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Association of Subclinical Airflow Obstruction with Cardiovascular Mortality and the Exploratory Statistical Indirect Effect of the Systemic Immune-Inflammation Index: A Cohort Study Based on NHANES 2007-2012

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Abstract

Background

Small airway dysfunction (SAD) is an early manifestation of airway pathology, yet its association with long-term cardiovascular mortality remains insufficiently understood. This study aimed to evaluate the association between subclinical airflow obstruction (SAO), assessed by forced expiratory flow at 25%-75% of forced vital capacity (FEF_{25-75}), and cardiovascular mortality, and to preliminarily explore whether the systemic immune-inflammation index (SII) serves as an indirect pathway in this association.

Methods

This cohort study included 12,677 adults aged 20–79 years from the National Health and Nutrition Examination Survey (NHANES) 2007–2012, linked to mortality data through December 31, 2019. SAO was defined as FEF_{25-75} z-score < − 1.645 (below the lower limit of normal) using the Global Lung Function Initiative 2012 reference equations. The primary outcome was cardiovascular mortality. Survey-weighted cause-specific Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Exploratory mediation analysis via Weibull accelerated failure time models with bootstrap resampling was performed to decompose the total effect of SAO on cardiovascular death-free time into direct and indirect effects through ln(SII).

Results

Over a median follow-up of 9.75 years, 270 cardiovascular deaths were recorded. SAO was independently associated with an increased risk of cardiovascular mortality (fully adjusted HR = 1.89, 95% CI 1.26–2.83, P = 0.002). This association remained consistent across multiple sensitivity analyses and persisted among individuals without traditional airflow obstruction. Exploratory mediation analysis suggested that ln(SII) accounted for an indirect effect time ratio of 0.976 (bootstrap 95% CI 0.960–0.991, P = 0.006), corresponding to a mediation proportion of approximately 6.3% (95% CI 2.4%-13.4%). Given the concurrent baseline measurement of SAO and SII and the strong assumptions required for mediation analysis, these indirect effect findings should be considered exploratory and hypothesis-generating.

Conclusions

Subclinical airflow obstruction, defined by FEF_{25-75} below the lower limit of normal, was independently associated with cardiovascular mortality in a nationally representative US adult population. The exploratory indirect effect via SII suggests that systemic inflammation may partially participate in this association, although the modest mediation proportion indicates that other pathways likely contribute.

FEF_{25-75} assessment may provide additional information for cardiovascular risk stratification even when conventional spirometry is within normal limits, though the clinical utility of this strategy requires further prospective validation.

1 Introduction

Cardiovascular disease (CVD) remains the leading cause of death and disability worldwide. Although management strategies targeting traditional risk factors-such as hypertension, dyslipidemia, diabetes, and smoking-have continued to improve and have substantially reduced the incidence of cardiovascular events at the population level, a considerable proportion of cardiovascular events still occur among individuals classified as being at "low to intermediate" risk[1–2]. This observation suggests that the current risk assessment system based on traditional risk factors still has information gaps, underscoring the urgent need to identify and integrate novel subclinical risk markers to improve the precision of primary prevention strategies.

In recent years, the association between pulmonary function impairment and cardiovascular disease has garnered increasing attention[3]. Numerous prospective studies have confirmed that reductions in both forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) are independently associated with an increased risk of cardiovascular events and mortality [4–5]. However, these measures primarily reflect large airway or restrictive ventilatory impairment and typically become abnormal only when pathological changes are more advanced [6–7]. By contrast, small airway dysfunction (SAD) is considered an earlier manifestation of airway pathological changes [8]. The small airways are defined as those with an internal diameter of less than 2 mm, and dysfunction of these airways can precede the onset of traditional obstructive ventilatory impairment (indicated by a reduced FEV_1/FVC ratio) by several years [9]. The forced expiratory flow at 25%-75% of forced vital capacity (FEF_{25-75}) is the core spirometric measure for assessing small airway function, and its high sensitivity to early airway pathology has led to its widespread use in the screening and prognostic evaluation of respiratory diseases [10]. Nevertheless, whether subclinical airway dysfunction, as reflected by FEF_{25-75}, is independently associated with long-term cardiovascular mortality risk remains insufficiently supported by evidence from large-scale population-based studies.

