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# Causal associations of self-reported walking pace with respiratory diseases

## A Mendelian randomization analysis

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**Abstract**

Although studies have indicated causality between brisk walking and various diseases, the relationships between walking pace and respiratory diseases lack thorough investigation. The underlying relationships between walking pace and various respiratory diseases were examined through univariable Mendelian randomization (MR) analyses. Furthermore, we performed multivariable MR analyses to observe whether relationships between walking pace and respiratory diseases change after adjustment of body mass index (BMI). The genome-wide association study data of self-reported walking pace, BMI, and 42 respiratory diseases were retrieved from publicly available datasets. We employed the inverse-variance weighted, weighted median, and MR-Egger methods for MR analysis. Using the inverse-variance weighted method in univariable MR, we identified statistically significant negative causal associations between self-reported walking pace and 4 respiratory traits, including chronic lower respiratory diseases (odds ratio [OR], 0.27 [95% confidence interval [CI], 0.18–0.41]), asthma (OR, 0.23 [95% CI, 0.14–0.38]), chronic obstructive pulmonary disease (OR, 0.15 [95% CI, 0.08–0.30]), and diseases of the respiratory system (OR, 0.54 [95% CI, 0.41–0.70]). Similar results were observed with the MR-Egger and weighted median methods. These associations remained significant, though slightly attenuated, after adjusting for BMI. A brisk walking pace may significantly benefit respiratory health and aid in disease prevention and risk stratification.

**Abbreviations:** BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, FDR = false discovery rate, FEV1 = forced expiratory volume in 1 second, GWAS = genome-wide association study, IV = instrumental variable, IVW = inverse-variance weighted, MR = Mendelian randomization, MVMR = multivariable Mendelian randomization, NO = nitric oxide, OR = odds ratio, SNP = single-nucleotide polymorphism, UVMR = univariable Mendelian randomization.

**Keywords:** FinnGen, Mendelian randomization, respiratory diseases, self-reported walking pace, UK Biobank

## 1. Introduction

Walking is beneficial to practically everyone's physical health because it increases energy expenditure and exercise levels.[1–4] Walking time and steps should be increased, according to public health standards, but walking pace is given less consideration.[5–8] As a crucial measure of total movement efficiency and functional capability, walking pace is a crucial component in the evaluation of locomotion.[9] Several studies have reported the association between walking pace and a variety of diseases.[10–23] For example, maintaining a brisk walking pace can alleviate the susceptibility to various diseases such as atrial fibrillation, stroke, heart failure, cancers, and even all-cause mortality.[5,13,24–26] In addition, there is ample evidence of the association between human breathing and walking.[27–36] Walking pace and chronic obstructive pulmonary disease (COPD) were found to be negatively causally associated in another investigation that used Mendelian randomization (MR).[37] However, contradictory evidence also exists. A 4-week

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exercise program that included faster walking did not enhance cardiopulmonary function in adults with COPD at submaximal exercise intensity.[38]

Given the possible inverse association between walking pace and respiratory conditions, we seek to employ MR to investigate potential causal relationships. MR analysis utilizes genetic data to establish causal relationships, effectively mitigating the impact of confounding factors bias in conventional epidemiological studies. We hypothesized that walking pace might be causally associated with some respiratory diseases. Therefore, we systematically investigated the effect of walking pace on respiratory diseases by univariable MR (UVMR) analyses and multivariable MR (MVMR) analyses, which were adjusted for body mass index (BMI), hoping to provide valuable insights into the preventive measures against respiratory diseases by adopting a healthy walking style.

## 2. Methods

### 2.1. Study design

Within MR, the estimation of the causality between exposure and outcome relies on instrumental variables (IVs), represented by single-nucleotide polymorphisms (SNPs). Summary statistics of IVs were acquired by gathering data from genome-wide association studies (GWASs). First, the effects of exposure (self-reported walking pace) on outcomes (respiratory diseases) were explored through UVMR analyses. Second, we accounted for BMI as a confounding variable based on prior reports indicating its linkage to walking pace.[39] We calculated the causal associations of BMI with walking pace and respiratory diseases and conducted MVMR analyses to observe whether the relationship between walking pace and respiratory diseases changes after adjusting for BMI. Figure 1, Supplemental Digital Content, http://links.lww.com/MD/O467, showcases a flowchart visually outlining the study design and data collection process.

