

Exploring the association between asthma and frailty: a cross-sectional and a bidirectional Mendelian randomization study

Shufei Peng¹, Huanxian Liu², Xianfeng Ren³, Lijuan Guo⁴, Shuai Li¹, Xiaohai Xu¹, Meikui Wu¹, Yi Tian¹, Bing Mu¹, Ruihang Chai¹, Zhixing Guo¹, Xiaoyan Liu¹, Hui Zheng¹, Cheng Ni^{1*}

¹Department of Anesthesiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

²Department of Neurology, Chinese PLA General Hospital, Beijing, China

³Department of Anesthesiology, China-Japan Friendship Hospital, Beijing, China

⁴Department of Lung transplantation, China-Japan Friendship Hospital, Beijing, China

Submitted: 5 January 2025; Accepted: 28 March 2025

Online publication: 18 May 2025

Arch Med Sci

DOI: <https://doi.org/10.5114/aoms/203471>

Copyright © 2025 Termedia & Banach

*Corresponding author:

Cheng Ni

Department of

Anesthesiology

National Cancer Center/

National Clinical Research

Center for Cancer/

Cancer Hospital

Chinese Academy of

Medical Sciences and

Peking Union

Medical College

Beijing, China

E-mail: nicheng@cicams.ac.cn

Abstract

Introduction: Observational studies suggest a potential association between asthma and frailty, but the causal relationship remains unclear. This study aimed to explore this association and determine its causal nature, with implications for targeted interventions that could improve patient management and quality of life.

Material and methods: This study analyzed cross-sectional data from the National Health and Nutrition Examination Survey and included 29,589 participants. Multivariate logistic regression was used to assess the association between asthma and frailty, with propensity score matching for reliability. Bidirectional Mendelian randomization (MR) was used, with genetic variants associated with asthma and frailty obtained from the FinnGen database and a large GWAS meta-analysis. Causal effects were estimated using inverse variance weighting, with sensitivity analyses for robustness.

Results: Cross-sectional analysis found a significant association between asthma and frailty (OR = 2.16; 95% CI: 2.01–2.31; $p < 0.001$). After adjusting for confounders using multiple methods, this association remained significant, with ORs ranging from 1.60 to 2.04, all $p < 0.001$. MR analysis revealed a bidirectional causal relationship: Genetically predicted asthma was significantly associated with an increased risk of frailty, with an OR of 1.091 (95% CI: 1.061–1.123). In the reverse direction analysis, genetic liability to frailty was also significantly associated with an increased risk of asthma, with an OR of 2.264 (95% CI: 1.503–3.409).

Conclusions: This study suggests a bidirectional causal association between asthma and frailty. Routine screening for frailty in asthma patients is recommended, and further research is needed to explore the underlying mechanisms.

Key words: asthma, frailty, cross-sectional study, Mendelian randomization, causal effect.

Introduction

Frailty is a complex syndrome characterized by diminished physiological function, escalating with age and reducing life expectancy at any

age [1–4]. Recognized as a critical aging concern, it increases susceptibility to stressors and the likelihood of adverse events such as falls, disabilities, and hospital admissions [5]. Prevalent among intensive care unit patients, frailty has emerged as a significant global health issue. Despite its recognition, standardized assessment criteria for frailty remain elusive. Commonly, frailty is delineated through two methodologies: the frailty phenotype [3] and the frailty index model. Alternative approaches include the simplified frailty phenotype and the prognostic frailty score. The frailty phenotype evaluation encompasses five domains: weight loss, weakness, exhaustion, slowness, and reduced physical activity [3, 6]. In contrast, the frailty index varies in terms of components and counts across studies, and is more effective in differentiating frailty levels [7–9].

Asthma, the most prevalent chronic respiratory disease, is characterized by narrowed, edematous airways obstructed with excessive mucus. It is estimated that over 300 million people globally suffer from asthma; its prevalence continues to rise worldwide, and it is responsible for nearly 250,000 deaths annually [10, 11]. The prevalence of frailty was observed to be the highest in the presence of severe airflow limitation, dyspnea, and frequent exacerbations [12]. However, the causal relationship between asthma and frailty has been minimally explored at the population level. There

remains uncertainty about whether a bidirectional causal association truly exists, or the observed co-existence is due to confounding factors or common risk elements such as inflammation. Establishing a definitive causal association between asthma and frailty is critical, as it would enhance our understanding of the disease etiology, guide the creation of effective interventions, and ultimately help to alleviate the growing burden of these conditions.

Establishing a causal association between asthma and frailty is challenging due to potential reverse causation and confounding factors. Mendelian randomization (MR) is an emerging approach in epidemiology that uses genetic variants, such as single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to evaluate the causal effects of exposures on outcomes [13]. Due to the unique advantages of IVs, MR analysis is not influenced by conventional confounders [14] and aligns with the established causal sequence [15]. Genome-wide association studies (GWAS) have provided robust and reliable IVs for MR research. Therefore, MR analysis can be employed to examine the potential causal association between genetic predisposition to asthma and frailty. Based on this understanding, we conducted a bidirectional MR analysis using recent large-scale GWAS data to investigate the causal relationship between asthma and frailty.