An increasing number of population-based studies have begun to focus on the direct link between small airway function and cardiovascular health. A cross-sectional study based on a Swiss urban population found that SAO, defined as MMEF < LLN (equivalent to FEF_{25-75} below the lower limit of normal), was significantly associated with both self-reported cardiac events (OR = 1.60, 95% CI 1.07–2.40) and medically confirmed cardiac conditions (OR = 1.85, 95% CI 1.05–3.27), with the associations remaining independent of confounders such as age, sex, smoking, and BMI[11]. Of greater interest, a recent longitudinal study based on nearly 140,000 individuals from the UK Biobank has clearly demonstrated that isolated small airway obstruction independently predicts incident cardiovascular disease risk[12].

These findings from different populations suggest that SAO may not be confined to the respiratory domain, but rather represents a systemic signal with pan-vascular health implications.

The potential biological plausibility of SAO influencing cardiovascular outcomes is well-grounded. Its pathological effects may be transmitted through three hierarchical levels: core inflammatory pathways, complementary neuro-vascular mechanisms, and distal behavioral changes. At the core mechanistic level, small airway dysfunction is often accompanied by local chronic inflammation, which can promote the release of inflammatory cytokines (such as IL-6 and TNF-α) into the circulation, thereby inducing or exacerbating systemic inflammation-a central driver of atherosclerosis initiation and progression[13–14]. Indeed, a study from the Italian Moli-sani cohort has demonstrated that low-grade systemic inflammation partially mediates the association between reduced FEV_1 and cardiovascular mortality, with the inflammatory score accounting for approximately 20% of the mediation proportion-a finding that provides direct empirical support for the hypothesis that inflammatory pathways serve as a key bridge in lung–heart crosstalk[15]. At the complementary mechanistic level, small airway abnormalities may lead to ventilation–perfusion mismatch and covert hypoxemia, activating the sympathetic nervous system and renin-angiotensin system, thereby increasing cardiac workload and promoting vascular endothelial injury[16]. At the distal behavioral level, SAO-related dyspnea or reduced exercise tolerance may limit an individual's physical activity level, indirectly affecting cardiovascular health[17]. Among these potential pathways, systemic inflammation is considered the most central hub, providing a theoretical basis for introducing the systemic immune-inflammation index (SII) as an exploratory indirect effect variable.

SII is a novel composite inflammatory marker calculated from routine peripheral blood test parameters (platelet count × neutrophil count / lymphocyte count), which reflects the balance between immunity and inflammation more comprehensively than traditional single inflammatory markers such as hs-CRP or white blood cell count [18–19]. In recent years, a prospective study based on over 300,000 individuals from the UK Biobank has confirmed that elevated SII is independently associated with incident cardiovascular disease risk (HR = 1.07, 95% CI 1.05–1.10) [20]. Additional studies have also observed significant associations between SII and both all-cause and cardiovascular mortality in patients with coronary atherosclerosis [21]. However, whether SII plays a statistical indirect effect role in the association between SAO and cardiovascular mortality remains unexplored to date.

Against the above background, the present study utilized nationally representative data from the National Health and Nutrition Examination Survey (NHANES) 2007–2012 to achieve two objectives: first, to systematically evaluate the prospective association between small airway dysfunction and cardiovascular mortality risk; and second, to preliminarily assess whether baseline systemic immune-inflammation index constitutes an identifiable indirect pathway in this association using an exploratory statistical pathway decomposition approach. These analyses will provide epidemiological evidence for the potential value of small airway function assessment in cardiovascular risk stratification, while also offering preliminary quantitative clues for the hypothesis that inflammatory pathways participate in lung-heart crosstalk.

2 Methods

2.1 Study population

This study is a secondary analysis of the National Health and Nutrition Examination Survey (NHANES) cycles 2007-2008, 2009-2010, and 2011-2012, linked to prospective mortality data from the National Death Index. NHANES is a nationally representative, cross-sectional survey of the non-institutionalized US population employing a complex, multistage probability sampling design.

To ensure the quality and reliability of the study results, strict exclusion criteria based on previous research were adopted [22]. Participants were included if they met all of the following criteria: age 20-79 years; eligible for mortality linkage; not pregnant at the time of the mobile examination center (MEC) visit; completed baseline spirometry with valid FEF_{25-75} measurements enabling SAO classification and had complete cardiovascular mortality follow-up data.