### 2.2. Data sources

Following the protocol of a 2-sample MR study, data for the exposure variable and outcome variable were obtained from different sources. With a participant pool of half a million individuals, the UK Biobank provides a wealth of health records for scientific exploration and analysis. We obtained the GWAS data of self-reported walking pace from the UK Biobank,[5] incorporating 450,967 participants who indicated their walking pace as slow, steady, and fast. The dataset for BMI was acquired from a large-scale GWAS.[40]

The GWASs focusing on respiratory diseases were selected from an extensive Finnish project known as FinnGen,[41] which has been widely utilized in MR studies.[42–46] We eliminated several phenotypes from consideration: nonrespiratory-related phenotypes, comparable phenotypes with a specific population or smaller number of participants, and phenotypes with a wide definition that cannot be classified as a particular disease. As a consequence, 42 respiratory diseases were kept as outcomes. In Table 1, Supplemental Digital Content, http://links.lww.com/MD/O467, comprehensive details on selected GWASs were displayed.

### 2.3. Statistical method

IVs for the MR analysis were chosen based on following standards as previously described[47–49]: at the genome level, IVs and exposure were strongly associated ($P < 5 \times 10^{-8}$); by performing the clumping step to remove linkage disequilibrium, independent IVs were selected within a genomic span of 10 Mb and an $R^2$ value <0.001; a minimum minor allele frequency of 0.01 is expected; and SNPs displaying palindromic patterns and an allele frequency in the intermediate range were excluded due to the uncertainty in determining the effect allele at these loci.[50] An F-statistic exceeding 10 signifies the robustness of the selected IVs.[51]

This MR study used 3 statistical methods, consistent with previous publications.[52,53] The primary MR analysis was conducted using the inverse-variance weighted (IVW) approach, while MR-Egger and weighted median methods were applied as supplementary techniques. The IVW method is based on regressing the association estimates of SNPs with the outcome against their association estimates with exposure.[54,55] In this approach, the regression line is restricted to intersect at zero.[55,56] The IVW method provides unbiased estimates only if all genetic variants meet the criteria for valid IVs.[57] Conversely, the MR-Egger and weighted median methods are generally more robust in situations where some IVs are invalid.[55] MR-Egger regression yields reliable estimates even when all genetic variants are invalid.[58] In comparison, the weighted median method produces consistent estimates as long as invalid instruments contribute <50% of the total weighting.[59] The MR-Egger method was applied to detect horizontal pleiotropy.[58] Outliers were identified and handled using the MR-PRESSO test. Heterogeneity among IVs was assessed with the Cochrane Q statistic. The robustness of the findings was assessed using the leave-one-out method. The estimation of causality was accomplished by employing odds ratios (OR) and 95% confidence interval (CI). Multiple comparisons were adjusted using a false discovery rate (FDR) level set at 5%. The TwoSampleMR package in R was utilized for the MR analyses.[50]

## 3. Results

In our MR analysis, 58 SNPs were shown to be the IVs for self-reported walking pace, and the F-statistics suggested a strong quality of the selected IVs, as exemplified in Table 2, Supplemental Digital Content, http://links.lww.com/MD/O467.

Four of the 42 respiratory diseases survived the FDR correction, according to the IVW method employed in UVMR, revealing a strong causal relationship with self-reported walking pace, including "chronic lower respiratory diseases" (OR, 0.27 [95% CI, 0.18–0.41]), "asthma" (OR, 0.23 [95% CI, 0.14–0.38]), "COPD" (OR, 0.15 [95% CI, 0.08–0.30]), and "diseases of the respiratory system" (OR, 0.54 [95% CI, 0.41–0.70]; Figs. 1 through 3; Table 3, Supplemental Digital Content, http://links.lww.com/MD/O467). Both the weighted median and MR-Egger strategies produced similar results (Figs. 2 and 3; Table 3, Supplemental Digital Content, http://links.lww.com/MD/O467). In addition, 6 respiratory diseases showed suggestive significant associations with self-reported walking pace ($P < .05$), including "chronic diseases of tonsils and adenoids" (OR, 0.60 [95% CI, 0.40–0.91]), "influenza and pneumonia" (OR, 0.67 [95% CI, 0.48–0.94]), "emphysema" (OR, 0.11 [95% CI, 0.02–0.72]), "all pneumonias" (OR, 0.67 [95% CI, 0.47–0.95]), "peritonsillar abscess" (OR, 0.38 [95% CI, 0.16–0.89]), and "chronic sinusitis" (OR, 0.48 [95% CI, 0.25–0.92]; Figs. 1 and 2). No significant presence of horizontal pleiotropy was observed, and no outlier IV was identified in MR-PRESSO (Table 4, Supplemental Digital Content, http://links.lww.com/MD/O467). Heterogeneity was discovered in the analyses of chronic lower respiratory diseases, diseases of the respiratory system, and asthma (Figure 2, Supplemental Digital Content, http://links.lww.com/MD/O467; Table 5, Supplemental Digital Content, http://links.lww.com/MD/O467). The causalities remained unaffected in the leave-one-out analyses (Fig. 4).

