# Exploring the Association Between Asthma and Frailty: A Cross-Sectional and A Bidirectional Mendelian Randomization study

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Cross-sectional study, Asthma, Mendelian randomization, Frailty, Causal effect

**Abstract**

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# Exploring the Association Between Asthma and Frailty: A Cross-Sectional and A Bidirectional Mendelian Randomization Study

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## Abstract

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## 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 heightens susceptibility to stressors and the likelihood of adverse events like 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 remains 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, 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, with its prevalence continuing to rise worldwide and 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 if the observed co-existence is due to confounding factors or common risk elements such as inflammation. Establishing a definitive causality between asthma and frailty is critical as it would enhance our understanding of the diseases' 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 link 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.

## Materials and Methods

### Overall study design

This study was divided into two sections. Initially, we analyzed data from NHANES to examine the link between asthma and frailty, controlling for potential confounders. propensity score matching (PSM) was utilized to validate the robustness of our results. Subsequently, bidirectional MR were 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 utilize multistage 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 cognitive 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 saturate 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 1. In this study, a 49-item frailty index derived from the NHANES dataset's clinical, laboratory, and survey data were utilized[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 like 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 delineated 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 one year but none in the last year), or current (12 or more drinks in the last year). For previous diseases like 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 like 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 the 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 were displayed through frequencies and percentages, and continuous data were summarized using 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 chi-square 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 utilized 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 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 ($P < 5\times10^{-8}$), 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 utilized pre-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. Post-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 evaluated horizontal pleiotropy. Further scrutiny for potential reverse causality was performed through reverse MR analysis. Additionally, scatter plots were created to visualize the relationships between SNP-exposure and SNP-outcome. 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/freestatistics/). $P < 0.05$ was considered statistically significant.

# Results

## Cross-sectional analysis

### Participants

This study utilized NHANES data from 2005 to 2018, initially involving 70,190 participants. Among these, 39,749 adults aged 20 and above completed the interview and 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 sociodemographic 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.

### 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 1 and Supplementary Table 2. Asthmatic participants typically trended toward being younger and predominantly male, with a significant

representation from non-Hispanic white and black backgrounds. 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 like 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 asthmatics and 19.8% (5,010 / 25,292) in non-asthmatic participants. The PSM analysis shows significant association between asthma and frailty. The crude OR is 2.16 (95% CI: 2.01-2.31), indicating a strong positive association before adjustments. After adjusting for multiple variables, the OR is 2.04 (95% CI: 1.87-2.23), still significant association. When adjusted for propensity scores, the OR is 1.71 (95% CI: 1.59-1.84), and PSM yields an OR of 1.60 (95% CI: 1.46-1.76), showing more conservative estimates. Weighted analyses using IPTW and SMRW provide 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 produce 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 reliable relationship that asthma increases the risk of frailty, with significant interactions observed in relation to age, family income, smoking status, alcohol status and hypertension (Figure 3). The 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 have never smoked, former smoker, and current smoker experienced frailty incidence of 25.7%, 42.4%, and 44.8% ($P$ = 0.016). Asthmatic participants who have never drunk, former drinker, and current drinker 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 (From asthma to frailty)

Following application of SNPs selection criteria ($P < 5\times10^{-8}$, $R^2 < 0.001$, kb = 10,000), 15 asthma-associated SNPs (Supplementary Table 3) 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 4a) showed that asthma was linked to the increased risk of frailty (with IVW method), and asthma patients had 1.091 times the risk of frailty ($P$ < 0.001). Weighted Median, Simple Mode, Weighted Mode results were consistent with the IVW result. The MR-Egger regression analysis results were inconsistent with the IVW result, it indicated the presence of potential biases or effect heterogeneity that needs to be considered. Scatter plots are presented in Supplementary Figure 1a. The forest plot showed a significant positive effect of asthma on frailty index (with IVW method, Supplementary Figure 1c). Leave-one-out analyses of the results described above are presented in Supplementary Figure 2a, showing minimal influence of individual SNP exclusions on the overall effect estimate.

### Sensitivity analysis

Supplementary Figure 2c showed a symmetric distribution of data and supported 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 (counteraction from frailty to asthma)**

Following the SNPs selection criteria, 13 frailty-associated SNPs (F-statistics > 10, Supplementary Table 4) were utilized 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**

In the Inverse MR analysis (Figure 4b) 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. The 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 1b. The forest plot supported these results (Supplementary Figure 1d). 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 2b).

**Sensitivity analysis**

Supplementary Figure 2d 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, except for the MR-Egger. Reverse analyses indicated that frailty was also positively associated with an increased risk of asthma, with consistent results across three methods, except for the MR-Egger and Weighted Mode. These results comprehensively revealed the 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 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 increase in the 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 utilized 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 like 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 linked to 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 link 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]. The 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 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 utilized 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, this study predominantly pertained to the 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.

## Conclusion

This study reveals 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.

## Conflict of interest

The authors declare that there is no conflict of interest.

## Author statement

This manuscript is an original work and is not being considered for publication elsewhere, either in whole or in part. All authors have contributed significantly to the study. SP collected and analyzed data, and wrote the manuscript; HL participated in statistical design and manuscript revision. XR, LG, SL and XX participated in data analysis and manuscript revision. MW, YT, BM, RC, ZG and XL participated in manuscript revision. HZ participated in manuscript design and revision. CN designed the study, wrote and revised the manuscript. All authors approved the final version submitted for publication.

## Ethics approval and consent to participate

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

## Statement of clinical trial registration

This study used the HNANES public database and public WGAS data without the need for additional clinical trial registration. So Clinical trial number: not applicable.

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683 **Table 1** 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 ± SD** | 49.5 ± 17.6 | 49.9 ± 17.6 | 47.3 ± 17.5 | <0.001 | 47.4 ± 17.4 | 47.3 ± 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 ± SD** | 29.2 ± 7.0 | 29.0 ± 6.8 | 30.8 ± 8.2 | <0.001 | 30.8 ± 8.1 | 30.7 ± 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 |

684 PSM, Propensity score matching; BMI, Body mass index; CHD, Coronary heart disease.

685

686 **Supplementary Table 1** Variables in the 49-item frailty index and their respective
687 scorings

| Variable | Scoring |
|---|---|
| Cognition | |
| 1. Experience confusion/memory problems | Yes = 1, No = 0 |
| Dependence | |
| 2. Managing money | Difficulty = 1, No Difficulty = 0 |
| 3. Stooping, crouching, kneeling | Difficulty = 1, No Difficulty = 0 |
| 4. Lifting or carrying | Difficulty = 1, No Difficulty = 0 |
| 5. House chore | Difficulty = 1, No Difficulty = 0 |
| 6. Preparing meals | Difficulty = 1, No Difficulty = 0 |
| 7. Standing up from armless chair | Difficulty = 1, No Difficulty = 0 |
| 8. Getting in and out of bed difficulty | Difficulty = 1, No Difficulty = 0 |
| 9. Using fork, knife, drinking from cup | Difficulty = 1, No Difficulty = 0 |
| 10. Dressing yourself | Difficulty = 1, No Difficulty = 0 |
| 11. Standing for long periods difficulty | Difficulty = 1, No Difficulty = 0 |
| 12. Grasp/holding small objects | Difficulty = 1, No Difficulty = 0 |
| 13. Attending social event | Difficulty = 1, No Difficulty = 0 |
| 14. Push or pull large objects | Difficulty = 1, No Difficulty = 0 |
| 15. Walking for a quarter mile difficulty | Difficulty = 1, No Difficulty = 0 |
| 16. Walking up 10 steps difficulty | Difficulty = 1, No Difficulty = 0 |
| Depressive Symptoms | |
| 17. Have little interest in doing things | Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0 |
| 18. Feeling down, depressed, or hopeless | Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0 |
| 19. Trouble sleeping or sleeping too much | Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0 |
| 20. Feeling tired or having little energy | Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0 |
| 21. Poor appetite or overeating | Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0 |
| 22. Feeling bad about yourself | Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0 |
| 23. Trouble concentrating on things | Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0 |
| Comorbidities | |
| 24. Arthritis | Yes = 1, Suspect = 0.5, No = 0 |
| 25. Thyroid problems | Yes = 1, Suspect = 0.5, No = 0 |
| 26. Chronic bronchitis | Yes = 1, Suspect = 0.5, No = 0 |
| 27. Cancer | Yes = 1, Suspect = 0.5, No = 0 |
| 28. Congestive heart failure | Yes = 1, Suspect = 0.5, No = 0 |
| 29. Coronary heart disease | Yes = 1, Suspect = 0.5, No = 0 |