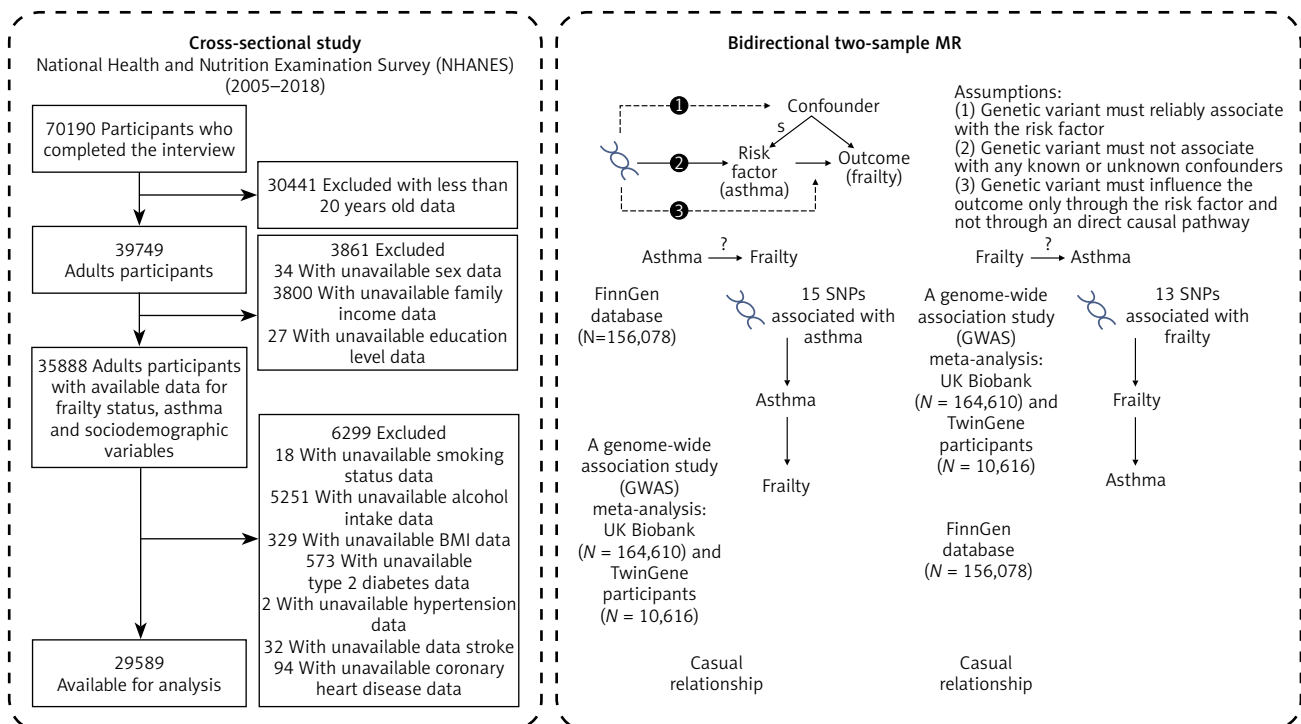


Figure 1. Cross-sectional study: Schematic diagram showing the study participants included in the present analysis from 2005 to 2018 NHANES. Bidirectional two-sample MR: Main assumptions of MR and overview of the design and main results of the MR. MR: Mendelian randomization

Material and methods

Overall study design

This study was divided into two sections. Initially, we analyzed data from NHANES to examine the association between asthma and frailty, controlling for potential confounders. Propensity score matching (PSM) was used to validate the robustness of our results. Subsequently, bidirectional MR was used to assess the genetic basis of asthma's impact on frailty, drawing on data from GWAS. A schematic representation of the study is shown in Figure 1.

Cross-sectional analysis

NHANES is an ongoing series of cross-sectional surveys conducted on noninstitutionalized civilians in the United States. The surveys use multi-stage probability sampling to select a sample that is representative of the nation and evaluate their health and nutritional status. The survey comprises household interviews, physical examinations, and laboratory tests. It was carried out by the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention (CDC). Details about the sampling method and data collection can be found in a previous publication [16]. The study obtained approval from the Ethics Review Board of the National Center for Health Statistics, and all participants provided written informed consent.

The study used data from the 2005–2018 NHANES a comprehensive health survey by CDC and the National Center for Health Statistics (NCHS). This survey assesses the health and nutritional status of a representative sample of the noninstitutionalized population in the United States. The survey protocol was approved by NCHS Research Ethics Review Board, and all participants gave their written informed consent. In this study, individuals aged 20 years or older with data on asthma and frailty were selected. In the NHANES dataset, key variables such as education level, marital status, and other adult-specific measures are collected only for participants aged 20 or older. To ensure robust analysis, we set an age cutoff of 20 years, consistent with standard NHANES research practices for data consistency and relevance. After excluding those with incomplete information on covariates, the final sample comprised 29,589 participants.

Diagnosis of frailty

Frailty was assessed using a frailty index based on the methodology and principles outlined by Searle *et al.* [7]. This index incorporates 49 variables across various systems, such as cog-

nitive function, dependency levels, depressive indicators, comorbid conditions, overall health status, hospital usage, physical capability, body measurements, and laboratory test results [8]. These variables represent health deficits that typically escalate with age yet avoid saturating too early. Each deficit, whether ordinal, continuous, or binary, was assigned a value ranging from 0 (absence of deficit) to 1 (maximum presence), reflecting its intensity. The computation of the frailty index involved summing the scores for these deficits and dividing by 49, the total count of deficits. A benchmark frailty index score of 0.21 was determined to identify individuals deemed 'frail,' who are at heightened risk of hospital-related complications [17, 18]. Details of the 49 variables and their assigned values are provided in Supplementary Table S1. In this study, a 49-item frailty index derived from the NHANES dataset's clinical, laboratory, and survey data was used [8, 9].

Definitions of asthma

A diagnosis of asthma was confirmed under any of these conditions: (1) a medical professional diagnosed the participant with asthma; (2) the participant was on medication for asthma; (3) individuals younger than 40 years, without a history of smoking, chronic bronchitis, or emphysema, were taking medications such as selective phosphodiesterase-4 inhibitors, mast cell stabilizers, leukotriene modifiers, or inhaled corticosteroids [19].

Other covariates

Various potential covariates were examined, as identified in the literature [20], including demographic and health-related factors such as age, sex, race/ethnicity, marital status, family income, education level, smoking and alcohol consumption habits, body mass index (BMI), and the presence of certain health conditions such as type 2 diabetes, hypertension, stroke and coronary heart disease. Race/ethnicity was divided into four categories: non-Hispanic White, non-Hispanic Black, Mexican American, and other races. Marital status was categorized as married, living with a partner, or living alone. Family income was classified into low, medium, and high groups based on the poverty income ratio (PIR) as per a US government report, with thresholds set at $PIR \leq 1.3$ for low, 1.3 to 3.5 for medium, and > 3.5 for high. Education was segmented into three levels: less than 9 years, 9 to 12 years, and more than 12 years. BMI calculation followed a standardized method using weight and height measurements. Smoking status was defined based on lifetime cigarette consumption, categorizing individuals as never smokers (fewer

than 100 cigarettes), current smokers, or former smokers (quit after 100 or more cigarettes). Alcohol consumption was classified as never (less than 12 drinks in a lifetime), former (12 or more drinks in 1 year but none in the last year), or current (12 or more drinks in the last year). For previous diseases such as hypertension, stroke, and coronary heart disease, classification relied on self-reported medical diagnoses. Type 2 diabetes identification adhered to the American Diabetes Association criteria, considering factors such as fasting plasma glucose, glycated hemoglobin, random blood glucose levels, results from an oral glucose tolerance test, physician-diagnosed diabetes, and medication usage for glucose control.

MR analysis – data source

The present study, deploying bidirectional two-sample MR within a European cohort, aimed to delineate the potential causal relationship between asthma and frailty. Genetic variants significantly associated with asthma were derived from FinnGen database (https://gwas.mrcieu.ac.uk/datasets/finn-b-J10_ASTHMA/, accessed on 2024-01-12) comprising 156,078 individuals, including 20,629 cases and 135,449 controls, with a total of 16,380,176 SNPs. Genetic variants significantly associated with the frailty index ($p < 5 \times 10^{-8}$) were obtained from a genome-wide association study (GWAS) meta-analysis of 164,610 UK Biobank and 10,616 TwinGene participants (<https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90020053>, accessed on 2024-01-12). All participants were of European ancestry. Reporting and analytic processes follow the STROBE-MR guidelines [21].