The self-reported walking pace and BMI were causally associated with each other in both directions, and causal associations were also found between BMI and 4 respiratory diseases, which survived the FDR correction in UVMR (Tables 6 and 7, Supplemental Digital Content, http://links.lww.com/MD/O467). After adjusting for BMI, the effects of walking pace on

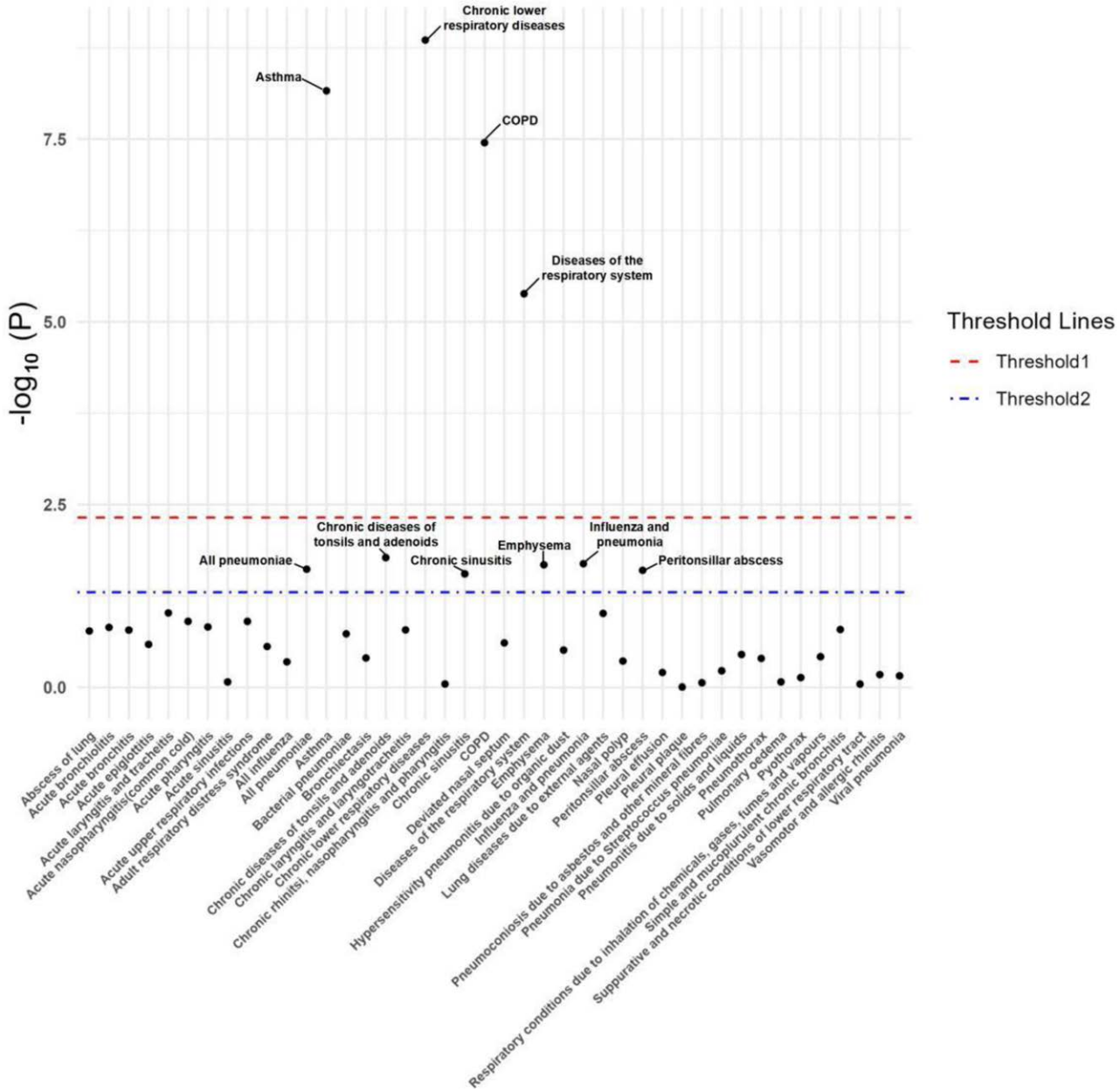


**Figure 1.** The distribution of *P* values for the associations between self-reported walking pace and 42 respiratory traits in the univariable Mendelian randomization analysis. The line labeled as threshold 1 indicates the significance threshold that has been adjusted to account for the false discovery rate. Threshold line 2 corresponds to the significance threshold established at a *P* value of .05. COPD = chronic obstructive pulmonary disease.