| | |
|---|---|
| 30. Angina | Yes = 1, Suspect = 0.5, No = 0 |
| 31. Heart attack | Yes = 1, Suspect = 0.5, No = 0 |
| 32. Stroke | Yes = 1, Suspect = 0.5, No = 0 |
| 33. Blood pressure | Yes = 1, Suspect = 0.5, No = 0 |
| 34. Diabetes | Yes = 1, Suspect = 0.5, No = 0 |
| 35. weak/failing kidneys | Yes = 1, Suspect = 0.5, No = 0 |
| 36. Urinary Leakage | Yes = 1, Suspect = 0.5, No = 0 |
| Hospital Utilization and Access to Care | |
| 37. Self-rated health | Fair, poor = 1, Excellent, very good, good = 0 |
| 38. Health now compared with 1 year ago | Worse = 1, About the same, better = 0 |
| 39. Overnight hospital patient in past year | Yes = 1, No = 0 |
| 40. Frequency of health care use during past year | None = 0, 1- 5 = 0.5, More than 5 = 1 |
| 41. Number of prescribed medications | None = 0, 1- 4 = 0.5, 5 and more = 1 |
| Physical Performance and Anthropometry | |
| 42. Body mass index | <18.5 or ≥ 30 = 1, 25-30 = 0.5, 18.5-25 = 0 |
| 43. Handgrip strength | Male: For BMI ≤ 24, GS ≤ 29; BMI 24.1-28, GS ≤ 30; BMI >28, GS ≤ 32 = 1 |
| Laboratory Values | |
| 44. Glycohemoglobin (%) | 0%-5.7% = 0, >5.7% = 1 |
| 45. Red blood cell count (million cells/ml) | Male: 4.7-6.1 = 0, Other = 1 |
| 46. Hemoglobin (g/dl) | Male: 13.5-18 = 0, Other = 1 |
| 47. Red cell distribution width (%) | 11.6-14.6 = 0, Other = 1 |
| 48. Lymphocyte percent (%) | 20-40 = 0, Other = 1 |
| 49. Segmented neutrophils percent (%) | 40- 80 = 0, Other = 1 |

688 BMI, Body mass index; GS, grip strength.

689

690

691 **Supplementary Table 2** Population characteristics by categories of asthma status in

692 original cohort

| Variables | Total | Without Asthma | Asthma | *P* value |
|---|---|---|---|---|
| **Participants (n)** | 29589 | 25292 | 4297 | |
| **Age (year), mean ± SD** | 49.5 ± 17.6 | 49.9 ± 17.6 | 47.3 ± 17.5 | < 0.001 |
| **Sex, n (%)** | | | | < 0.001 |
| Male | 14814 (50.1) | 12373 (48.9) | 2441 (56.8) | |
| Female | 14775 (49.9) | 12919 (51.1) | 1856 (43.2) | |
| **Race / Ethnicity, n (%)** | | | | < 0.001 |
| Non-Hispanic white | 13119 (44.3) | 11054 (43.7) | 2065 (48.1) | |
| Non-Hispanic black | 6285 (21.2) | 5231 (20.7) | 1054 (24.5) | |
| Mexican American | 4428 (15.0) | 4046 (16) | 382 (8.9) | |
| Others | 5757 (19.5) | 4961 (19.6) | 796 (18.5) | |
| **Marital status, n (%)** | | | | < 0.001 |
| Married or living with a partner | 17666 (59.7) | 15382 (60.8) | 2284 (53.2) | |
| Living alone | 11923 (40.3) | 9910 (39.2) | 2013 (46.8) | |
| **Family income, n (%)** | | | | < 0.001 |
| Low | 9156 (30.9) | 7588 (30) | 1568 (36.5) | |
| Medium | 11196 (37.8) | 9707 (38.4) | 1489 (34.7) | |
| High | 9237 (31.2) | 7997 (31.6) | 1240 (28.9) | |
| **Education level (year), n (%)** | | | | < 0.001 |
| < 9 | 2836 (9.6) | 2518 (10) | 318 (7.4) | |
| 9-12 | 10891 (36.8) | 9340 (36.9) | 1551 (36.1) | |
| > 12 | 15862 (53.6) | 13434 (53.1) | 2428 (56.5) | |
| **Smoking status, n (%)** | | | | < 0.001 |
| Never | 16149 (54.6) | 14020 (55.4) | 2129 (49.5) | |
| Former | 7240 (24.5) | 6164 (24.4) | 1076 (25) | |
| Current | 6200 (21.0) | 5108 (20.2) | 1092 (25.4) | |
| **Alcohol status, n (%)** | | | | < 0.001 |
| Never | 4102 (13.9) | 3601 (14.2) | 501 (11.7) | |
| Former | 4848 (16.4) | 4115 (16.3) | 733 (17.1) | |
| Current | 20639 (69.8) | 17576 (69.5) | 3063 (71.3) | |
| **BMI, mean ± SD** | 29.2 ± 7.0 | 29.0 ± 6.8 | 30.8 ± 8.2 | < 0.001 |
| **Type 2 Diabetes, n (%)** | | | | < 0.001 |
| No | 24120 (81.5) | 20742 (82) | 3378 (78.6) | |
| Yes | 5469 (18.5) | 4550 (18) | 919 (21.4) | |
| **Hypertension, n (%)** | | | | < 0.001 |
| No | 16970 (57.4) | 14674 (58) | 2296 (53.4) | |
| Yes | 12619 (42.6) | 10618 (42) | 2001 (46.6) | |
| **Stroke, n (%)** | | | | < 0.001 |

| | | | | |
|---|---|---|---|---|
| No | 28433 (96.1) | 24375 (96.4) | 4058 (94.4) | |
| Yes | 1156 (3.9) | 917 (3.6) | 239 (5.6) | |
| **CHD (%)** | | | | 0.025 |
| No | 28390 (95.9) | 24294 (96.1) | 4096 (95.3) | |
| Yes | 1199 (4.1) | 998 (3.9) | 201 (4.7) | |
| **Frailty Status, n (%)** | | | | < 0.001 |
| No | 23086 (78.0) | 20282 (80.2) | 2804 (65.3) | |
| Yes | 6503 (22.0) | 5010 (19.8) | 1493 (34.7) | |