Statistical analysis

Descriptive analysis was conducted on the participants. Categorical data are presented as frequencies and percentages, and continuous data are presented as means and standard deviations (SD) for normally distributed variables, or medians and interquartile ranges (IQR) for non-normally distributed variables. Different statistical tests were applied based on data characteristics: the χ^2 test was used for categorical variables, the independent samples *t*-test was used for normally distributed continuous variables, and the Mann-Whitney *U* test or Kruskal-Wallis test was used for non-normally distributed continuous variables. Specifically, the Mann-Whitney *U* test was applied for comparisons between two independent groups, while the Kruskal-Wallis test was used for comparisons involving more than two groups. These non-parametric tests were chosen because the data did not meet the assumptions required for parametric tests (e.g.,

normality and homogeneity of variance). This approach supported our comprehensive comparative analysis. Moreover, a multivariable logistic regression model was used to derive propensity scores for asthma and non-asthma participants, aiding in a PSM analysis. Through 1 : 1 nearest neighbor matching with a 0.2 caliper width, baseline characteristic biases were minimized. The PSM efficacy was evaluated via the standardized mean difference, aiming to reduce it, with values under 0.1 indicating effective cohort matching. This study included various methods, such as inverse probability of treatment weighting (IPTW), standardized mortality ratio weighting (SMRW), pairwise algorithmic (PA), and overlap weighting (OW), to establish a weighted cohort [22], refining the assessment of the independent effect of asthma on frailty. The E-value was calculated to assess the influence of unmeasured confounders on the conclusion, thus strengthening the validity [23].

In the bidirectional MR analysis, IVs (SNPs) were selected based on stringent criteria: genome-wide significance ($p < 5 \times 10^{-8}$) and linkage disequilibrium ($r^2 < 0.001$ within a 10,000 kb window). Weak instruments were excluded if the F-statistic was below 10. The MR-PRESSO test was used before the analysis to identify and remove outliers, enhancing the causal estimate's reliability. Data harmonization procedures also involved removing palindromic SNPs to maintain consistency between outcome and exposure datasets. After filtering, the remaining SNPs underwent rigorous analysis, with the inverse variance weighting (IVW) method as the primary analysis tool. The stability of results was cross-validated through MR-Egger, weighted median, simple mode, and weighted mode approaches. Heterogeneity was assessed via Cochran's *Q* test, and the MR-Egger intercept test was used to evaluate horizontal pleiotropy. Further scrutiny for potential reverse causality was performed through reverse MR analysis. Additionally, scatter plots were created to illustrate the relationships between SNP–exposure and SNP–outcome associations. To assess the potential impact of individual variants on the estimates, a leave-one-out analysis was conducted by sequentially excluding each SNP and then applying the IVW method to the remaining SNPs. Furthermore, the study included a funnel plot analysis to detect directional pleiotropy, analogous to evaluating publication bias in meta-analyses. All statistical analyses were performed using R software (version 4.3.2) with the “TwoSampleMR” package and Free Statistics (version 1.9, <http://www.clinicalscientists.cn/freestatics/>). $P < 0.05$ was considered statistically significant.

Results

Cross-sectional analysis

Participants

This study used NHANES data from 2005 to 2018, initially involving 70,190 participants. Among these, 39,749 adults aged 20 and above completed the interview and Mobile Examination Center (MEC) screening process. Following the initial screening, data on frailty status and asthma were complete for all participants, but 3,861 participants were excluded due to incomplete socio-demographic data, specifically 34 participants for

missing sex data, 3,800 for missing family income data, and 27 for missing education level data. Additionally, 6,299 participants were excluded based on missing covariate information. This included 18 participants for missing smoking status data, 5,251 for missing alcohol intake data, 329 for missing BMI data, 573 for missing type 2 diabetes data, 2 for missing hypertension data, 32 for missing stroke data, and 94 for missing coronary heart disease data. Ultimately, 29,589 participants were included in the final analysis. The detailed selection and exclusion process is illustrated in the flow chart presented in Figure 1.

Table I. Baseline characteristics of participants

Covariate	All participants	Unmatched participants			PSM participants		
		Without asthma	Asthma	P-value	Without asthma	Asthma	P-value
N	29589	25292	4297		4293	4293	
Age [years], mean \pm SD	49.5 \pm 17.6	49.9 \pm 17.6	47.3 \pm 17.5	< 0.001	47.4 \pm 17.4	47.3 \pm 17.5	0.816
Female, sex, n (%)	14775 (49.9)	12919 (51.1)	1856 (43.2)	< 0.001	1855 (43.2)	1856 (43.2)	0.983
Race/ethnicity, n (%)				< 0.001			0.494
Non-Hispanic White	13119 (44.3)	11054 (43.7)	2065 (48.1)		2003 (46.7)	2064 (48.1)	
Non-Hispanic Black	6285 (21.2)	5231 (20.7)	1054 (24.5)		1083 (25.2)	1053 (24.5)	
Mexican American	4428 (15.0)	4046 (16.0)	382 (8.9)		411 (9.6)	382 (8.9)	
Others	5757 (19.5)	4961 (19.6)	796 (18.5)		796 (18.5)	794 (18.5)	
Marital status, living alone, n (%)	11923 (40.3)	9910 (39.2)	2013 (46.8)	< 0.001	2036 (47.4)	2010 (46.8)	0.574
Family income, n (%)				< 0.001			0.717
Low	9156 (30.9)	7588 (30.0)	1568 (36.5)		1564 (36.4)	1564 (36.4)	
Medium	11196 (37.8)	9707 (38.4)	1489 (34.7)		1519 (35.4)	1489 (34.7)	
High	9237 (31.2)	7997 (31.6)	1240 (28.9)		1210 (28.2)	1240 (28.9)	
Education level (year), n (%)				< 0.001			0.768
< 9	2836 (9.6)	2518 (10.0)	318 (7.4)		324 (7.5)	318 (7.4)	
9–12	10891 (36.8)	9340 (36.9)	1551 (36.1)		1519 (35.4)	1551 (36.1)	
> 12	15862 (53.6)	13434 (53.1)	2428 (56.5)		2450 (57.1)	2424 (56.5)	
Smoking status, n (%)				< 0.001			0.960
Never	16149 (54.6)	14020 (55.4)	2129 (49.5)		2142 (49.9)	2129 (49.6)	
Former	7240 (24.5)	6164 (24.4)	1076 (25.0)		1067 (24.9)	1075 (25.0)	
Current	6200 (21.0)	5108 (20.2)	1092 (25.4)		1084 (25.3)	1089 (25.4)	
Alcohol status, n (%)				< 0.001			0.860
Never	4102 (13.9)	3601 (14.2)	501 (11.7)		514 (12.0)	501 (11.7)	
Former	4848 (16.4)	4115 (16.3)	733 (17.1)		719 (16.7)	733 (17.1)	
Current	20639 (69.8)	17576 (69.5)	3063 (71.3)		3060 (71.3)	3059 (71.3)	
BMI, mean \pm SD	29.2 \pm 7.0	29.0 \pm 6.8	30.8 \pm 8.2	< 0.001	30.8 \pm 8.1	30.7 \pm 8.1	0.933
Type 2 diabetes, n (%)	5469 (18.5)	4550 (18.0)	919 (21.4)	< 0.001	961 (22.4)	918 (21.4)	0.262
Hypertension, n (%)	12619 (42.6)	10618 (42.0)	2001 (46.6)	< 0.001	2010 (46.8)	1997 (46.5)	0.779
Stroke, n (%)	1156 (3.9)	917 (3.6)	239 (5.6)	< 0.001	256 (6.0)	239 (5.6)	0.431
CHD, n (%)	1199 (4.1)	998 (3.9)	201 (4.7)	0.025	221 (5.1)	201 (4.7)	0.318

PSM – propensity score matching, BMI – body mass index, CHD – coronary heart disease.

