Small airways obstruction predicts cardiovascular disease incidence: a longitudinal study of UK Biobank

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Shareable abstract (@ERSpublications)
Isolated small airways obstruction is common and UK Biobank data show it is associated with a modest increased risk of incident cardiovascular disease. The underlying mechanism for this increased risk requires further investigation. https://bit.ly/4sAPkJF

Cite this article as: Bartlett-Pestell S, Quintero Santofimio V, Potts J, *et al*. Small airways obstruction predicts cardiovascular disease incidence: a longitudinal study of UK Biobank. *ERJ Open Res* 2026; 12: 01190-2025 [DOI: 10.1183/23120541.01190-2025].

Received: 2 Sept 2025
Accepted: 24 Dec 2025

Background Isolated small airways obstruction (SAO) is common, a precursor of COPD and associated with increased cardiovascular disease (CVD) mortality. Whether isolated SAO predicts CVD incidence is unknown.
Methods Using longitudinal data on 139 568 UK Biobank participants (median age 58 years), we calculated CVD incidence in those with, *versus* without, isolated SAO defined as forced expiratory volume in 3 s (FEV_3)/forced expiratory volume in 6 s (FEV_6) <lower limit of normal (LLN) with a normal forced expiratory volume in 1 s (FEV_1)/FEV_6 ratio. A second analysis was performed where isolated SAO was defined as forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25–75\%}$) <LLN with a normal FEV_1/FEV_6 ratio. Using mixed effects quasi-Poisson regression models, we assessed the association between isolated SAO and CVD, investigating differences in association by sex and smoking status.
Results At baseline, 10 480 participants (7.5%) had isolated SAO. During follow-up (median 9.2 years), CVD was diagnosed in 30 763 (22%) participants, more commonly among those with isolated SAO at baseline (risk ratio 1.05 (95% CI 1.01–1.09)). This association was not significant in males (risk ratio 1.03 (95% CI 0.98–1.08)) nor in never-smokers (risk ratio 1.02 (95% CI 0.97–1.09)). The risk of CVD was increased when isolated SAO was defined using $FEF_{25–75\%}$.
Conclusions Adults with isolated SAO have a modest increased risk of developing CVD. However, this association is potentially driven by smoking. Further research should explore underlying mechanisms for this increased risk and how best this can be mitigated.

Introduction

Small airways obstruction (SAO) is a key pathological feature in COPD that precedes the development of an abnormal forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio [1, 2].

There is no gold standard test for SAO; however, it is commonly defined as reduced forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$), and in the absence of airflow obstruction is defined as isolated SAO. $FEF_{25–75\%}$ is dependent on FVC and is highly variable between individuals [3]. As a result, the use of forced expiratory volume in 3 s (FEV_3)/FVC as a diagnostic marker for isolated SAO is increasing [1, 2, 4–6]. Isolated SAO is common, with an estimated prevalence up to 30% when using $FEF_{25–75\%}$ [7] and up to 12% when using FEV_3/FVC criteria [2], and is associated with increased respiratory symptoms [1, 4, 6] and progression to airflow obstruction [1, 2, 7].

Several studies have reported the association between COPD and CVD [8], which is likely explained by shared risk factors, especially tobacco smoking and increased systemic inflammation among other potential causes. Cross-sectional data on over 21 000 participants from the Burden of Obstructive Lung Disease

(BOLD) study have shown that isolated SAO is associated with coexisting self-reported CVD [4]. Among 250 000 participants in the UK Biobank, isolated SAO is also associated with increased risk of mortality, including cardiovascular mortality [5]. However, no studies have explored if isolated SAO predicts future incidence of CVD, thereby offering a way to identify and optimise CVD risk earlier.

In this study, we used longitudinal UK Biobank data to investigate whether the incidence of CVD is associated with isolated SAO and whether this relationship could be explained by systemic inflammation.

Methods

Study population

The UK Biobank cohort consists of 502 414 adults recruited from 22 centres across England, Scotland and Wales between 2006 and 2010. At baseline, participants were invited to complete a questionnaire, blood tests and perform several physical measurements, including spirometry [9]. Those who used their inhaler 1 h prior to spirometry being performed, those with no follow-up data (no follow-up visits, linked primary care, secondary care or death data), those with unknown smoking status, those with airflow obstruction and those with a CVD diagnosis prior to the first visit were excluded (figure 1).