A total of 15,762 adults met the initial age, mortality linkage, and pregnancy criteria. After excluding 3,036 individuals who did not complete baseline spirometry, 12,726 participants remained. An additional 49 were excluded due to invalid or missing spirometric measures precluding SAO classification, yielding an analytic survival cohort of 12,677 participants (1,446 with SAO and 11,231 without) for descriptive analyses, incidence density estimation, and survey-weighted Kaplan-Meier analysis. Among these, 2,132 were further excluded due to incomplete core covariates, leaving 10,545 participants for survey-weighted multivariable Cox regression. For the exploratory mediation analysis, an additional 352 participants were excluded due to missing ln(SII) or mediator model covariates, resulting in a final mediation sample of 10,193 participants (Figure 1).

2.2 Ethical Statement

The National Center for Health Statistics (NCHS) Ethics Review Board approved the NHANES study protocol. All participants provided written informed consent prior to participation. As this study relies on the analysis of publicly available, de-identified datasets, it was exempt from local institutional ethical approval.

2.3 Exposure, Outcome, and Exploratory Mediator

The primary exposure in this study was small airway obstruction (SAO), which was assessed using forced expiratory flow at 25%-75% of forced vital capacity (FEF_{25-75}). FEF_{25-75} is the average expiratory flow during the forced exhalation phase of 25% to 75% of forced vital capacity and primarily reflects the functional state of small airways with diameters less than 2 mm. Due to its high sensitivity to early airway lesions, it is widely used as a core assessment indicator for subclinical small airway damage.

FEF_{25-75} was measured via spirometry performed before bronchodilator administration. Predicted values and z-scores were calculated using the Global Lung Function Initiative 2012 (GLI-2012) reference

equations, stratified by age, sex, height, and race/ethnicity. SAO was defined as an FEF_{25-75} z-score below-1.645 (i.e., below the 5th percentile of the reference population, corresponding to the lower limit of normal). For continuous exposure analyses, the FEF_{25-75} z-score was inversed (multiplied by-1), such that each 1-unit increase represented a 1-unit worsening in small airway function. In sensitivity analyses, FEF_{25-75} <65% of predicted value was used as an alternative definition of SAO to test the robustness of the exposure definition.

The primary outcome was cardiovascular mortality, defined as deaths with an underlying cause coded as heart disease (UCOD_LEADING=1) or cerebrovascular disease (UCOD_LEADING=5) in the linked mortality data. Since deaths from other causes constitute competing events, we adopted a cause-specific hazard model framework, in which deaths from other causes were treated as censored at the time of death to estimate the cause-specific hazard of SAO on cardiovascular mortality. Follow-up time was calculated from the date of the MEC examination to the date of cardiovascular death, death from other causes, or administrative censoring (December 31, 2019), whichever occurred first. Follow-up person-months (PERMTH_EXM) were divided by 12 to convert to years; participants with a follow-up time of 0 months were assigned a value of 0.5 months to avoid zero follow-up time.

The exploratory mediator was the systemic immune-inflammation index (SII), a composite peripheral blood inflammatory marker integrating platelet, neutrophil, and lymphocyte counts, which reflects the immune-inflammatory balance more comprehensively than traditional single inflammatory indicators. It was calculated as:

$$\mathrm{SII} = \frac{platelet\ count \times neutrophil\ count}{\mathrm{neutrophil\ count}}$$

SII was included as an exploratory mediator to preliminarily assess whether systemic inflammation may explain part of the indirect effect in the association between SAO and cardiovascular mortality. Given its right-skewed distribution, SII was natural log-transformed for regression analyses and denoted as ln(SII).

2.4 Covariates

Covariates included sociodemographic characteristics (age, sex, race/ethnicity, education level, poverty-income ratio), lifestyle factors (smoking status, cumulative smoking amount, physical activity, alcohol consumption), anthropometric measures (body mass index), and comorbidities (hypertension, diabetes), with further adjustment for survey cycle. In an extended model, we additionally adjusted for baseline cardiovascular disease and respiratory conditions.

Age, BMI, poverty-income ratio, and cumulative smoking amount (pack-years) were included as continuous variables. Race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, other/multiracial), education level (< high school, high school/GED, > high school), smoking status (never, former, current), physical activity (active/inactive), alcohol consumption (<12 drinks/year, ≥12 drinks/year), hypertension (yes/no), diabetes (yes/no), and survey cycle (2007-2008, 2009-2010,

2011-2012) were included as categorical variables. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or self-reported physician diagnosis, or use of antihypertensive medication. Diabetes was defined as glycated hemoglobin ≥6.5%, fasting plasma glucose ≥126 mg/dL, or self-reported physician diagnosis, or use of glucose-lowering medication. Baseline cardiovascular disease included self-reported coronary heart disease, myocardial infarction, heart failure, or stroke. Respiratory disease included chronic bronchitis, emphysema, or asthma. All covariate definitions were based on NHANES questionnaire data, physical examination, and laboratory measurements.