693 BMI, Body mass index; CHD, Coronary heart disease.

694

**Supplementary Table 3** Mendelian randomization analysis for the effects of asthma on frailty risk (Exposure: Asthma || finn-b-J10_ASTHMA; Outcome: Frailty index || ebi-a-GCST90020053)

| SNP | EAE | OAE | EAO | OAO | Exposure | | | Outcome | | | F |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | se | beta | *P* value | se | beta | *P* value | |
| rs11667612 | T | G | T | G | 0.0259 | 0.1471 | 1.43E-08 | 0.01 | 8.00E-04 | 0.9344 | 32.25714 |
| rs118013485 | A | G | A | G | 0.0197 | -0.1108 | 1.92E-08 | 0.0068 | -0.0083 | 0.2205 | 31.63349 |
| rs12761415 | G | A | G | A | 0.0155 | 0.0857 | 3.17E-08 | 0.0043 | 0.0134 | 0.00170098 | 30.5702 |
| rs17293632 | T | C | T | C | 0.0131 | 0.099 | 4.66E-14 | 0.0039 | 0.0088 | 0.02329 | 57.11206 |
| rs1837253 | C | T | C | T | 0.0137 | 0.1345 | 1.23E-22 | 0.0037 | 0.0065 | 0.0846408 | 96.38366 |
| rs186856025 | T | C | T | C | 0.0248 | -0.1571 | 2.32E-10 | 0.0053 | -0.0112 | 0.0366303 | 40.12814 |
| rs2325259 | C | T | C | T | 0.0134 | -0.0758 | 1.69E-08 | 0.0035 | -0.005 | 0.151 | 31.99844 |
| rs35656734 | T | C | T | C | 0.0131 | -0.1122 | 1.00E-17 | 0.0038 | -0.0193 | 2.94E-07 | 73.35726 |
| rs60227565 | A | G | A | G | 0.0161 | -0.1189 | 1.74E-13 | 0.0049 | -0.0189 | 0.000124 | 54.5396 |
| rs62192043 | A | G | A | G | 0.014 | -0.1015 | 3.51E-13 | 0.0038 | -0.0175 | 3.97E-06 | 52.5625 |
| rs6894249 | G | A | G | A | 0.0116 | 0.0932 | 9.29E-16 | 0.0034 | 0.006 | 0.0747894 | 64.55291 |
| rs7035413 | G | A | G | A | 0.0148 | 0.1302 | 1.69E-18 | 0.0039 | 0.0053 | 0.175 | 77.39244 |
| rs7126418 | T | A | T | A | 0.0118 | 0.0655 | 2.60E-08 | 0.0033 | 0.0072 | 0.0313798 | 30.81191 |
| rs74630264 | A | G | A | G | 0.0214 | -0.1501 | 2.49E-12 | 0.0202 | 0.0013 | 0.95 | 49.19646 |
| rs8074437 | G | T | G | T | 0.0117 | 0.0981 | 4.17E-17 | 0.0033 | 0.0049 | 0.141 | 70.30178 |

SNP: single nucleotide polymorphism; EAE: effect allele exposure; OAE: other allele exposure; EAO: effect allele outcome; OAO: other allele outcome; SE: standard error; F: F value.

**Supplementary Table 4** Mendelian randomization analysis for the effects of frailty on asthma risk (Exposure: Frailty index || ebi-a-GCST90020053; Outcome: asthma || finn-b-J10_ASTHMA)

| SNP | EAE | OAE | EAO | OAO | Exposure | | | Outcome | | | F |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | se | beta | *P* value | se | beta | *P* value | |
| rs10891490 | C | T | C | T | 0.0034 | -0.0188 | 2.00E-08 | 0.0121 | -0.0349 | 0.00399797 | 30.57439 |
| rs12739243 | C | T | C | T | 0.004 | -0.0242 | 1.28E-09 | 0.0127 | -0.0128 | 0.3126 | 36.6025 |
| rs1363103 | C | T | C | T | 0.0034 | -0.0191 | 2.23E-08 | 0.0119 | -0.0233 | 0.0503802 | 31.55796 |
| rs17612102 | C | T | C | T | 0.0034 | 0.0187 | 2.85E-08 | 0.0118 | 0.0065 | 0.5822 | 30.25 |
| rs2071207 | C | T | C | T | 0.0033 | -0.0187 | 1.47E-08 | 0.0116 | -0.0367 | 0.001562 | 32.11111 |
| rs2396766 | A | G | A | G | 0.0033 | 0.0201 | 1.22E-09 | 0.0116 | 6.00E-04 | 0.9594 | 37.09917 |
| rs3959554 | G | A | G | A | 0.0034 | 0.0189 | 1.74E-08 | 0.0124 | 0.0151 | 0.2241 | 30.90052 |
| rs4146140 | T | C | T | C | 0.0034 | -0.0198 | 6.83E-09 | 0.0123 | 0.0147 | 0.232 | 33.91349 |
| rs4952693 | T | C | T | C | 0.0034 | -0.0194 | 1.47E-08 | 0.0118 | -0.0132 | 0.2648 | 32.55709 |
| rs56299474 | A | C | A | C | 0.0044 | 0.0241 | 3.94E-08 | 0.0158 | 0.0031 | 0.846 | 30.00052 |
| rs583514 | C | T | C | T | 0.0033 | 0.0199 | 1.65E-09 | 0.0117 | 0.0247 | 0.0342397 | 36.36455 |
| rs8089807 | T | C | T | C | 0.0043 | -0.0248 | 6.50E-09 | 0.0165 | -0.0343 | 0.0375803 | 33.26339 |
| rs82334 | C | A | C | A | 0.0035 | -0.0223 | 3.13E-10 | 0.0117 | -0.0281 | 0.0168702 | 40.5951 |

SNP: single nucleotide polymorphism; EAE: effect allele exposure; OAE: other allele exposure; EAO: effect allele outcome; OAO: other allele outcome; SE: standard error; F: F value.

## Figure legends

### Figure 1

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### Figure 2

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**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. The 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.

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**Mendelian randomization analysis of genetically predicted asthma and frailty.** (a) Asthma on frailty. (b) Frailty on asthma. OR: odds ratio, CI: confidence interval.

## Supplementary Figure Legends

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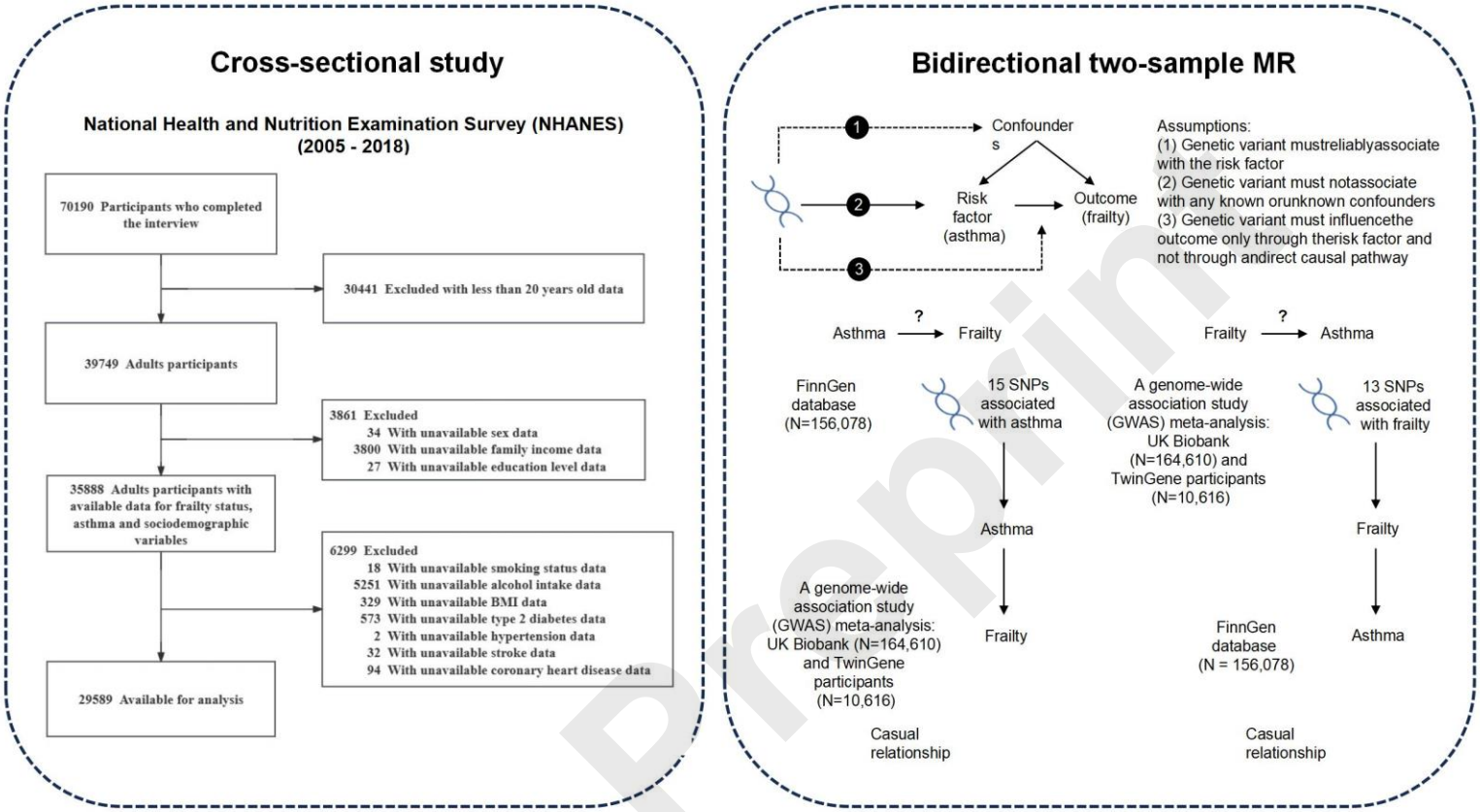
**Figure 1**