4 respiratory diseases were slightly weaker but still significant (Fig. 5; Table 8, Supplemental Digital Content, http://links.lww.com/MD/O467).

## 4. Discussion

Physical activity is important for health, and low physical activity has been reported as a contributing factor to the risk of various diseases.[60–65] As one of the most common forms of physical activity, regular walking is recognized for a variety of health benefits,[26] and the ability to walk is frequently used as an indicator of health or potential complications in clinical studies.[66–70] We systematically investigate the causal relationships of self-reported walking pace with various respiratory diseases. The findings indicated that maintaining a high speed of walking can significantly reduce the risk of certain respiratory diseases.

Previous epidemiological studies support our findings that brisk walking benefits respiratory health. For example, high-level physical activities, such as a high walking pace, served as a protective factor against respiratory system diseases.[10] Without altering lung function, physical training can help asthmatics with their cardiopulmonary fitness,[71] and engaging in regular physical activities can reduce the risk of asthma attacks, such as brisk walking for 20 minutes, 3 times a week.[72] A cross-sectional study has shown that physical activity benefits patients with COPD by enhancing lung function and reducing the degree of airflow obstruction.[73] Despite this, in individuals with COPD, walking more quickly and intensely had no discernible impact on lung function (spirometry, lung volumes, or arterial blood gas levels).[38] The disparity in results might be attributed to the severity of COPD, which limits the impact of walking. Furthermore, differences in the definition of walking pace across studies might account

