healthcare professionals or because of their own inappropriate exercise, and then become skeptical of physical exercise, should not be ignored in the clinical setting.

We believe that the above may be related to the type of exercise the patient participates in, the intensity of the exercise, the frequency of the exercise, the environment in which the exercise is performed, and even the age group of the patient.^{58–60} It is worth mentioning that the results of the current study support the ability of physical activity to reduce the risk of disease in asthma and COPD, which proves that physical activity as a tool is not problematic, and can be helpful in regaining confidence in exercising for people with asthma and COPD. Therefore, in the chronic disease management of asthma and COPD, healthcare professionals should recommend and actively guide patients to engage in appropriate physical exercise. In future studies specific to physical activity in COPD and asthma populations, attention to the variability associated with different exercise modalities, exercise intensities, exercise frequencies, exercise environments, and patient age groups seems warranted. In addition, exercise plans that are applicable to the majorities of the population may not be applicable to the asthma and COPD populations, considering that the underlying physical condition of the asthma and COPD populations is weaker than that of the normal population. Therefore, further research is needed on exercise plans that are applicable to asthma and COPD populations.

The current study is an MR study based on the publicly available GWAS database (IEU OpenGWAS) to analyze whether there is a genetic risk relationship between physical activity and asthma and COPD. It must be recognized that there are limitations to our study. First, we used the publicly available GWAS database for our study and analysis, and we did not have access to comprehensive demographic information on factors such as age, educational attainment, and household income to poverty ratios, so we were unable to stratify the data or adjust for covariates. Second, our GWAS data were derived from European populations, and the findings cannot be generalized to other populations outside of Europe. Finally, it has been suggested that the heritability of physical activity decreases with age, which may bias our findings somewhat.⁶¹

Conclusion

In conclusion, our findings suggest that SSOE reduces the risk of asthma and COPD, which clarifies that a certain level of intensity of physical activity can bring new benefits in the treatment of asthma and COPD, in which frailty plays a mediating role. Therefore, patients with asthma and COPD need to regain their confidence in exercising, and healthcare professionals need to actively guide their patients while giving physical activity a proper name.

Data Sharing Statement

The statistics for this study can all be found in the IEU OpenGWAS project(<https://gwas.mrcieu.ac.uk/>).

Ethics Approval and Consent to Participate

The study was reviewed by the Ethics Committee of the Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine. At the same time, this study did not require the requirement of informed consent because the data sources were all publicly available.

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Disclosure

The authors declare that there is no conflict of interest in this study.

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