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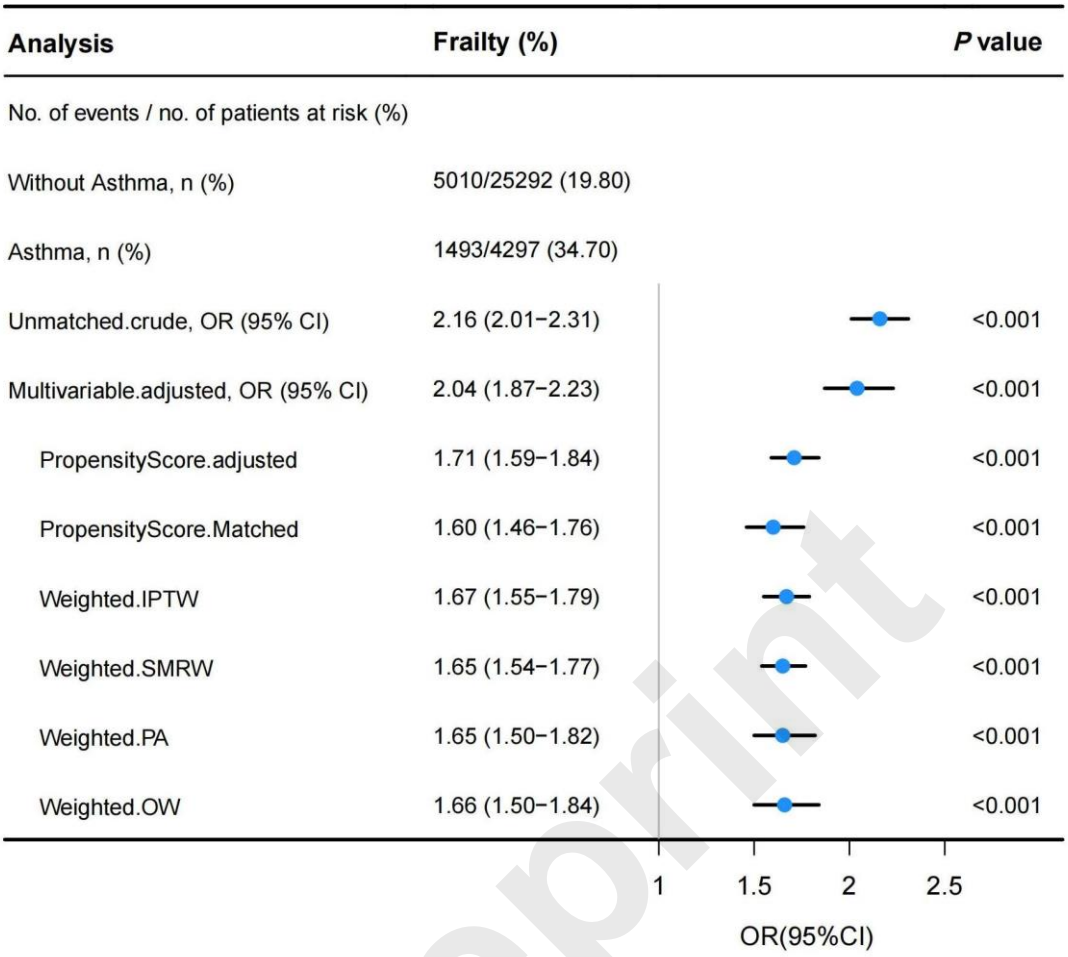


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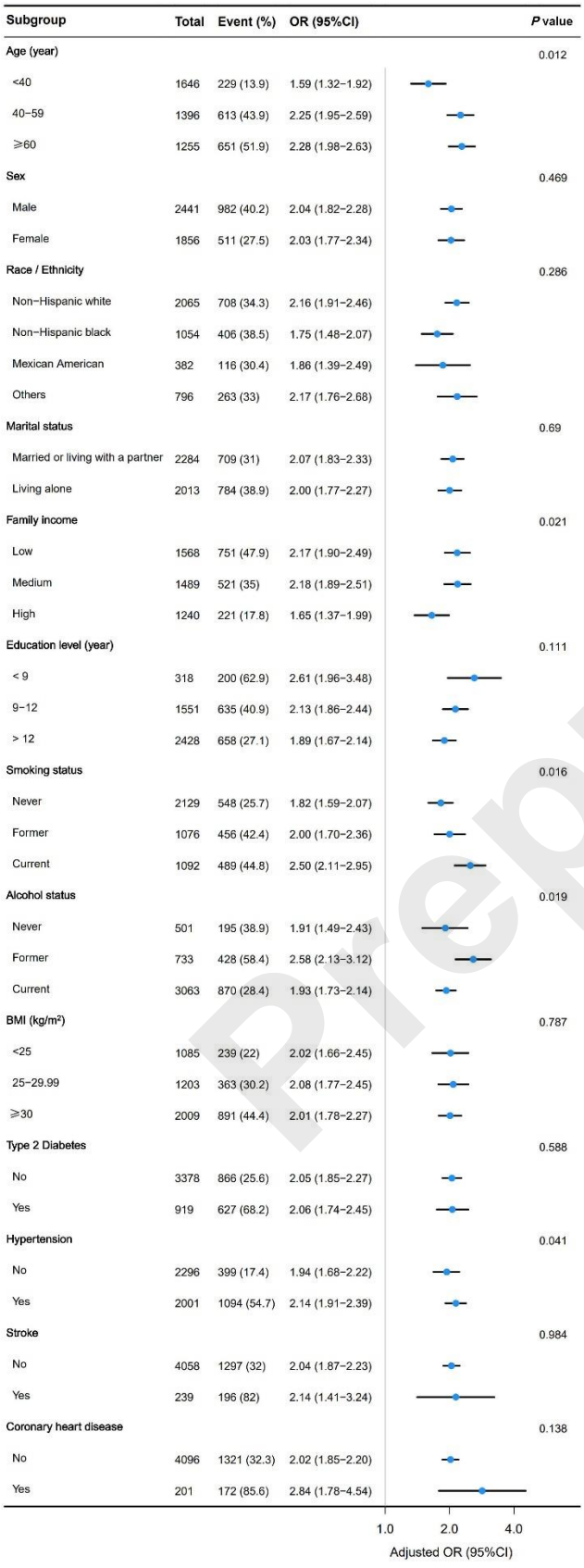