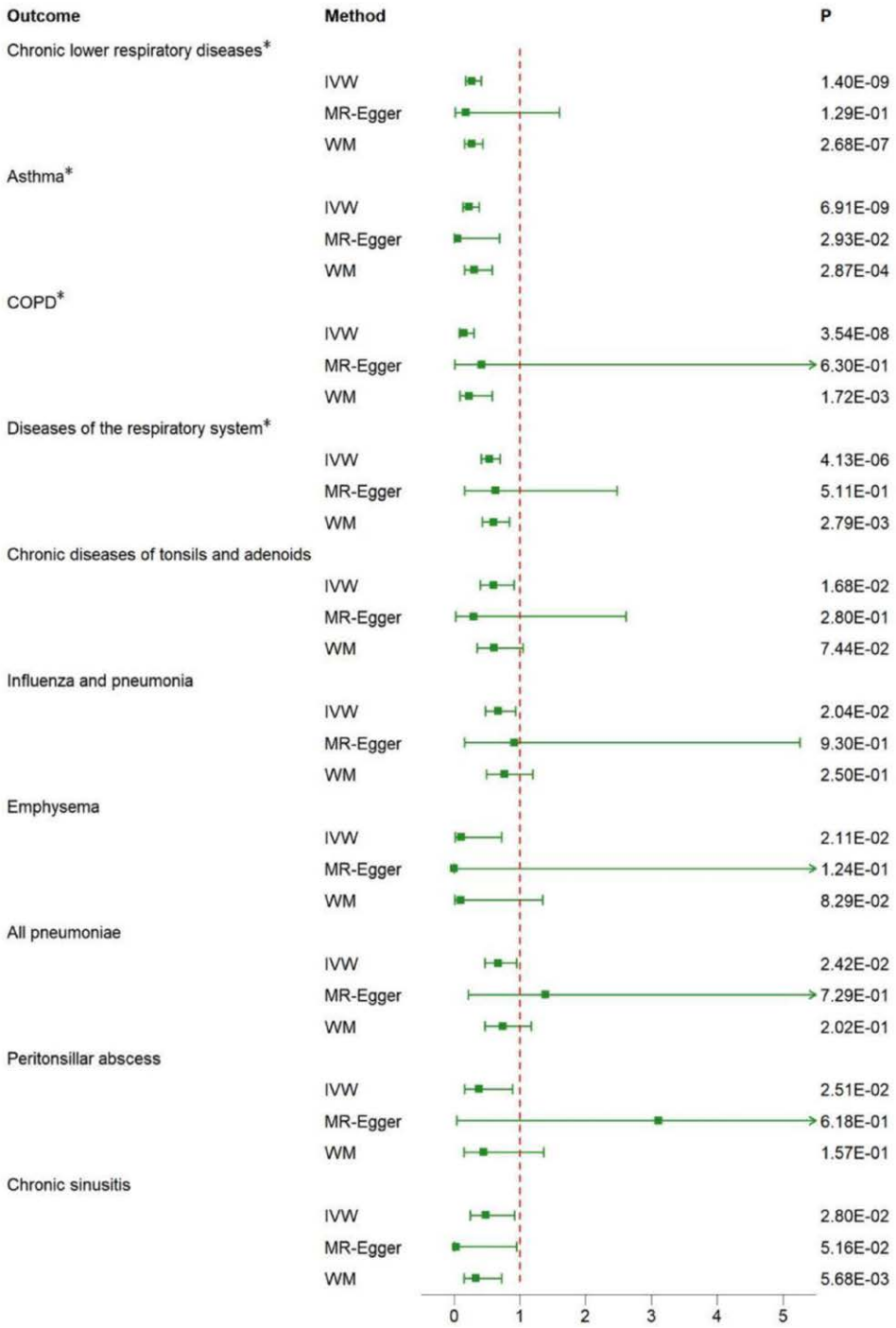


**Figure 2.** Causal effects of self-reported walking pace on 10 respiratory diseases in the univariable Mendelian randomization analysis, showing odds ratios and corresponding 95% CIs. Among these, 4 respiratory diseases remained significant after the false discovery rate (FDR) adjustment, denoted by *. In addition, suggestive significant causal associations between self-reported walking pace and other 6 respiratory diseases were found ($P < .05$). COPD = chronic obstructive pulmonary disease; IVW = inverse-variance weighted; MR = Mendelian randomization; WM = weighted median.

for the varying outcomes. More study is needed to determine the best exercise types and intensities for people with diverse illnesses.

An increase in walking pace normally produces a greater respiratory rate, which improves lung ventilation and oxygenation.[74] In individuals with interstitial lung diseases, oxygen during walking helps to attenuate the rise in heart rate, breathing rate, tidal volume, and minute ventilation, minimizing the load on both the cardiovascular system and respiratory muscles, and relieving dyspnea.[75] The pathophysiology of COPD involves the destruction of lung parenchymal and remodeling of small airways, causing limitations in airflow, a continuous decline in forced expiratory volume in 1 second (FEV1), and the manifestation of emphysema.[76,77] Physical activity can enhance circulatory function, boost blood circulation and oxygen delivery, and lower pulmonary arterial hypertension and pulmonary vascular pressure in people with COPD.[78] In addition, appropriate physical exercise significantly stimulates oxidative metabolism and oxygen utilization, increases maximum oxygen uptake and ventilation, and decreases bronchial hyperresponsiveness