Baseline characteristics

In the 29,589 participants, 4,297 (14.5%) had an asthma diagnosis. Through PSM, we aligned 4,293 patient pairs, ensuring a balanced distribution of covariates across both groups. The baseline variables of unmatched and PSM groups were uniformly comparable, as shown in Table I and Supplementary Table SII. Asthmatic participants tended to be younger and predominantly male, with a higher representation of non-Hispanic White and Black individuals. Compared to non-asthmatic participants, asthmatic participants often had lower household incomes, were more likely to be in a marital or cohabiting relationship, and possessed higher educational levels. Lifestyle analysis showed that asthmatics were more likely to smoke, but less inclined to consume alcohol, and they generally exhibited elevated BMI. Furthermore, the prevalence of severe conditions such as type 2 diabetes, hypertension, stroke, and coronary heart disease was higher in asthmatics.

Asthma is an independent predictor of frailty

The overall frailty incidence was 22.0% (6,503/29,589), with 34.7% (1,493/4,297) in asth-

matics and 19.8% (5,010/25,292) in non-asthmatic participants. The PSM analysis revealed a significant association between asthma and frailty. The crude OR was 2.16 (95% CI: 2.01–2.31), indicating a strong positive association before adjustments. After adjusting for multiple variables, the OR was 2.04 (95% CI: 1.87–2.23), still a significant association. When adjusted for propensity scores, the OR was 1.71 (95% CI: 1.59–1.84), and PSM yielded an OR of 1.60 (95% CI: 1.46–1.76), showing more conservative estimates. Weighted analyses using IPTW and SMRW provided OR of 1.67 (95% CI: 1.55–1.79) and 1.65 (95% CI: 1.54–1.77), respectively, both indicating significant associations. Similarly, PA and OW produced OR of 1.65 (95% CI: 1.50–1.82) and 1.66 (95% CI: 1.50–1.84), respectively, maintaining significant associations. These results suggest that asthma is a significant independent predictor of frailty, with the association strength slightly varying across different methodological approaches (Figure 2). For this analysis, the E-value ranged between 1.71 and 1.84.

Subgroup analysis showed a robust and consistent association between asthma and increased risk of frailty, with significant interactions observed in relation to age, family income, smoking

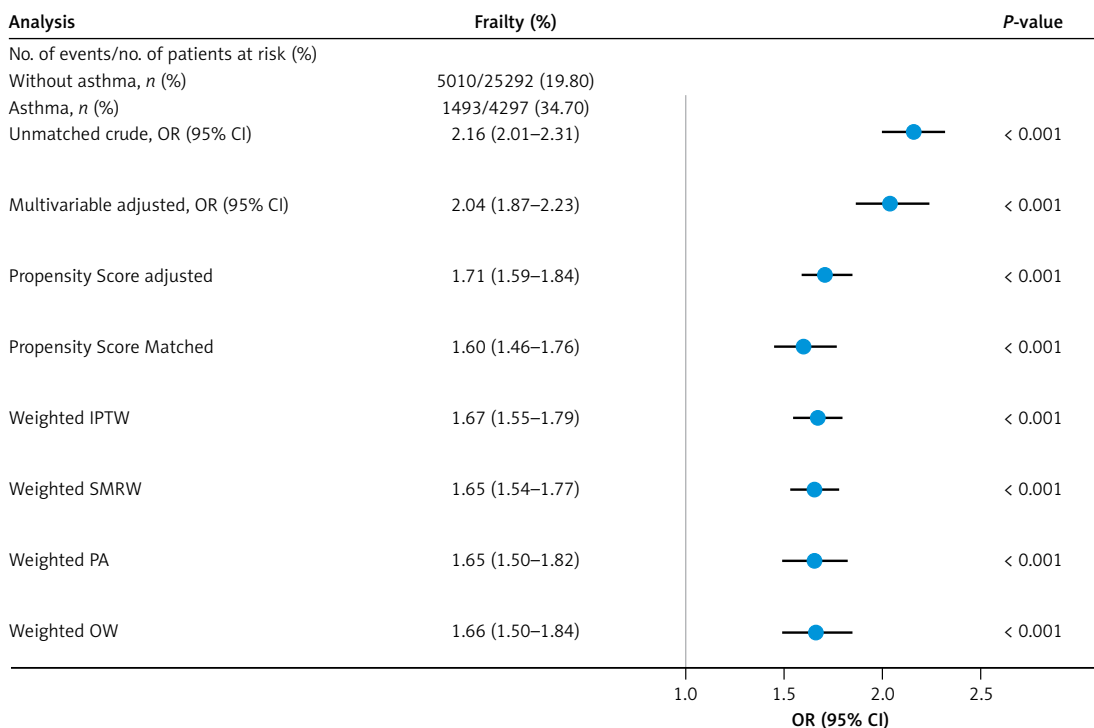


Figure 2. Forest plot of frailty incidence among asthma patients. This forest plot illustrates the ORs comparing the incidence of frailty between asthma patients and non-asthma controls across multiple analytical models. Each line represents a different model, including crude unmatched, multivariable-adjusted, propensity score-adjusted, and various weighted models such as IPTW, SMRW, PA, and OW. The plot provides a comprehensive overview of the effect sizes with 95% CIs, assessing the robustness of the association between asthma and frailty

IPTW – inverse probability of treatment weighting, SMRW – standardized mortality ratio weighting, PA – pairwise algorithmic, OW – overlap weighting.