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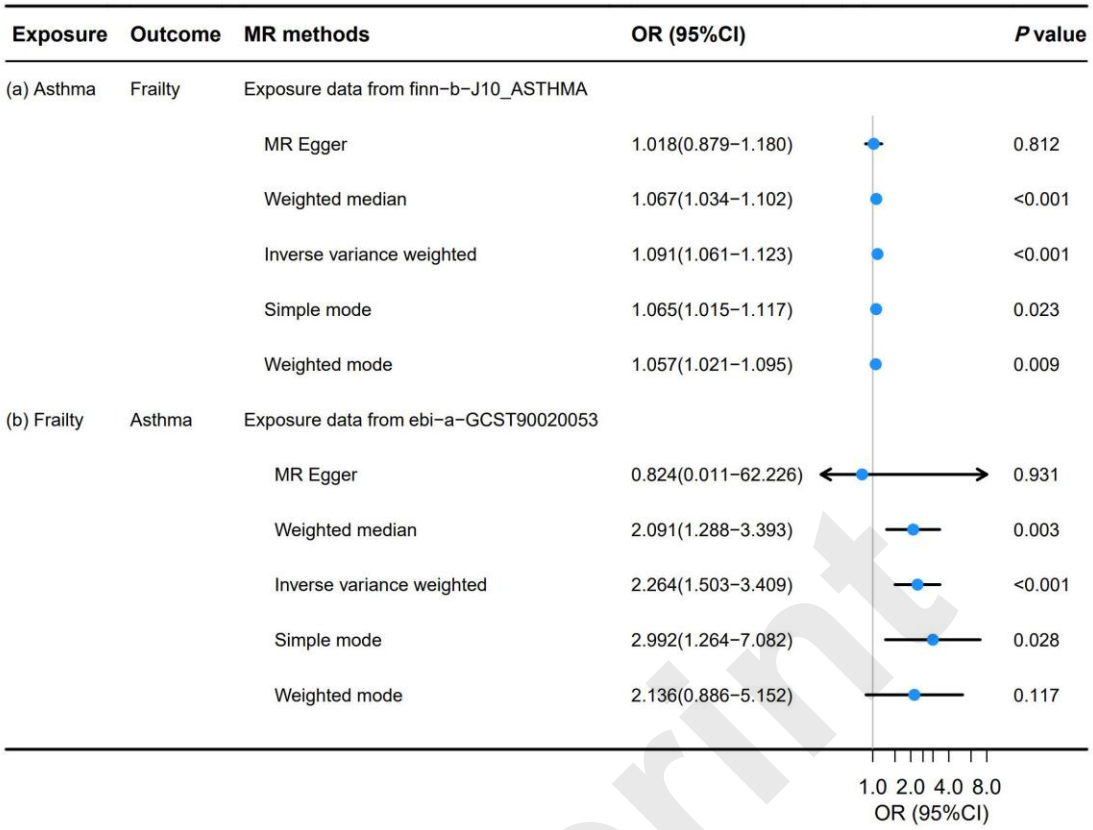


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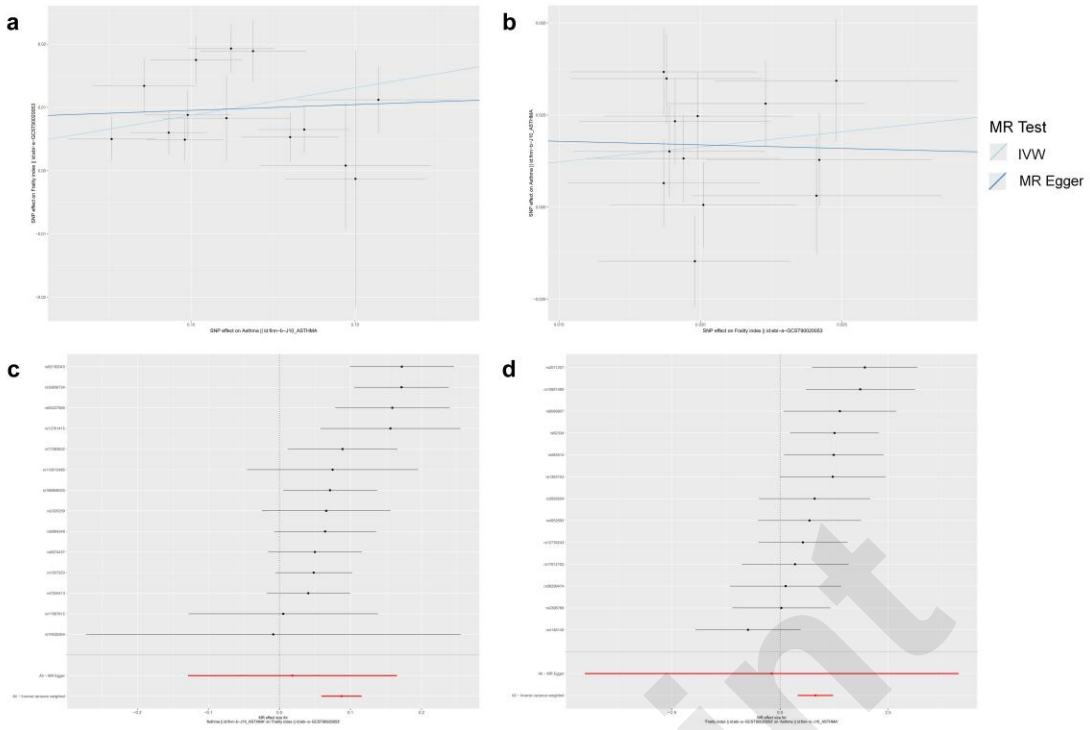


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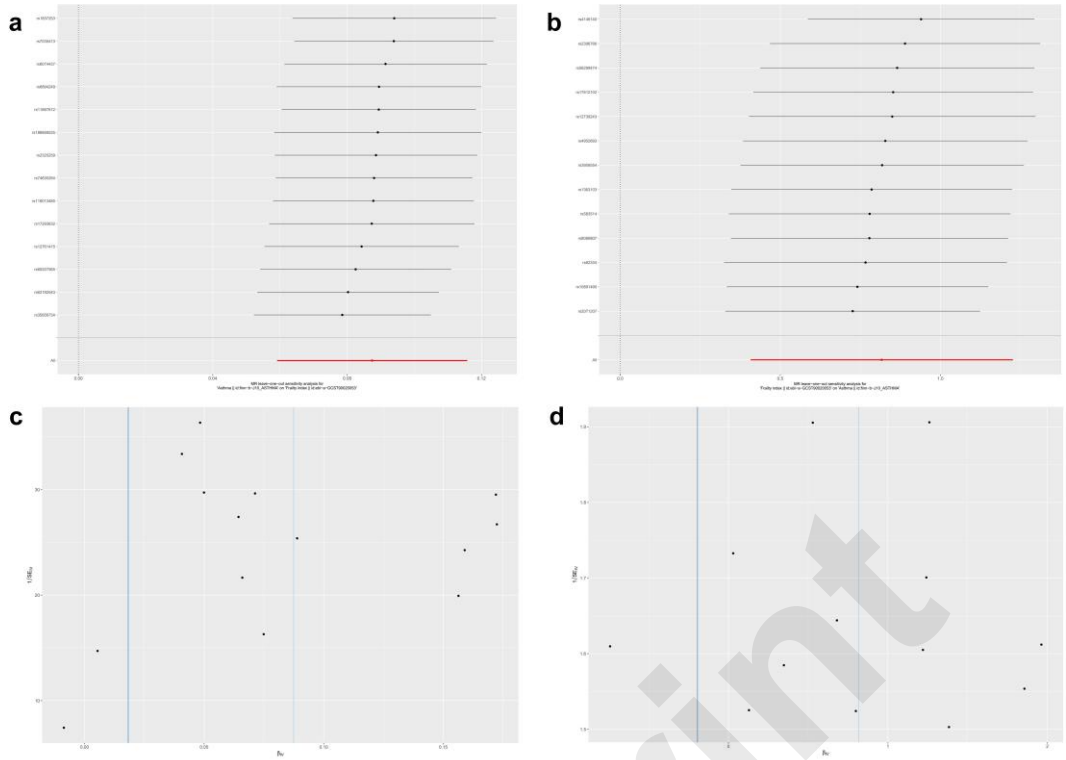