2.5 Statistical Analysis

All analyses accounted for NHANES' complex survey design using 6-year MEC examination weights and Taylor series linearization for variance estimation. Baseline characteristics were compared using design-adjusted t-tests and Rao-Scottχ^2tests. Survey-weighted Kaplan-Meier curves and log-rank tests were used to compare cardiovascular event-free survival between groups.

Survey-weighted cause-specific Cox proportional hazards models were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between SAO and cardiovascular mortality, with other deaths treated as censored at the time of death. Three sequential models were constructed: Model 1 was unadjusted; Model 2 adjusted for age, age^2/100, sex, and race/ethnicity; Model 3 (primary model) additionally adjusted for education, poverty-income ratio, BMI, smoking status, smoking amount, hypertension, diabetes, physical activity, alcohol consumption, and survey cycle. The proportional hazards assumption was assessed using Schoenfeld residuals.

Sensitivity analyses and smoking interaction tests were performed to evaluate the robustness of findings and potential effect modification. For exploratory mediation analysis, survey-weighted linear regression was used to estimate the association between SAO and ln(SII) (path a). A Weibull accelerated failure time model was then fitted to decompose the total effect of SAO on cardiovascular death-free time into direct and indirect effects (via ln[SII]) on the log-time scale, with estimates exponentiated as time ratios (TR). A stratified bootstrap with 1,000 PSU-level resamples was used to construct percentile 95% CIs; All tests were two-sided, and statistical significance was defined as $P < 0.05$. All analyses were completed using R 4.5.2.

3 Results

3.1 Sample Screening and Outcome Events

A total of 15,762 adults aged 20-79 years, eligible for mortality linkage and non-pregnant, were initially assessed, of whom 12,677 had valid spirometry measures, classifiable SAO status, and complete cardiovascular mortality follow-up data, comprising the final analytic survival cohort (1,446 with SAO [11.4%] and 11,231 without). Among these, 10,545 had complete core covariate data for multivariable Cox regression, and 10,193 had complete data for the exploratory mediation analysis (including ln[SII]

and all mediator model covariates) (Figure 1; Table 1). The detailed sample selection process is shown in Figure 1, and the corresponding sample sizes at each selection step are summarized in Table 1.

In the primary survival cohort of 12,677 participants, 270 cardiovascular deaths and 750 non-cardiovascular deaths were observed. Median follow-up time was 9.75 years in both the SAO and non-SAO groups. The complete-case Cox regression sample included 232 cardiovascular deaths, and the mediation sample included 223 cardiovascular deaths.

3.2 Baseline Analysis

The survey-weighted baseline characteristics of the study population, stratified by SAO status, are presented in Table 2. Compared with the non-SAO group, the SAO group was older (48.63 vs 44.82 years), had lower BMI (28.00 vs 28.91 kg/m²), lower poverty-income ratio (2.86 vs 3.13), and greater cumulative smoking exposure (18.49 vs 6.07 pack-years); the proportions of current smokers (44.5% vs 19.1%), physically inactive individuals (53.4% vs 41.2%), and individuals with hypertension (33.5% vs 27.5%) were higher in the SAO group. The SAO group also had a higher mean ln(SII) (6.252 vs 6.148, P<0.001). No significant differences were observed in sex, diabetes, or survey cycle distribution between the two groups.

3.3 Weighted KM Curves and Cardiovascular Mortality Incidence Density

The survey-weighted Kaplan-Meier curve (Figure 2) demonstrated that the SAO group consistently exhibited lower cardiovascular event-free survival probability throughout the entire follow-up period compared with the non-SAO group. The survey-weighted incidence density of cardiovascular mortality was 3.77 per 1,000 person-years (95% CI 2.54-5.00) in the SAO group and 1.24 per 1,000 person-years (95% CI 1.02–1.46) in the non-SAO group. The survey-weighted log-rank test yielded P < 0.001.