The data used in this study were accessed under Data Access Application 80 005 and are available to any researcher upon request to the UK Biobank. The UK Biobank has ethics approval from the North West – Haydock Research Ethics Committee (21/NW/0157) and all participants provided written consent.

Isolated SAO

Spirometry in the UK Biobank was performed pre-bronchodilator using the Pneumotrac 6800 spirometer (Vitalograph, Maids Moreton, UK). Up to three blows were recorded over a maximum of 6 min to obtain two acceptable blows [10]. In this analysis, we used only high-quality spirometry data, as described elsewhere [11], and only the values from the best curve (highest FEV_1 and FVC). FEV_3, forced expiratory volume in 6 s (FEV_6) and $FEF_{25–75\%}$ were derived from the raw data [12].

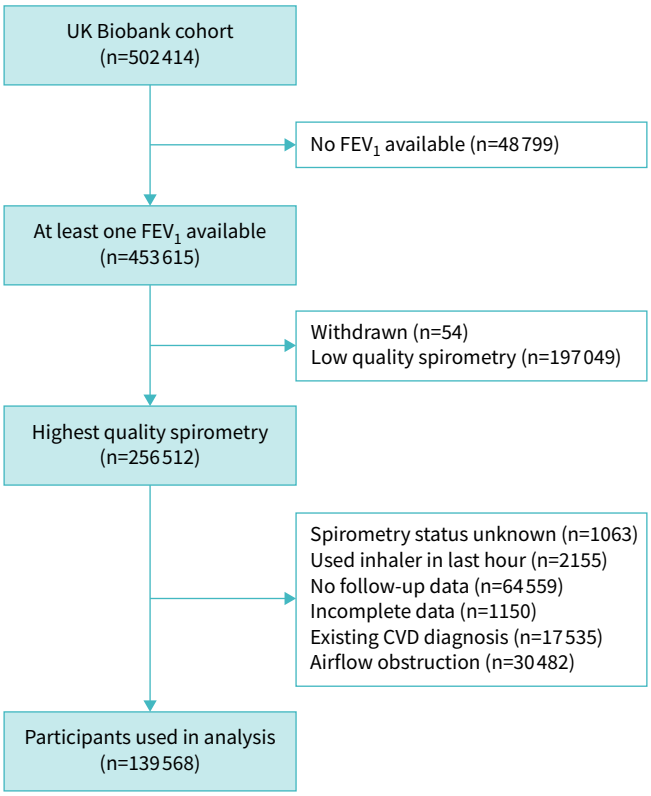

FIGURE 1 Study flow diagram. FEV_1: forced expiratory volume in 1 s; CVD: cardiovascular disease.

Due to the dependence on FVC for $FEF_{25–75\%}$ and its high variability, we defined isolated SAO as FEV_3/FEV_6 <lower limit of normal (LLN) in the presence of normal FEV_1/FEV_6 (>LLN). As secondary analysis, we also defined isolated SAO as $FEF_{25–75\%}$ <LLN with FEV_1/FEV_6 >LLN.

Restriction was defined as FEV_6 <LLN. In this cohort, mean FEV_6 is similar to mean FVC, suggesting that FVC is underestimated [12]. Also, FEV_6 involves less effort and is easier to reproduce than FVC [13].

Spirometry LLN values were calculated using the reference equations for people of White ethnic background generated from the Third National Health and Nutrition Examination Survey (NHANES III) [14, 15].

CVD incidence

We defined a new CVD case as the first diagnosis of ischaemic heart disease, arrythmia, heart failure or stroke reported anytime following the baseline visit. The composite of CVD was determined *a priori* in the research question and to increase the number of events included in the analysis. Data were obtained from self-reported diagnoses and linked general practitioner (GP), Hospital Episode Statistics (HES) and death registry data. The UK Biobank data codes, International Classification of Diseases, 10th Revision classifications and Read codes used for diagnoses are given in supplementary table S1. The UK Biobank data codes included algorithmically developed codes, which used self-reported and linked health data to determine the first date of disease diagnosis.

The latest mortality data update for the UK Biobank dataset used in this analysis was March 2023. We calculated follow-up time as the difference between the date of either the last visit in the UK Biobank follow-up, the last updated diagnosis date from GP records, the last HES diagnosis date or date of death and the date of the baseline visit. The median (interquartile range (IQR)) follow-up time was 9.2 (7.2–11.8) years and 649 participants had a follow-up time of <1 year.