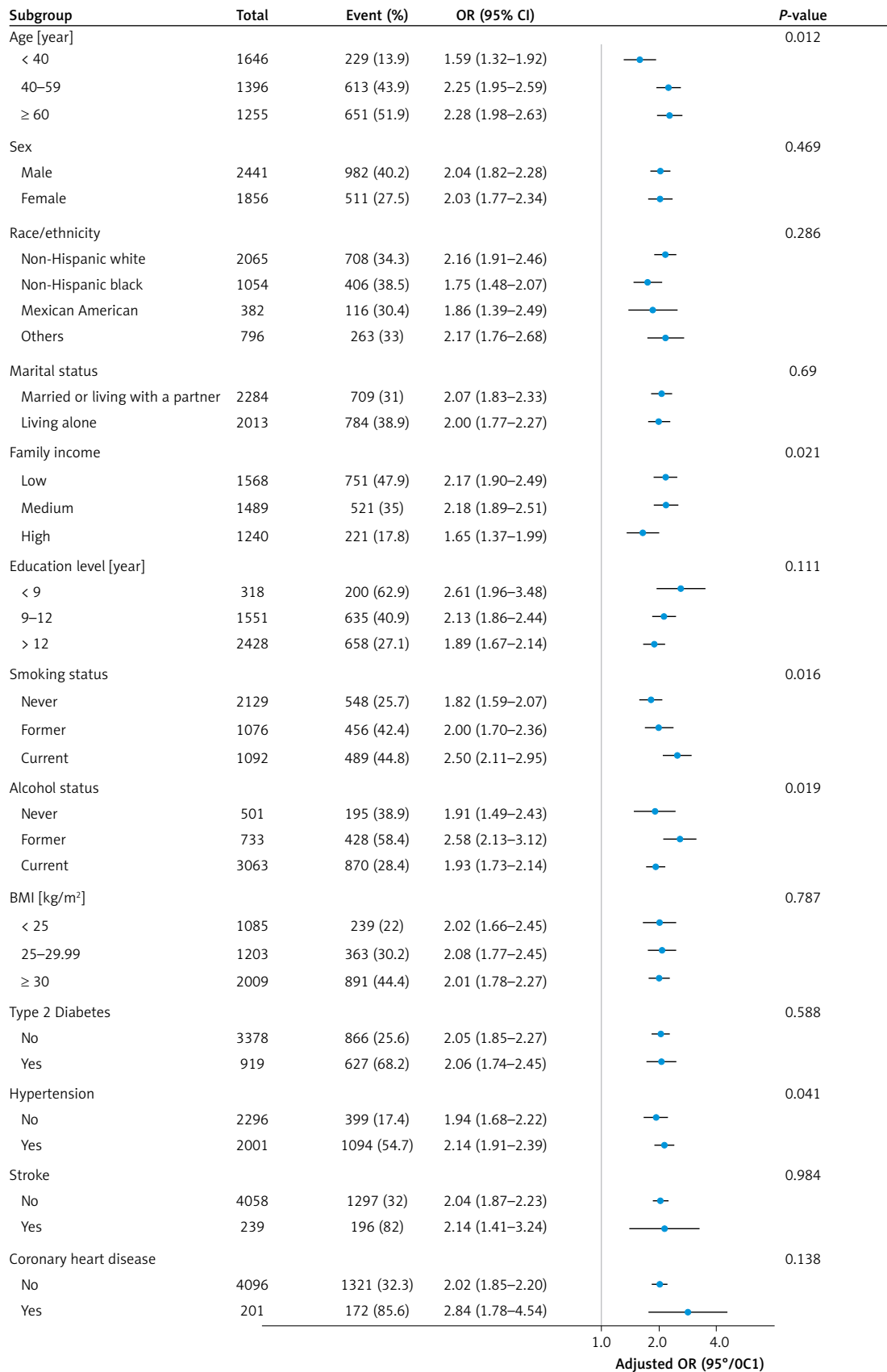


Figure 3. Stratified multivariable analysis of the association between asthma and frailty according to baseline characteristics. Each stratification adjusts for all factors except the stratification factor itself. Adjusted factors include age, sex, race/ethnicity, marital status, family income, education level, smoking status, alcohol status, BMI, type 2 diabetes, hypertension, stroke, and coronary heart disease

status, alcohol status, and hypertension (Figure 3). Asthmatic participants aged <40, 40-59, and >60 years experienced frailty incidence of 13.9%, 43.9%, and 51.9%, respectively ($p = 0.012$). Asthmatic participants with low, medium and high family income experienced frailty incidence of 47.9%, 35.0%, and 17.8% ($p = 0.021$). Asthmatic participants who had never smoked, former smokers, and current smokers experienced frailty incidence of 25.7%, 42.4%, and 44.8% ($p = 0.016$). Asthmatic participants who had never drunk, former drinkers, and current drinkers experienced frailty incidence of 38.9%, 58.4%, and 28.4% ($p = 0.019$). Asthmatic participants with and without hypertension experienced frailty incidences of 54.7% and 17.4% ($p = 0.041$).

MR analysis

Selection of genetic SNP for MR (asthma \rightarrow frailty)

Following application of SNP selection criteria ($P < 5 \times 10^{-8}$, $R^2 < 0.001$, $kb = 10,000$), 15 asthma-associated SNPs (Supplementary Table SIII) were identified as exposure SNPs (F -statistics > 10). During the selection process, outliers detected with MR-PRESSO analysis were excluded; ambiguous and palindromic ones were removed.

Causal effects of asthma on frailty

The MR analysis (Figure 4 A) showed that asthma was associated with increased risk of frailty (with the IVW method), and asthma patients had 1.091 times the risk of frailty ($p < 0.001$). Weighted median, simple mode, and weighted mode results were consistent with the IVW results. However, the MR-Egger regression analysis results were inconsistent with the IVW results, indicating the presence of potential biases or effect heterogeneity that needs to be considered. Scatter plots are presented in Supplementary Figure S1 A. The forest plot showed a significant positive effect of asthma on frailty index (with IVW method, Supplementary Figure S1 C). Leave-one-out analyses of the results described above are presented in Supplementary Figure S2 A, showing the minimal influence of individual SNP exclusions on the overall effect estimate.

Sensitivity analysis

Supplementary Figure 2 C shows symmetrical distribution of data, supporting the reliability of the MR analysis results. In the MR-PRESSO global test and MR-Egger intercept test, all p -values exceeded 0.05. Cochran's Q test indicated heterogeneity in the effects of asthma on frailty (IVW, $p = 0.024$; MR Egger, $p = 0.027$).

Selection of SNP for reverse MR (frailty \rightarrow asthma)

Following the SNP selection criteria, 13 frailty-associated SNPs (F -statistics > 10 , Supplementary Table SIV) were used as exposure SNPs in the reverse MR study. Outliers detected through the MR-PRESSO analysis were excluded, and ambiguous and palindromic SNPs were removed.

Causal effects of frailty on asthma

The inverse MR analysis (Figure 4 B) indicated a significant causal effect of frailty on the risk of developing asthma (IVW method, OR = 2.264, $p < 0.001$). The weighted median and simple mode results were consistent with the IVW result. Inconsistency between the MR-Egger, weighted mode, and IVW results usually suggests the presence of pleiotropy or effect heterogeneity in the instrumental variables, or differences in statistical power among the methods. Scatter plots are presented in Supplementary Figure S1 B. The forest plot supported these results (Supplementary Figure S1 D). The leave-one-out analysis indicated that the relationship between frailty index and asthma risk was not significantly influenced by any single SNP (Supplementary Figure S2 B).

Sensitivity analysis

Supplementary Figure S2 D showed that most SNPs were positively associated with asthma due to higher frailty levels, and both MR methods confirmed the robustness of this causal relationship, with no significant pleiotropic biases. In the MR-PRESSO global test and MR-Egger intercept test, all p -values were above 0.05. Cochran's Q test indicated no significant heterogeneity in the effects of frailty on asthma (IVW, $p = 0.100$; MR-Egger, $p = 0.077$).