3.4 Weighted Cox Regression for the Association Between SAO and Cardiovascular Mortality

In the unadjusted model, SAO was associated with a higher cause-specific hazard of cardiovascular mortality (HR=2.90, 95% CI 2.13-3.93, P<0.001). After adjustment for age, age²/100, sex, and race/ethnicity, the HR was 2.33 (95% CI 1.67-3.24, P<0.001); the association remained statistically significant in the fully adjusted model (HR=1.89, 95% CI 1.26-2.83, P=0.002) (Table 3).

Continuous exposure analysis showed that each 1-unit worsening in FEF_{25-75} z-score was associated with an increased risk of cardiovascular mortality (HR=1.27, 95% CI 1.06-1.53, P=0.010). The overall Wald test for the 3-knot natural cubic spline yielded F=4.20 (3 and 27 degrees of freedom), P=0.0146, supporting an overall association between FEF_{25-75} z-score and cardiovascular mortality.

3.5 Sensitivity Analysis for the Association Between SAO and Cardiovascular Mortality

Auxiliary diagnostics based on Schoenfeld residuals suggested no violation of the proportional hazards assumption for the SAO term (P=0.780) or for the global model (P=0.589); however, age (P=0.0066) and

age²/100 (P=0.0041) showed potential time-varying effects. Since these diagnostics were based on weighted partial likelihood with PSU-clustered robust variance rather than full NHANES survey linearization, they are presented only as auxiliary references for model fit.

A piecewise survey-weighted Cox model using a 2-year cutpoint yielded an HR of 2.86 (95% CI 0.95-8.63, P=0.062; 23 cardiovascular deaths during this period) for 0-2 years and an HR of 1.81 (95% CI 1.22-2.69, P=0.003; 209 cardiovascular deaths) for >2 years. The difference in SAO effects between the two periods was not statistically significant (HR ratio=0.63, 95% CI 0.22-1.80, interaction P=0.391), with the early estimate having a wider confidence interval due to the limited number of events. A separate 2-year landmark analysis, conditional on being alive, free of cardiovascular death, and under observation at 2 years, yielded an HR of 1.80 (95% CI 1.20-2.68, P=0.004).

All other prespecified sensitivity analyses yielded consistent directions of effect (Table 4): restricting to high-quality spirometry (grades A/B), excluding baseline cardiovascular disease, isolating SAO without traditional airflow obstruction, using alternative SAO definitions, and continuous exposure analysis all reached statistical significance. After additional adjustment for baseline cardiovascular disease and respiratory conditions, the HR for SAO was 1.74 (95% CI 1.14-2.66, P=0.010). Interaction terms between SAO and former or current smoking were not statistically significant (P=0.845 and P=0.461, respectively).

3.6 Exploratory Mediation Analysis of SII

Survey-weighted mediation models showed that SAO was associated with higher ln(SII) (path a: β=0.064, 95% CI 0.025–0.103, P=0.002). In the same mediation sample, the HRs for SAO were 1.88 (95% CI 1.24-2.85) and 1.80 (95% CI 1.17-2.76) without and with adjustment for ln(SII), respectively; ln(SII) was associated with cardiovascular mortality (HR=1.85, 95% CI 1.24-2.76, P=0.003). The change in the SAO coefficient in the Cox models is presented for descriptive purposes only and was not used to calculate indirect effects or mediation proportions.

In the Weibull AFT decomposition, the path b coefficient for ln(SII) on log survival time was -0.377 (bootstrap 95% CI -0.556 to -0.176). The direct time ratio for SAO was 0.696 (95% CI 0.565-0.880), and the indirect time ratio was 0.976 (95% CI 0.960-0.991, bootstrap P=0.006). The indirect TR being less than 1 suggests that SAO was associated with shorter cardiovascular event-free time through higher ln(SII).

The observed total time ratio was 0.677 (95% CI 0.548-0.850), and the decomposed total time ratio was 0.680 (95% CI 0.548-0.859), demonstrating close consistency. Among bootstrap replicates with concordant directions, the estimated mediation proportion was 6.3% (95% CI 2.4%-13.4%). The SAO × ln(SII) interaction term was not statistically significant (β=0.236, P=0.285) (Table 5).

The AIC values for the fitted AFT distributions were 1899.36 for log-logistic, 1900.98 for Weibull, and 1908.33 for log-normal, indicating a marginal difference in fit between log-logistic and Weibull models.