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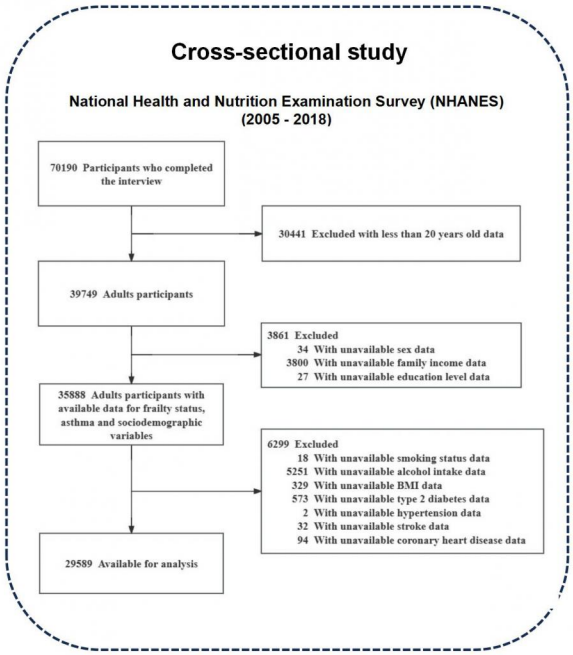

Cross-sectional study
National Health and Nutrition Examination Survey (NHANES)
(2005 - 2018)
70190 Participants who completed the interview
30441 Excluded with less than 20 years old data
39749 Adults participants
3861 Excluded
34 With unavailable sex data
3800 With unavailable family income data
27 With unavailable education level data
35888 Adults participants with available data for frailty status, asthma and sociodemographic variables
6299 Excluded
18 With unavailable smoking status data
5251 With unavailable alcohol intake data
329 With unavailable BMI data
573 With unavailable type 2 diabetes data
2 With unavailable hypertension data
32 With unavailable stroke data
94 With unavailable coronary heart disease data
29589 Available for analysis

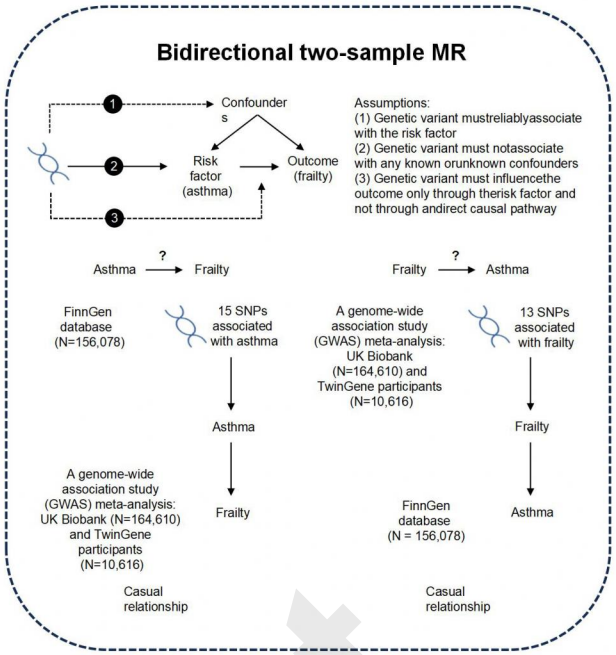
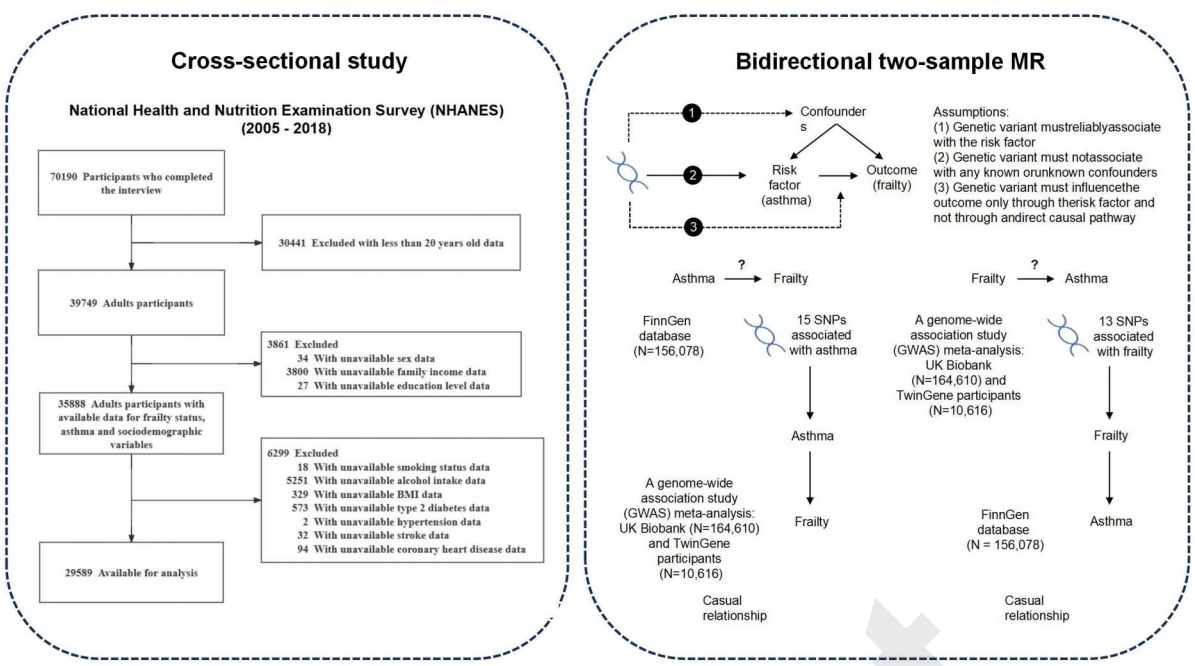

Bidirectional two-sample MR
Confounder s
Risk factor (asthma)
Outcome (frailty)
Assumptions:
(1) Genetic variant mustreliablyassociate with the risk factor
(2) Genetic variant must notassociate with any known orunknown confounders
(3) Genetic variant must influencethe outcome only through therisk factor and not through andirect causal pathway
Asthma ? Frailty
Frailty ? Asthma
FinnGen database (N=156,078)
15 SNPs associated with asthma
Asthma
Frailty
A genome-wide association study (GWAS) meta-analysis: UK Biobank (N=164,610) and TwinGene participants (N=10,616)
13 SNPs associated with frailty
Frailty
Asthma
A genome-wide association study (GWAS) meta-analysis: UK Biobank (N=164,610) and TwinGene participants (N=10,616)
Casual relationship
FinnGen database (N = 156,078)
Casual relationship

**Table1** 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 ± SD** | 49.5 ± 17.6 | 49.9 ± 17.6 | 47.3 ± 17.5 | <0.001 | 47.4 ± 17.4 | 47.3 ± 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 ± SD** | 29.2 ± 7.0 | 29.0 ± 6.8 | 30.8 ± 8.2 | <0.001 | 30.8 ± 8.1 | 30.7 ± 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.