Systemic inflammation

C-reactive protein (CRP) is an accessible, commonly used marker of systemic inflammation. We used high-sensitivity CRP measured by immunoturbidimetry in an AU5800 Series Clinical Chemistry Analyser (Beckman Coulter, Little Chalfont, UK), from blood collected at baseline, as a marker of systemic inflammation.

Statistical analysis

Parametric continuous variables are presented as mean with standard deviation and non-parametric continuous variables are presented as median with IQR. We used Pearsons's Chi-squared to compare the number of those with isolated SAO and CVD to those without isolated SAO and CVD.

We estimated the association between isolated SAO at baseline and CVD at follow-up using mixed effects quasi-Poisson regression models adjusted for age (years), sex (male, female), ethnicity (White, non-White), body mass index (BMI) ($kg \cdot m^{-2}$), smoking status (never-smoker, ex-smoker, current smoker), Townsend deprivation index and assessment centre (as a random variable) (model 1). We used a directed acyclic graph to decide on the variables (confounders) to adjust the models for *a priori* (supplementary figure S1). To reduce the possibility of residual confounding from smoking, we also ran a second model including all variables in model 1 and, in addition, pack-years of smoking (model 2). To investigate possible effect modification, we performed stratified analyses by sex (male, female) and smoking status (never-smoker, ever-smoker) and examined interaction terms.

To test whether pre-existing asthma (causing isolated SAO) or spirometric restriction (causing CVD) may be driving any observed associations, we conducted sensitivity analyses excluding those with pre-existing asthma and restriction, respectively. To investigate whether other CVD risk factors may account for any observed effects, we conducted sensitivity analyses excluding those with pre-existing hypertension, diabetes and high cholesterol. Pre-existing diabetes and hypertension were determined by self-reported diagnoses, linked GP data and linked HES data. High cholesterol was defined as serum total cholesterol >5 $mmol \cdot L^{-1}$ at the baseline visit. A further analysis was conducted excluding those who developed airflow obstruction (FEV_1/FEV_6 <LLN) during any follow-up visit.

To reduce the possible negative effect of a short follow-up time or short time to CVD diagnosis from baseline, we performed a sensitivity analysis excluding those with a follow-up time or time to diagnosis <1 year from baseline.

We ran a *post hoc* quasi-Poisson regression analysis (model 1) for isolated SAO ($FEF_{25–75\%}$ definition) in the subgroups of participants with FEV_1 <LLN and FEV_6 <LLN.

We used the Wilcoxon rank sum test to measure the association between CRP and isolated SAO. In addition, we performed univariable and multivariable (adjusted for sex (male, female), age, BMI ($kg·m^{-2}$), ethnicity (White, non-White) and smoking status (never-smoker, ex-smoker, current smoker)) generalised linear models with log link function, with CRP as the dependent variable and isolated SAO as the independent variable. To test the role of smoking in any observed effect, we conducted a sensitivity analysis restricted to never-smokers.

We performed subgroup analysis in those with isolated SAO only to test the association of CRP with CVD diagnosis. We performed mixed effects quasi-Poisson regression models (model 1). To ensure any observed effects were not due to smoking, we conducted a sensitivity analysis restricted to never-smokers.

All statistical analysis was performed using R version 4.3.3 [16] and R Studio build 2024.12.1+563 [17]. Results were considered significant if $p<0.05$.

Results

Of the 139 568 participants included in the analysis, 60% were female, 95% were of White ethnic background and the median age was 58 years. Of these, 10 480 (7.5%) had isolated SAO (defined by FEV_3/FEV_6 <LLN) at baseline. Compared to the group without isolated SAO, those with isolated SAO were more likely to be female, current smokers and have lower spirometry values. The baseline demographics are shown in table 1.

During the follow-up period, 30 763 participants were diagnosed with CVD (supplementary table S3). The median (IQR) time to CVD diagnosis was 6.9 (IQR 3.6–10.3) years and 2411 participants had a CVD diagnosis within 1 year of their baseline visit.