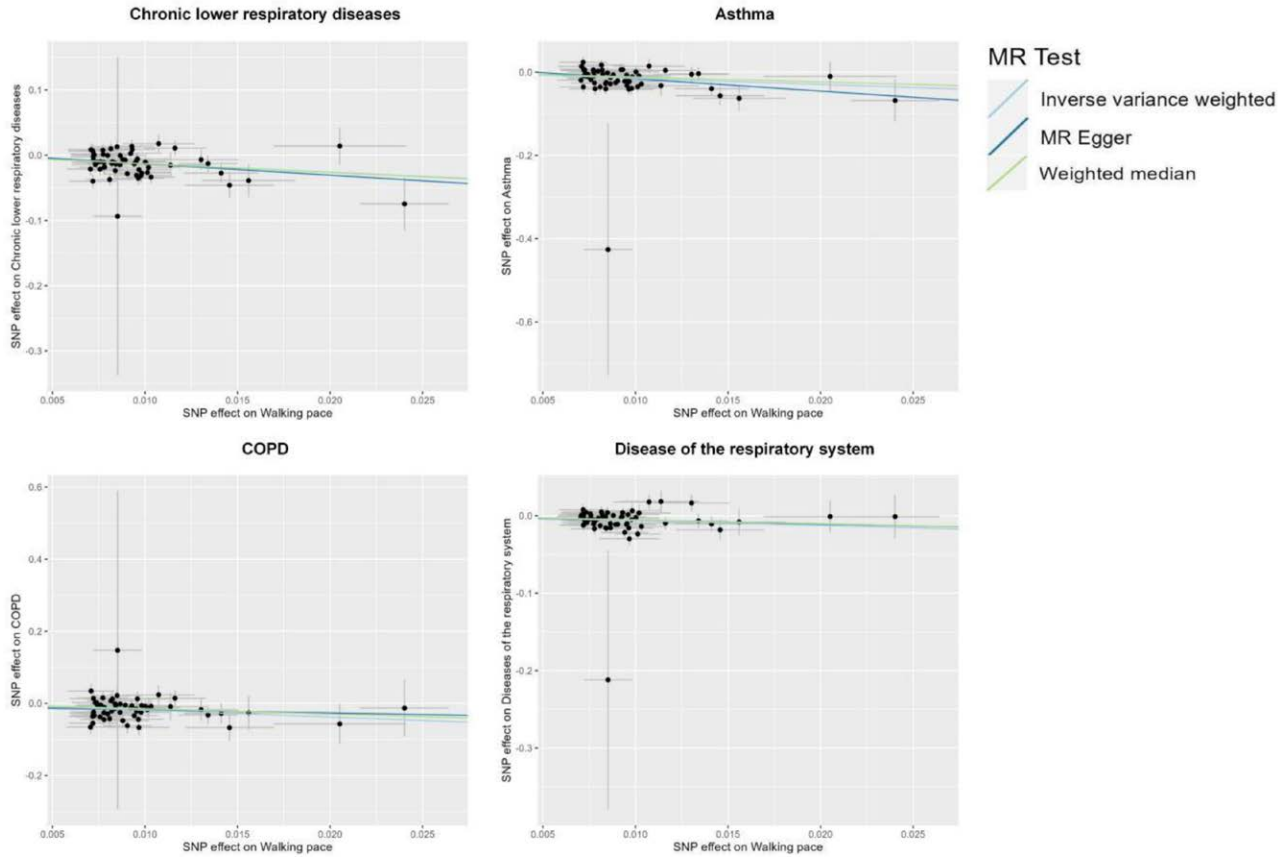


**Figure 3.** Scatter plot indicating the causal associations between self-reported walking pace and 4 respiratory diseases. COPD = chronic obstructive pulmonary disease, MR = Mendelian randomization, SNP = single-nucleotide polymorphism.

in asthmatics.[71,79,80] Thus, designing walkable neighborhoods with safe pedestrian walkways, parks, and green spaces, as well as encouraging walking as a regular physical activity, can be a low-cost technique for avoiding and controlling respiratory illness.[81–83] Concurrently, healthcare providers may counsel patients with respiratory issues to incorporate moderate brisk walking into their daily routines, utilizing wearable devices to track their speed and develop personalized objectives to improve their respiratory health. The following are some possible methods via which increased walking pace may lessen respiratory illnesses, such as COPD and asthma.

The inflammatory response may be involved in the causal relationships between walking pace and respiratory illnesses. COPD is closely associated with neutrophil inflammation.[84–86] Long-term moderate exercise has been tied to an increase in immune cell count and activity, as well as higher levels of antibodies in the blood.[87,88] Moderate exercise increases circulating neutrophils or macrophages, which is related to higher plasma levels of immunomodulatory hormones and inflammatory responses.[89] In addition, the regular practice of exercise has been proven to lower the expression of toll-like receptors on monocyte surfaces and reduce excessive immune activation and systemic inflammation, indicating a significant role in managing respiratory diseases.[90]

Type 2 airway inflammation poses a considerable risk for asthma and exhibits a close relationship with eosinophilic cells and levels of exhaled nitric oxide (NO) in the airways.[91] Research indicates a notable reduction in serum eosinophilic cationic protein levels after exercise, suggesting that the activation of eosinophils indirectly improves the severity of airway inflammation in asthma.[84,92] The overexpression of NO synthase leads to an overproduction of NO, resulting in heightened concentrations of exhaled NO.[93–95] Existing research indicates that regularly participating in moderate exercise can promote NO bioavailability and mitigate the severity of exercise-induced bronchoconstriction.[96,97] These positive modifications in airway and systemic inflammation are linked to an increase in immediate FEV1, ultimately providing relief from asthma symptoms,[98] consistent with our research findings. Nevertheless, exercise can also induce an increase in exercise-induced bronchoconstriction, resulting in aggravated airway obstruction and reductions in FEV1 and peak expiratory flow values.[99,100] The reason behind this could be the excessively intense nature of the exercise.

Exercise's effect on disorders of the respiratory system also involves oxidative stress. For the respiratory system's host defense systems to function well in preventing pathogens, maintaining redox balance is crucial.[101–103] Chronic lower respiratory diseases including asthma and COPD are influenced by oxidative stress.[101] Children with asthma showed a reduction in blood indicators of oxidative stress after exercise.[79] In mice with COPD induced by cigarette smoke exposure, exercise-induced secretion of irisin from muscle has been found to possess protective effects against oxidative stress and improve emphysema, mediating through the activation of the nuclear factor erythroid 2-related factor 2 and heme oxygenase-1 pathways.[104] In contrast, the intensity of physical activity can trigger oxidative stress in respiratory ailments, expediting the development of the illnesses.[101,105,106] This may be ascribed to prolonged, intense exercise that exceeds the body's tolerance level and causes oxidative stress, such as nonstop walking without enough rest. Continued research is essential to uncover the significance of oxidative stress in the link between walking pace and respiratory diseases.