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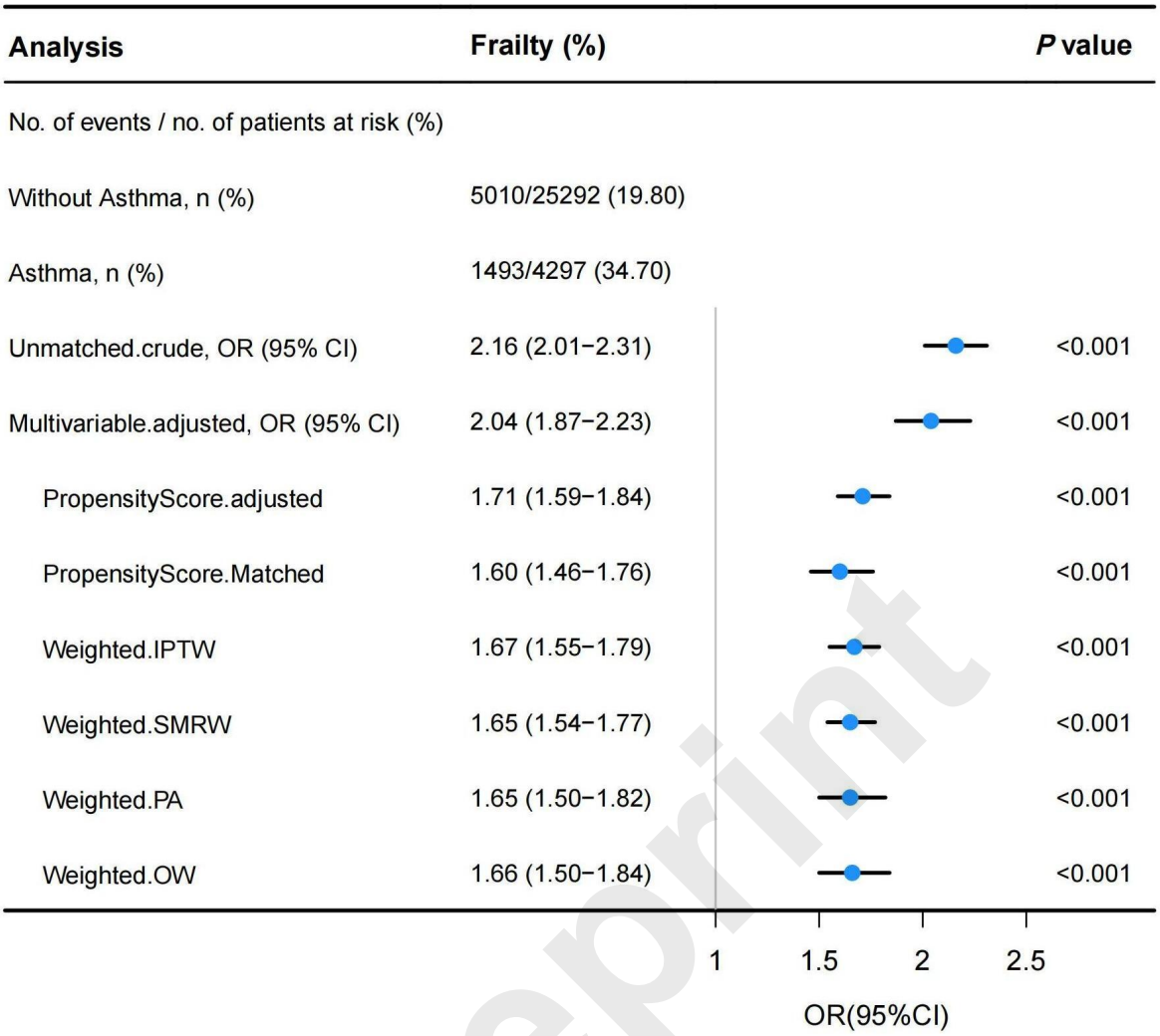


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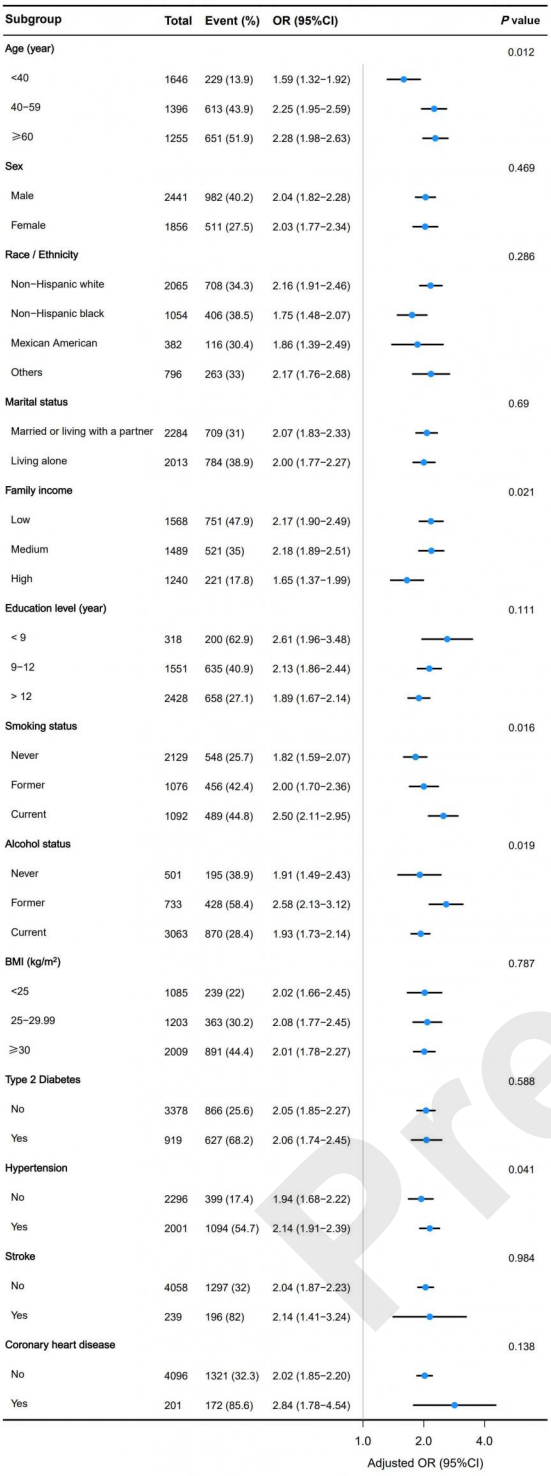


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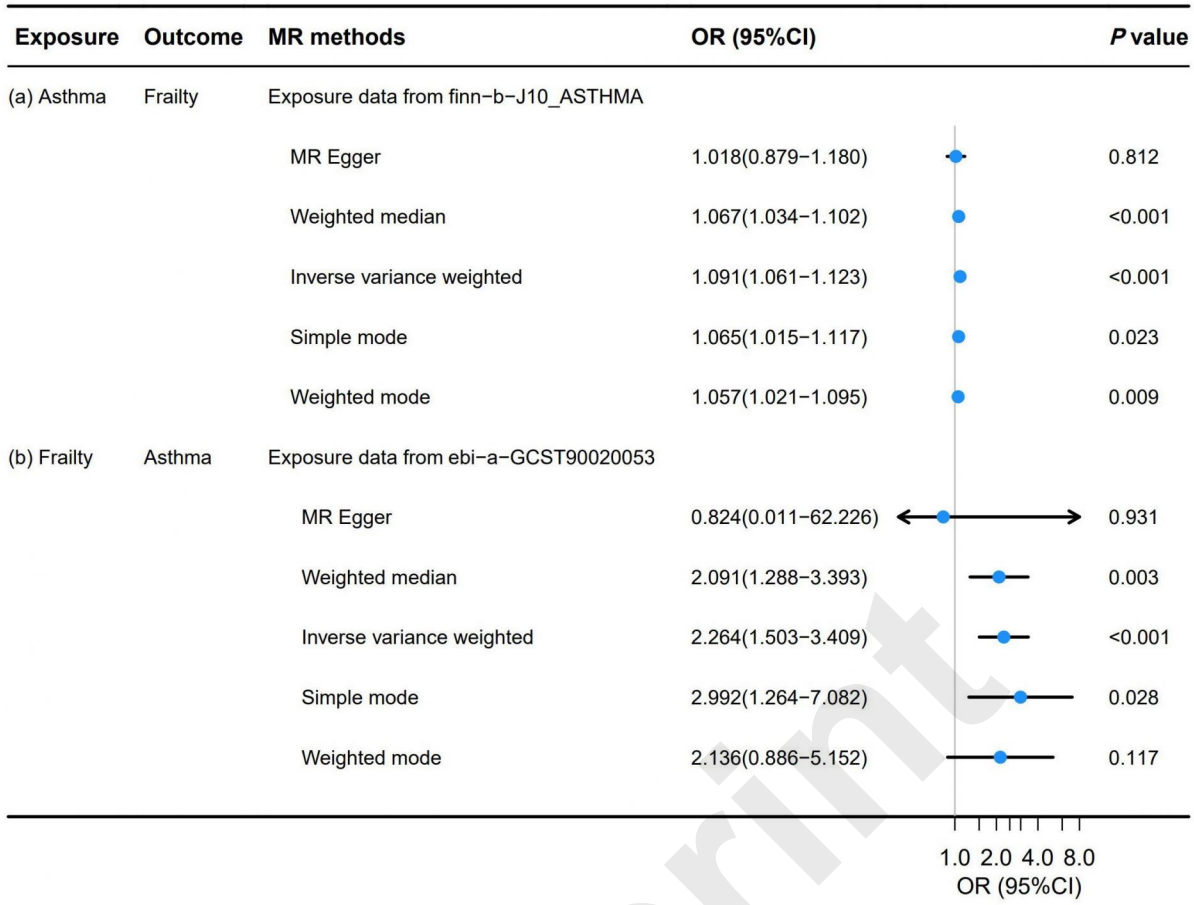