Discussion

In this study, using survey data from NHANES, the cross-sectional analysis revealed a significant association between asthma and frailty. The bidirectional MR study showed a positive effect of asthma on the risk of frailty, with consistent results across four methods, excluding the MR-Egger. Reverse analyses indicated that frailty was also positively associated with an increased risk of asthma, with consistent results across three methods, excluding the MR-Egger and weighted mode. These results provide comprehensive evidence for a causal relationship between asthma and frailty by combining data from large-scale observational studies with MR analysis of extensive genetic data.

Asthma is a significant health issue affecting individuals across all age groups. Meanwhile, the

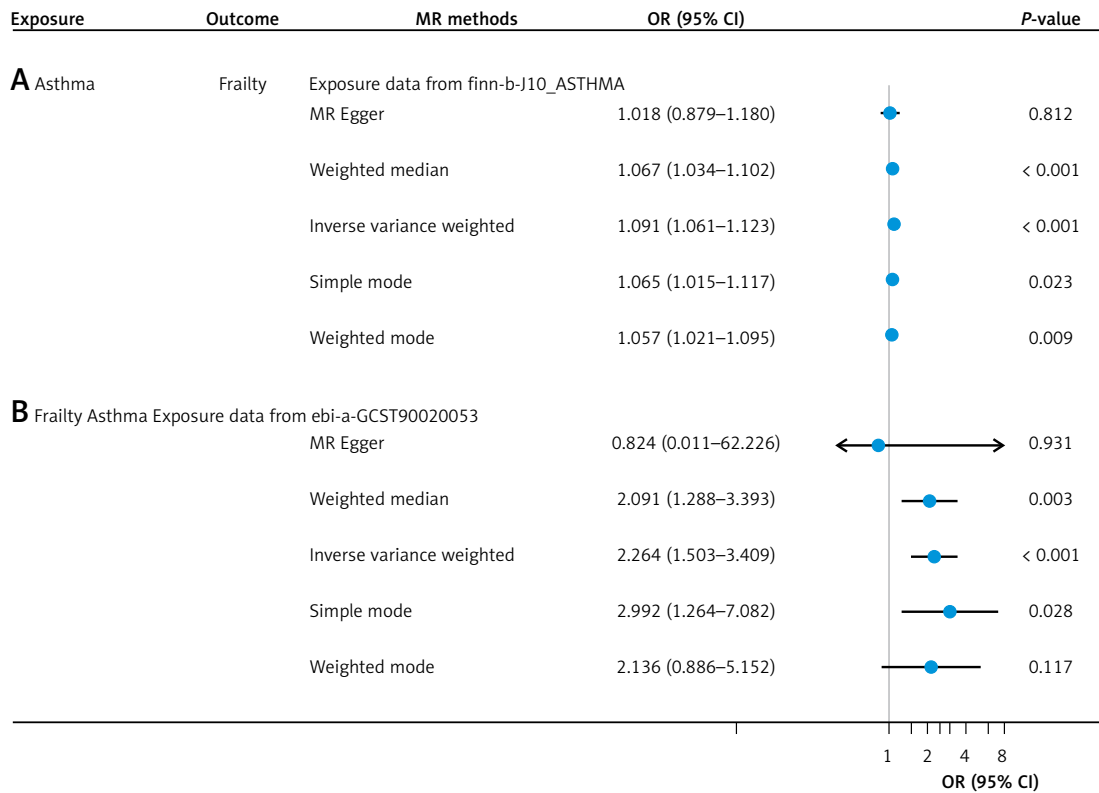


Figure 4. Mendelian randomization analysis of genetically predicted asthma and frailty. **A** – Effect of asthma on frailty. **B** – Effect of frailty on asthma

OR – odds ratio, CI – confidence interval.

rapid aging of populations is emerging as a major public health concern globally, including those with asthma [24]. In a cross-sectional observational study focusing on older adults with asthma, 52 out of 69 outpatient participants aged over 65 (representing 75.4%) were classified as frail [25]. A cross-sectional study involving 224,142 older adults aged 60 years or older revealed that older adults with asthma experienced a 3.3-fold higher prevalence of frailty compared to their counterparts without asthma [26]. Evidence also indicated that frailty was a significant risk factor for the development and progression of asthma [27]. Among the 12,345 community-dwelling adults in the GAZEL cohort, individuals with current asthma had an increased risk of frailty, regardless of the specific questions used to assess asthma status [24]. The observational studies often encountered challenges from confounding variables, making it difficult to establish causality. However, the present two-sample MR analysis used various approaches with data from the GWAS database and revealed a bidirectional causal relationship between asthma and frailty. The OR of 1.091 for the causal effect of asthma on frailty appears modest. However, we believe it may have clinical value for the following reasons. First, given the high global prevalence of asthma, although the increase in

risk is relatively small, this association could have significant implications at the population level. Second, frailty is a multifactorial condition, and asthma may contribute to its development alongside other risk factors. Third, existing evidence suggests that chronic inflammatory conditions such as asthma may play a role in the development of frailty [28, 29]. Fourth, identifying asthma as a potential risk factor for frailty could inform preventive strategies and early interventions in clinical practice.

The bidirectional relationship between asthma and frailty could arise from shared pathophysiological mechanisms, particularly dysregulated inflammation [30–33]. Chronic systemic inflammation is strongly associated with the development of frailty, especially among older adults with asthma [34, 35]. Numerous inflammatory markers identified in frail individuals have also been detected in those with asthma, indicating a significant overlap in underlying biological processes [36]. Asthma, characterized by persistent airway inflammation, often coexisted with frailty, further complicating this relationship, yet the precise mechanisms linking frailty and asthma remain unclear [37]. Immunosenescence in frail elderly patients exacerbated this inflammatory state, leading to worsening asthma symptoms, while

the inflammation triggered by asthma could also contribute to the onset of frailty [38]. Our subgroup analysis revealed that the incidence of frailty among asthma patients increased with age, highlighting the importance of recognizing this intersection. Additionally, chronic inflammation in asthmatic patients could extend beyond the respiratory system, resulting in elevated levels of peripheral blood eosinophils, total blood IgE, and type 2 cytokines [39]. Beyond inflammation, oxidative stress and mitochondrial dysfunction may further connect asthma and frailty, as excessive reactive oxygen species (ROS) impair lung function, promote muscle degradation, and accelerate cellular aging [40–43]. Additionally, autonomic nervous system dysregulation, characterized by increased bronchoconstriction in asthma and reduced vagal tone in frailty, may exacerbate disease severity in both conditions [44]. Metabolic disturbances, including insulin resistance, sarcopenic obesity, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation, further contribute to frailty progression and poor asthma control [45–47]. Moreover, emerging evidence highlights the role of gut microbiome dysbiosis in both conditions, as disruptions in the gut-lung axis can exacerbate systemic inflammation and immune dysfunction [48–50]. Reduced physical activity in asthma patients due to dyspnea and airway obstruction may lead to muscle atrophy and sarcopenia, reinforcing frailty development, while frail individuals with weakened respiratory muscles and immune dysfunction face greater challenges in asthma management [51, 52]. Sleep disturbances, including nocturnal hypoxia and obstructive sleep apnea, further amplify systemic inflammation, oxidative stress, and metabolic dysfunction, exacerbating both frailty and asthma severity [53]. Given these interconnections, early identification of frailty risk factors and targeted interventions, such as anti-inflammatory and antioxidant therapies, microbiome modulation, structured exercise programs, and sleep optimization, are crucial to mitigating or delaying frailty onset in asthma patients. Further research is warranted to elucidate the precise molecular pathways underlying this bidirectional relationship and develop tailored therapeutic strategies for at-risk populations.