Our study exhibits several notable strengths. This MR analysis is the pioneering effort to systematically assess the effects of walking pace on a series of respiratory conditions. This

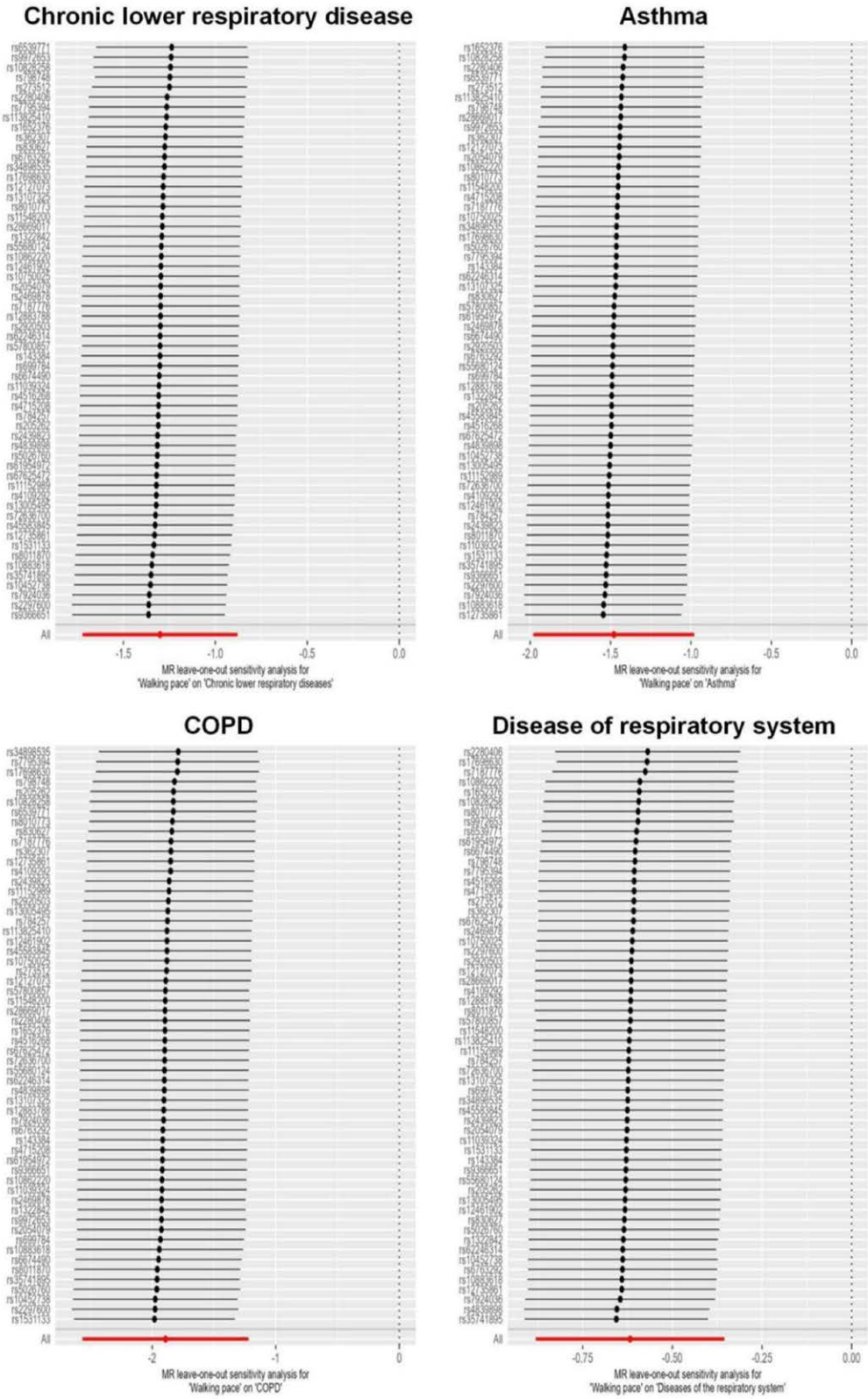


**Figure 4.** Leave-one-out sensitivity analysis using the inverse-variance weighted (IVW) method to investigate the causal estimates of self-reported walking pace on 4 respiratory diseases after excluding a particular single-nucleotide polymorphism (SNP) from the analysis. COPD = chronic obstructive pulmonary disease, MR = Mendelian randomization.

approach enabled us to effectively overcome the bias associated with confounding factors and reverse causation that is typically seen in traditional epidemiological studies. In addition, we performed MVMR analysis to carefully control for BMI as a potential confounder, thereby ensuring the rigor and dependability of our study.