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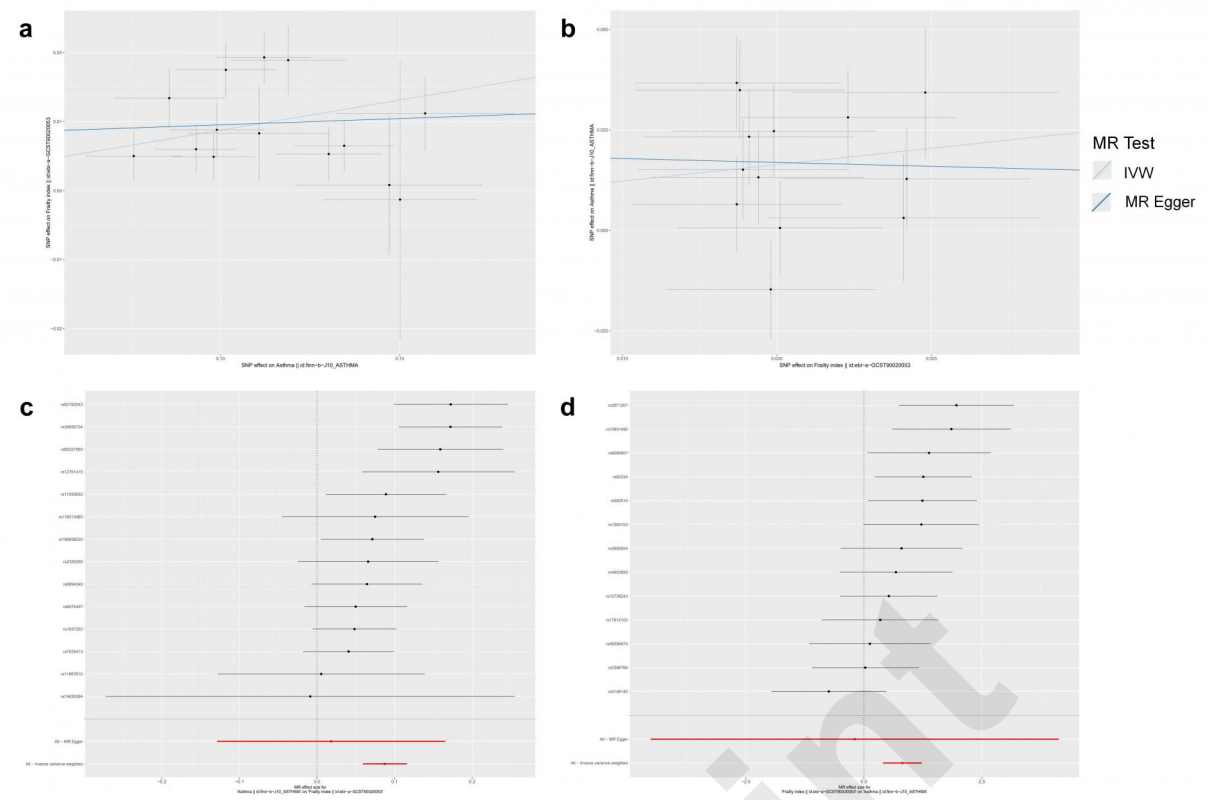


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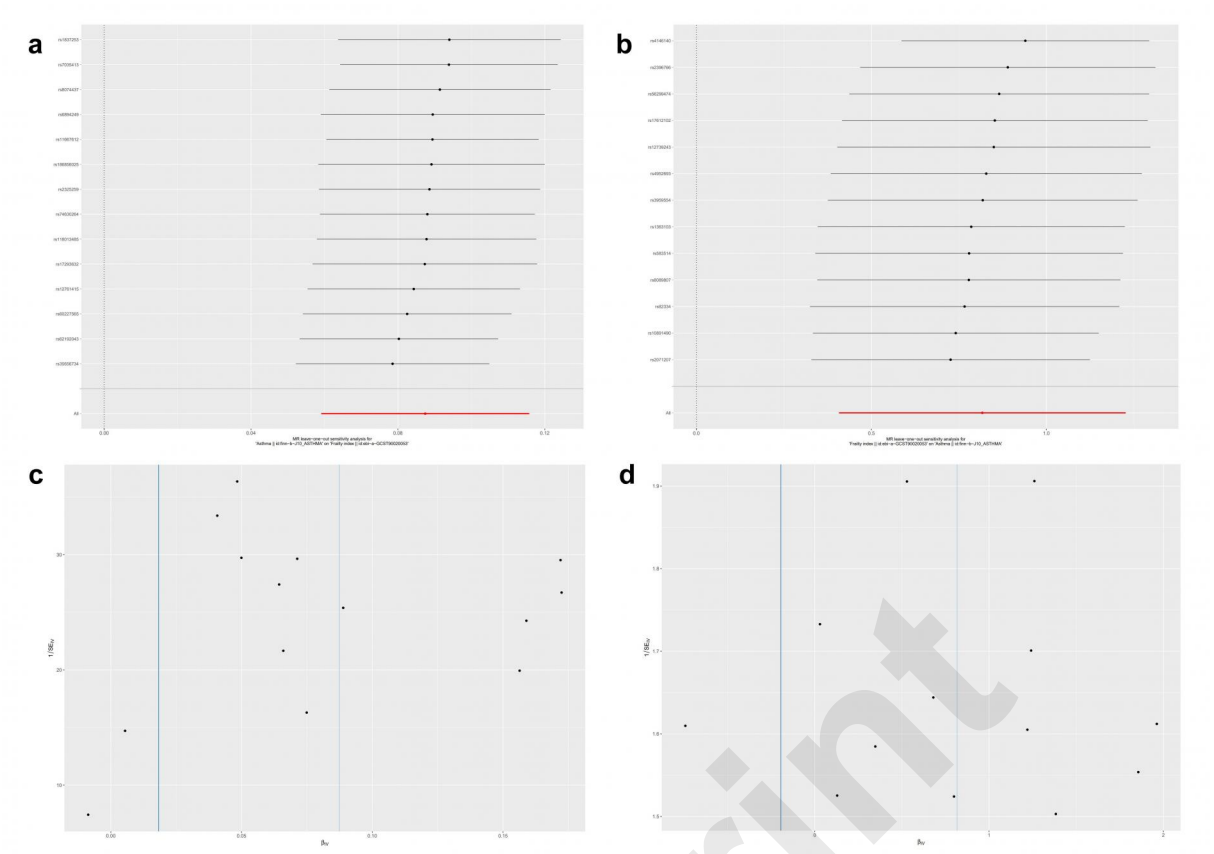


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