Other factors also contribute to this bidirectional relationship. Individuals with frailty were more susceptible to developing respiratory impairments, while those with respiratory issues were at a higher risk of experiencing frailty [54]. Common risk factors, including tobacco use, aging and endocrine dysfunction, were associated with frailty and respiratory impairment [5, 55, 56]. Reduced physical activity made older adults with asthma

more prone to sarcopenia, which was a critical factor in the progression of frailty syndromes [57]. Immune system dysfunction in frail patients [58, 59], combined with reduced physical activity and weakened respiratory muscles, made managing asthma more challenging [3, 38]. Asthma associated airway obstruction and breathing difficulties could restrict physical activity and exacerbate frailty. Frail older adults experienced swallowing dysfunction, which increased the risk of aspiration and choking, potentially leading to respiratory diseases [60]. Gastro-esophageal reflux disease (GORD) is a significant trigger for asthma, driven by mechanisms such as microaspiration of gastric acid into the airways, vagal-mediated reflux, and direct esophageal stimulation by acid [61]. The prevalence of GORD among individuals with asthma was particularly high, with studies reporting rates ranging from 34% to 89% [62–67]. Therefore, it is essential to identify risk factors for frailty and implement early targeted interventions in asthma patients to mitigate or delay the onset of frailty.

This study used a combination of observational analysis and MR study to explore the association between asthma and frailty. By analyzing data from NHANES, we first found a significant association between asthma and frailty. In addition, we further validated this observational result with the MR study, revealing a possible two-way causal relationship between asthma and frailty. The main strengths of this study included the use of NHANES data and a two-way multi-database MR method, which generally reduced susceptibility to causality errors often seen in observational studies due to confounding factors and reverse causality. Additionally, all participants in the GWAS dataset were homozygous and of European ancestry, which minimized population heterogeneity. Due to the potential overlap between the asthma-related genes in the UK Biobank and the frailty-related genes from the same source, we opted to focus exclusively on the FinnGen database for our analysis of asthma genes. However, there are some limitations to acknowledge. First, NHANES data, being self-reported, were inevitably subject to recall bias. Diagnoses of asthma were primarily based on questionnaires without corroborative laboratory data on respiratory function, potentially introducing selection bias. Secondly, identifying all multi-effect SNPs can be challenging, as the complex interactions among certain phenotypes are not yet fully understood. This study used data from the UK Biobank and the FinnGen database, employing various models to validate the MR hypothesis, which produced generally consistent results, though some uncertainties remain. Furthermore, as this study predominantly pertained

to individuals of European descent, the findings may not be applicable to other populations. Caution should be exercised in interpreting these results, and further validation in larger, more diverse datasets is necessary.

In conclusion, this study revealed a bidirectional causal relationship between asthma and frailty, both of which are global health concerns. Effective asthma management is crucial for reducing the risk of frailty. Therefore, routine screening for frailty in asthma patients is recommended, along with the implementation of appropriate treatment and management strategies.

Statement of clinical trial registration

This study used publicly available NHANES and GWAS data and did not require additional clinical trial registration. Clinical trial number: not applicable.

Acknowledgments

We express our gratitude to all the personnel at the National Center for Health Statistics of the Centers for Disease Control and Prevention for their efforts in planning and conducting NHANES, as well as for providing access to the NHANES datasets through their website. We also extend our sincere thanks to the investigators and participants of the UK Biobank and FinnGen database for providing the GWAS data that made this research possible. The availability of these comprehensive datasets has significantly contributed to advancing our understanding of the genetic basis of asthma and frailty. We would like to thank the Free Statistic software team for providing technical assistance and valuable tools for data analysis and visualization.

Funding

This work was supported by Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (No. 2023-JKCS-25), National Natural Science Foundation of China (No. 82171195) and Beijing Natural Science Foundation (No. 7232131).

Ethical approval

Ethical approval and informed consent are not required for this study, as we used publicly available datasets, including NHANES and GWAS. Ethical approval and participant consent have already been obtained in the NHANES and original GWAS studies.

Conflict of interest

The authors declare no conflict of interest.

References

- Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc* 2010; 58: 681-7.
- The Lancet. Bringing frailty into all realms of medicine. *Lancet* 2019; 394: 1298.
- Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146-56.
- Angulo J, El Assar M, Rodríguez-Mañas L. Frailty and sarcopenia as the basis for the phenotypic manifestation of chronic diseases in older adults. *Mol Aspects Med* 2016; 50: 1-32.
- Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013; 381: 752-62.
- Hanlon P, Nicholl BI, Jani BD, et al. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health* 2018; 3: e323-32.
- Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. *BMC Geriatr* 2008; 8: 24.
- Hakeem FF, Bernabé E, Sabbah W. Association between oral health and frailty among American older adults. *J Am Med Dir Assoc* 2021; 22: 559-63.e2.
- Jiang Z, Wang J, Cai X, et al. L-shaped association of serum α -Klotho and frailty among the middle-aged and older adults: results from NHANES 2007-2016. *BMC Geriatr* 2023; 23: 716.
- Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017; 5: 691-706.
- Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol* 2015; 15: 57-65.
- Osadnik CR, Brighton LJ, Burtin C, et al. European Respiratory Society statement on frailty in adults with chronic lung disease. *Eur Respir J* 2023; 62: 2300442.
- Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003; 32: 1-22.
- Nattel S. Canadian Journal of Cardiology January 2013: genetics and more. *Can J Cardiol* 2013; 29: 1-2.
- Haycock PC, Burgess S, Wade KH, et al. Best (but oft-forgotten) practices: the design, analysis, and interpretation of Mendelian randomization studies. *Am J Clin Nutr* 2016; 103: 965-78.
- The National Health and Nutritional Examination Survey (NHANES) Analytic and Reporting Guidelines [<https://www.cdc.gov/nchs/nhanes/index.htm>].
- Hoover M, Rotermann M, Sanmartin C, et al. Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. *Health Rep* 2013; 24: 10-7.
- Blodgett J, Theou O, Kirkland S, et al. Frailty in NHANES: Comparing the frailty index and phenotype. *Arch Gerontol Geriatr* 2015; 60: 464-70.
- Wang X, Wen J, Gu S, et al. Frailty in asthma-COPD overlap: a cross-sectional study of association and risk factors in the NHANES database. *BMJ Open Respir Res* 2023; 10: e001713.
- Slavin M, Li H, Khatri M, et al. Dietary magnesium and migraine in adults: a cross-sectional analysis of the National Health and Nutrition Examination Survey 2001-2004. *Headache* 2021; 61: 276-86.

21. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the STROBE-MR statement. *JAMA* 2021; 326: 1614-21.
22. Brookhart MA, Wyss R, Layton JB, et al. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes* 2013; 6: 604-11.
23. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. *JAMA* 2019; 321: 602-3.
24. Landré B, Nadif R, Goldberg M, et al. Asthma is associated with frailty among community-dwelling adults: the GAZEL cohort. *BMJ Open Respir Res* 2020; 7: e000526.
25. Kusunose M, Sanda R, Mori M, et al. Are frailty and patient-reported outcomes independent in subjects with asthma? A cross-sectional observational study. *Clin Respir J* 2021; 15: 216-24.
26. Zeng XZ, Meng LB, Jia N, et al. Epidemiological status and associated factors of frailty and pre-frailty in older adults with asthma in China: a national cross-sectional study. *Front Public Health* 2023; 11: 1136135.
27. Figueiredo RG, Pinheiro GP, Arata V, et al. Impact of frailty in elderly patients with moderate to severe asthma. *PLoS One* 2022; 17: e0270921.
28. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev* 2016; 31: 1-8.
29. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; 370: 797-9.
30. Swanson SA, Tiemeier H, Ikram MA, et al. Nature as a trialist? Deconstructing the analogy between mendelian randomization and randomized trials. *Epidemiology* 2017; 28: 653-9.
31. Marengoni A, Vetrano DL, Manes-Gravina E, et al. The relationship between COPD and frailty: a systematic review and meta-analysis of observational studies. *Chest* 2018; 154: 21-40.
32. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med* 2000; 51: 245-70.
33. Roubenoff R. Catabolism of aging: is it an inflammatory process? *Curr Opin Clin Nutr Metab Care* 2003; 6: 295-9.
34. Zhu J, Zhou D, Wang J, et al. Frailty and cardiometabolic diseases: a bidirectional Mendelian randomisation study. *Age Ageing* 2022; 51: afac256.
35. Dunn RM, Busse PJ, Wechsler ME. Asthma in the elderly and late-onset adult asthma. *Allergy* 2018; 73: 284-94.
36. Lee SY, Nyunt MSZ, Gao Q, et al. Co-occurrence of physical frailty and COPD and association with disability and mortality: Singapore Longitudinal Ageing Study. *Chest* 2022; 161: 1225-38.
37. Bates JHT, Poynter ME, Frodella CM, et al. Pathophysiology to phenotype in the asthma of obesity. *Ann Am Thorac Soc* 2017; 14: S395-8.
38. Hanania NA, King MJ, Braman SS, et al. Asthma in the elderly: current understanding and future research needs--a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol* 2011; 128: S4-24.
39. Ryu K, Fukutomi Y, Nakatani E, et al. Frailty and muscle weakness in elderly patients with asthma and their association with cumulative lifetime oral corticosteroid exposure. *Allergol Int* 2023; 72: 252-61.
40. MacNee W. Oxidative stress and lung inflammation in airways disease. *Eur J Pharmacol* 2001; 429: 195-207.
41. Kirkwood TB. Understanding the odd science of aging. *Cell* 2005; 120: 437-47.
42. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature* 2000; 408: 239-47.
43. Manke A, Wang L, Rojanasakul Y. Mechanisms of nanoparticle-induced oxidative stress and toxicity. *Biomed Res Int* 2013; 2013: 942916.
44. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. *Physiol Rev* 2010; 90: 513-57.
45. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann N Y Acad Sci* 2002; 966: 290-303.
46. Ferrucci L, Guralnik JM, Studenski S, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. *J Am Geriatr Soc* 2004; 52: 625-34.
47. Barzilai N, Huffman DM, Muzumdar RH, et al. The critical role of metabolic pathways in aging. *Diabetes* 2012; 61: 1315-22.
48. Budden KF, Gellatly SL, Wood DL, et al. Emerging pathogenic links between microbiota and the gut-lung axis. *Nat Rev Microbiol* 2017; 15: 55-63.
49. Dickson RP, Huffnagle GB. The lung microbiome: new principles for respiratory bacteriology in health and disease. *PLoS Pathog* 2015; 11: e1004923.
50. He Y, Wu W, Zheng HM, et al. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. *Nat Med* 2018; 24: 1532-5.
51. Landi F, Liperoti R, Russo A, et al. Sarcopenia as a risk factor for falls in elderly individuals: results from the ILSIRENTE study. *Clin Nutr* 2012; 31: 652-8.
52. de Vries NM, Staal JB, van Ravensberg CD, et al. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011; 10: 104-14.
53. Lim AS, Yu L, Kowgier M, et al. Modification of the relationship of the apolipoprotein E ϵ 4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurol* 2013; 70: 1544-51.
54. Vaz Fragoso CA, Enright PL, McAvay G, et al. Frailty and respiratory impairment in older persons. *Am J Med* 2012; 125: 79-86.
55. Leng SX, Cappola AR, Andersen RE, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. *Ageing Clin Exp Res* 2004; 16: 153-7.
56. Varadhan R, Walston J, Cappola AR, et al. Higher levels and blunted diurnal variation of cortisol in frail older women. *J Gerontol A Biol Sci Med Sci* 2008; 63: 190-5.
57. Attaix D, Mosoni L, Dardevet D, et al. Altered responses in skeletal muscle protein turnover during aging in anabolic and catabolic periods. *Int J Biochem Cell Biol* 2005; 37: 1962-73.
58. Sahin E, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. *Nature* 2010; 464: 520-8.
59. Miller RA. The aging immune system: primer and prospectus. *Science* 1996; 273: 70-4.
60. Duncan S, McAuley DF, Walshe M, et al. Interventions for oropharyngeal dysphagia in acute and critical care: a systematic review and meta-analysis. *Intensive Care Med* 2020; 46: 1326-38.
61. Astarita C, Gargano D, Cutajar M, et al. Gastroesophageal reflux disease and asthma: an intriguing dilemma. *Allergy* 2000; 55 Suppl 61: 52-5.
62. Goldman J, Bennett JR. Gastro-oesophageal reflux and respiratory disorders in adults. *Lancet* 1988; 2: 493-5.

63. Sontag SJ, O'Connell S, Khandelwal S, et al. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. *Gastroenterology* 1990; 99: 613-20.
64. Alexander JA, Hunt LW, Patel AM. Prevalence, pathophysiology, and treatment of patients with asthma and gastroesophageal reflux disease. *Mayo Clin Proc* 2000; 75: 1055-63.
65. Thakkar K, Boatright RO, Gilger MA, et al. Gastroesophageal reflux and asthma in children: a systematic review. *Pediatrics* 2010; 125: e925-30.
66. Leggett JJ, Johnston BT, Mills M, et al. Prevalence of gastroesophageal reflux in difficult asthma: relationship to asthma outcome. *Chest* 2005; 127: 1227-31.
67. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. *Gut* 2007; 56: 1654-64.