No complete fitting failures were recorded across the 1,000 bootstrap resamples; valid repetitions for individual estimates ranged from 965 to 1,000, with 973 to 974 for the primary time ratio effects.

4 Discussion

This study, based on the nationally representative NHANES cohort, evaluated the association between small airway dysfunction and cardiovascular mortality, and employed an exploratory statistical pathway decomposition approach to preliminarily assess whether the systemic immune-inflammation index (SII) constitutes an identifiable indirect pathway in this association. The study found that subclinical airflow obstruction was independently associated with an increased risk of cardiovascular mortality, with a fully adjusted hazard ratio of 1.89 (95% CI 1.26-2.83, P=0.002). This association remained consistent across multiple sensitivity analyses and persisted among individuals without traditional airflow obstruction. Exploratory pathway decomposition analysis suggested an indirect effect time ratio of 0.976 (bootstrap 95% CI 0.960-0.991, P=0.006) via ln(SII), corresponding to a mediation proportion of approximately 6.3% (95% CI 2.4%-13.4%). It should be emphasized that, since both SAO and SII were measured concurrently at baseline, and this decomposition method relies on strong assumptions such as the absence of unmeasured confounding, the indirect effect results presented herein are exploratory and should not be interpreted as confirmatory causal inference. SII, as a composite inflammatory marker, has been independently associated with cardiovascular disease risk in multiple large-scale prospective studies[23-24].

The magnitude of the association between SAO and cardiovascular mortality was notable on the relative scale. After full adjustment for traditional cardiovascular risk factors, SAO remained associated with an 89% increased risk of cardiovascular mortality, independent of a wide range of confounders including age, sex, race/ethnicity, socioeconomic status, BMI, smoking, hypertension, and diabetes. The direction and statistical significance of the association were consistent across various sensitivity analyses, including exclusion of individuals with baseline cardiovascular disease, restriction to high-quality spirometry data, and use of alternative SAO definitions, supporting the robustness of the primary findings. Previous studies on lung function and cardiovascular prognosis have largely focused on $FEV_1$and FVC, whereas the present study shifted the focus to an earlier stage of small airway dysfunction[25-26]. FEF_{25-75} is often overlooked in routine pulmonary function reports. The findings of this study suggest that its abnormality may carry incremental information on future cardiovascular mortality risk[27]. For individuals with reduced FEF_{25-75}, even when FEV_1 and FVC remain within the normal range, clinicians may consider enhanced assessment and monitoring of cardiovascular risk factors. However, the net benefit of this strategy warrants further validation in prospective studies.

After excluding individuals with traditional airflow obstruction, the isolated SAO subgroup still demonstrated a significant association, suggesting that SAO may be linked to the cardiovascular system through mechanisms independent of large airway obstruction. Traditionally, clinicians have focused on whether FEV_1/FVC is reduced in pulmonary function reports, whereas abnormalities in FEF_{25-75} have

often been attributed to "non-specific changes" and have not received sufficient attention[9]. The findings of this study suggest that independent assessment of small airway function may provide additional prognostic information even in the absence of traditional obstructive ventilatory impairment.

In the exploratory mediation analysis, the indirect effect via ln(SII) was statistically significant (indirect time ratio=0.976, P=0.006), corresponding to a mediation proportion of approximately 6.3%. Although this proportion is modest, identifying a statistically significant indirect pathway within a multifactorial biological network may still provide clues for future research. SII integrates information from three cell lines-platelets, neutrophils, and lymphocytes-and may reflect the immune-inflammatory balance more comprehensively than single inflammatory markers. The positive association between SAO and ln(SII) observed in this study is consistent with previous research[28-30]. A hypothesis worthy of testing in future research is that local inflammation associated with small airway dysfunction may release inflammatory cytokines into the circulation, activate systemic immune responses, and thereby promote vascular endothelial dysfunction and atherosclerotic progression[31-32]. However, the 6.3% mediation proportion suggests that SII only accounts for a partial indirect pathway in the statistical association between SAO and cardiovascular mortality. Other potential pathways may include hypoxemia, sympathetic nervous system activation, and reduced physical activity[33-34]. The interaction term between SAO and ln(SII) was not statistically significant (P=0.285), suggesting that this indirect pathway may not exhibit a clear gradient across severity levels of SAO. Its biological robustness warrants further validation.