Our research still has some limitations. First, the walking pace was self-reported rather than directly measured. While

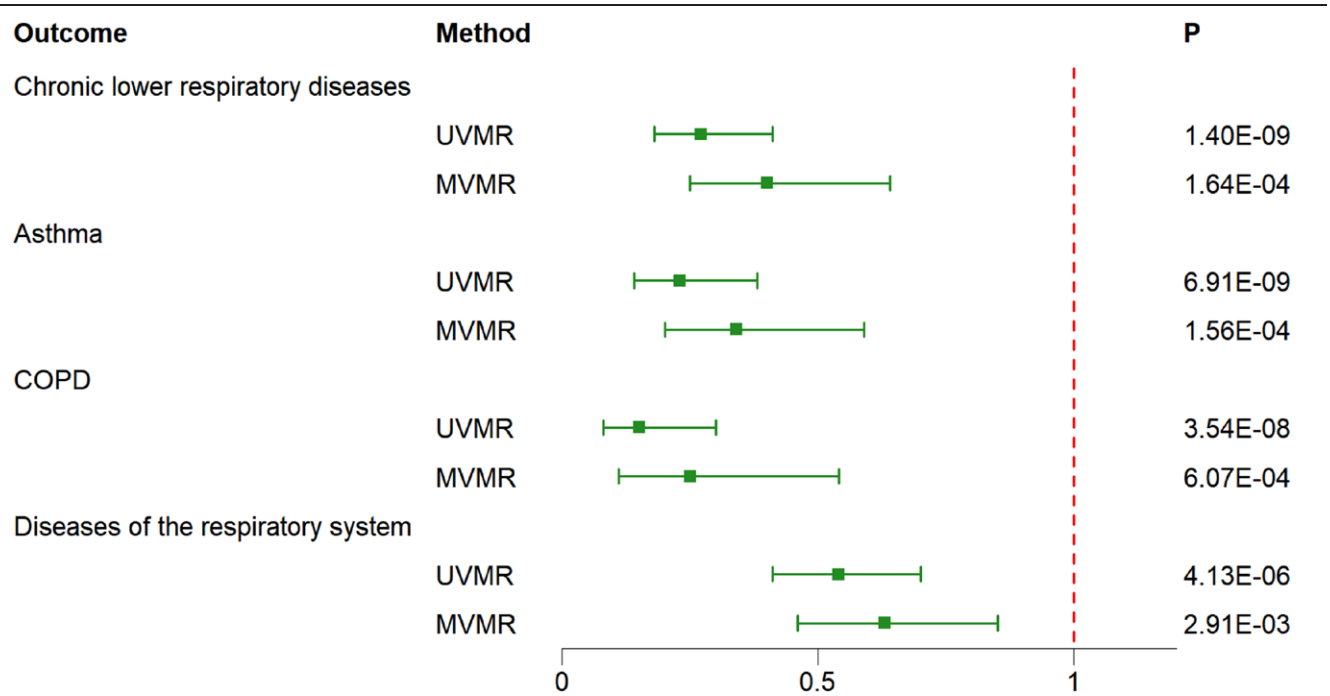


**Figure 5.** The multivariable Mendelian randomization (MVMR) analysis with the inverse-variance weighted (IVW) method revealed the effects of self-reported walking pace on 4 respiratory diseases after adjusting for body mass index (BMI). The results of univariable Mendelian randomization (UVMR; unadjusted) and MVMR (adjusted for BMI) were presented as odds ratios and corresponding 95% CIs. COPD = chronic obstructive pulmonary disease.

closely related to objective methods,[107] self-reports may introduce measurement bias. Future research should consider using more accurate objective measures, such as smartwatches, to assess walking pace. Second, 6 respiratory diseases did not meet the FDR significance threshold but indicated a potential causal relationship. To address this, future studies could increase the sample size to confirm these associations. Third, as our findings were exclusively based on European populations, their generalizability to other ethnic groups is limited. Future studies should consider conducting MR analyses in more diverse populations or incorporating experimental research for further validation.

## 5. Conclusion

Brisk walking plays a key role in reducing the risk of respiratory diseases, including asthma and COPD. This finding underscores its importance in disease prevention, risk stratification, clinical decision-making, and shaping public health policies.

## Author contributions

**Writing – original draft:** Chunxia Huang, Ting Jiang, Bin Zeng.
**Formal analysis:** Yining Ding, Shuling Xu, Rumeng Chen.
**Writing – review & editing:** Meihua Bao, Binsheng He, Qingming Fu, Sen Li.

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