A previous study based on the Italian Moli-sani population reported that FEF_{25-75} abnormalities were associated with all-cause mortality but did not find a significant association with cardiovascular mortality. The discrepancy with our findings may be attributable to differences in population composition, baseline cardiovascular mortality profiles, and covariate adjustment sets across the studies. A recent longitudinal study from the UK Biobank, including nearly 140,000 individuals, found that isolated small airway obstruction independently predicted incident cardiovascular disease risk (approximately 20% increased risk), whereas the association between SAO and cardiovascular mortality in our study was more pronounced (89% increased risk). This discrepancy may be attributable to differences in the nature of the endpoint events or may reflect a more substantial role of SAO at the stage of disease progression to death[12]. Both studies utilized the GLI-2012 reference equations and the same z-score cut-point for defining SAO, which enhances the comparability of effect estimates across cohorts. Furthermore, recent NHANES-based studies have begun to investigate the relationship between different pulmonary function phenotypes and prognosis. Compared with preserved ratio impaired spirometry (PRISm), isolated SAO represents an earlier phenotype of functional impairment. The findings of our study suggest that FEF_{25-75} provides additional prognostic information beyond conventional pulmonary function classification.

The strengths of this study include the use of a nationally representative sample from NHANES, rigorous survey-weighted analyses, multiple prespecified sensitivity analyses, and a systematic evaluation of the statistical indirect effect of SII. However, several limitations should be acknowledged. SAO and SII were

measured concurrently at baseline, and the mediation analysis relies on the strong assumption of no unmeasured confounding; thus, the indirect effect results should be interpreted as exploratory decompositions of statistical associations intended for hypothesis generation rather than causal inference. The observational study design precludes the establishment of causal relationships, and despite adjustment for a wide range of covariates, residual confounding may persist. Classification of cause of death relied on death certificates, which may introduce misclassification bias; however, NHANES mortality follow-up data have undergone rigorous quality control, and the impact of such bias is likely within an acceptable range. Measurement of FEF_{25-75} depends on the quality of spirometry, and measurement error may attenuate effect estimates toward the null. Additionally, pre-bronchodilator spirometry data were used in this study, which may be influenced by airway reversibility. Future research could leverage longitudinal repeated measurements to evaluate the dynamic association between FEF_{25-75} trajectories and cardiovascular outcomes, prioritize testing the independent indirect effects of specific inflammatory markers such as hs-CRP, IL-6, and TNF-αwith pathway comparisons to SII, and employ Mendelian randomization designs to provide complementary evidence for causal inference.

5 Conclusion

This prospective cohort analysis, based on a nationally representative US population (NHANES 2007-2012), demonstrated that small airway dysfunction (defined as $FEF_{25–75}$ below the lower limit of normal) was an independent correlate of cardiovascular mortality among US adults aged 20-79 years (HR=1.89, 95%CI 1.26-2.83). This association remained robust across multiple sensitivity analyses and persisted among individuals without traditional airflow obstruction. This study extends the lung–cardiovascular prognosis axis to the earlier stage of small airway function, suggesting that $FEF_{25–75}$ abnormalities may carry excess risk information even when conventional spirometry reports are considered "normal." Exploratory mediation analysis revealed a statistically identifiable indirect pathway via baseline SII in the association between SAO and cardiovascular mortality (indirect time ratio=0.976, 95%CI 0.960-0.991), providing preliminary quantitative evidence for the hypothesis that inflammatory pathways may participate in lung–heart crosstalk. However, these findings require independent validation in studies with temporal data and should not be interpreted as confirmatory causal inference. At the clinical level, $FEF_{25–75}$ assessment may offer additional reference information for early cardiovascular risk stratification; for individuals with reduced $FEF_{25–75}$, enhanced management of cardiovascular risk factors may be considered, though its clinical utility warrants further validation in prospective studies.

Declarations

Conflict of Interest

The authors declare that there are no commercial or financial relationships that could give rise to any potential conflicts of interest in relation to this study.

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Author Contribution

Yifan Wu made substantial contributions to data collection and analysis, drafting of the manuscript and served as the first authors of the manuscript. Ting Jiang and Wenjun Xiong made substantial contributions to study design,intellectual direction, and revision of the drafting of the manuscript. Xiaoyue Qi, Qian Zhang, Na Zhong, Nana Xiong made contributions to data collection and analysis.All authors read and approved the final manuscript.

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Tables

Tables 1 to 5 are available in the supplementary files section.

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