TABLE 1 Characteristics of UK Biobank participants at baseline visit

	Overall (n=139 568)	FEV_3/FEV_6 >LLN (n=129 088)	FEV_3/FEV_6 <LLN (n=10 480)
Sex			
Male	56 047 (40)	52 294 (41)	3753 (36)
Female	83 521 (60)	76 794 (59)	6727 (64)
Age, years	58 (50–63)	58 (50–63)	56 (49–62)
Ethnic background			
White	133 269 (95)	123 529 (96)	9740 (93)
Non-White	6299 (5)	5559 (4)	740 (7)
BMI, $kg·m^{-2}$	26.9 (24.4–30.1)	27.0 (24.4–30.2)	26.1 (23.7–29.2)
Smoking status			
Current	11 630 (8)	10 029 (8)	1601 (15)
Ex-smoker	49 350 (36)	45 661 (35)	3689 (35)
Never-smoker	78 588 (56)	73 398 (57)	5190 (50)
Pack-years of smoking#	17 (9–29)	17 (9–28)	21 (12–33)
FEV_1, L	2.74 (2.31–3.31)	2.76 (2.33–3.33)	2.52 (2.14–3.00)
FEV_1 <LLN	10 267 (7)	8507 (7)	1760 (17)
$FEF_{25–75\%}$, L	2.48 (1.99–3.08)	2.54 (2.05–3.14)	1.85 (1.51–2.22)
FEV_3, L	3.28 (2.76–3.96)	3.29 (2.77–3.99)	3.09 (2.62–3.70)
FEV_6, L	3.49 (2.95–4.22)	3.50 (2.95–4.23)	3.38 (2.88–4.05)
FEV_6 <LLN	15 538 (11)	13 760 (11)	1778 (17)
FEV_1/FEV_6	0.78 (0.76–0.81)	0.79 (0.76–0.81)	0.74 (0.73–0.75)
FEV_3/FEV_6	0.94 (0.93–0.95)	0.94 (0.93–0.95)	0.91 (0.91–0.92)
Pre-existing diabetes	4969 (4)	4672 (4)	297 (3)
Pre-existing hypertension	39 885 (29)	37 132 (29)	2753 (26)
Raised cholesterol	100 291 (72)	92 849 (72)	7442 (71)

Data are presented as n (%) or median (interquartile range). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; LLN: lower limit of normal; $FEF_{25–75\%}$: forced expiratory volume at 25–75% of forced vital capacity; FEV_3: forced expiratory volume in 3 s; FEV_6: forced expiratory volume in 6 s. #: only in current and ex-smokers (defined as number of years of smoking×(cigarettes smoked per day/20)).

The incidence rate of CVD was similar between those with isolated SAO (25.72 (95% CI 24.67–26.79) per 1000 person-years) and those without isolated SAO (26.20 (95% CI 25.90–26.50) per 1000 person-years). Prior to adjustment for confounders there was no difference in CVD incidence between participants with isolated SAO and those without isolated SAO (p=0.286).

After adjustment for confounders, the risk of incident CVD was greater among participants with isolated SAO (risk ratio 1.05 (95% CI 1.01–1.09)) compared to those without isolated SAO. There was no difference in the effect size between model 1 and model 2 (risk ratio 1.04 (95% CI 1.00–1.08)) (figure 2). This association was significant among females (risk ratio 1.08 (95% CI 1.02–1.14)) but not among males (risk ratio 1.03 (95% CI 0.98–1.08)). It was also significant among ever-smokers (risk ratio 1.09 (95% CI 1.03–1.14)) but not among never-smokers (risk ratio 1.02 (95% CI 0.97–1.09)). However, neither the interaction term with sex (p=0.25) nor smoking (p=0.07) was statistically significant and the confidence intervals overlap, suggesting there is no difference in association between groups and there is no multiplicative modification effect. The risk of CVD was similar when isolated SAO was defined by $FEF_{25–75\%}$ (risk ratio 1.19 (95% CI 1.10–1.30)) (supplementary table S6).

Based on model 1, people with isolated SAO had a 1% higher risk of CVD over 9 years (risk difference 0.01 (95% CI 0.00–0.02); p=0.03).

Although formal statistical significance was not achieved, effect estimates remained stable when excluding those with pre-existing asthma (risk ratio 1.05 (95% CI 1.01–1.10)), restriction (risk ratio 1.04 (95% CI 0.99–1.08)), diabetes (risk ratio 1.05 (95% CI 1.01–1.15)), cholesterol >5 $mmol \cdot L^{-1}$ (risk ratio 1.05 (95% CI 1.01–1.15)), hypertension (risk ratio 1.04 (95% CI 0.99–1.09)), excluding those who developed obstruction during the follow-up period (risk ratio 1.05 (95% CI 1.01–1.09)) and when excluding those who developed CVD within 1 year of the baseline visit (risk ratio 1.04 (95% CI 1.01–1.09)).

The median CRP (n=131 617) was similar in those with isolated SAO and those without; however, using multivariable generalised linear log link regression there was an 9% increase in CRP in those with isolated SAO (p<0.001) (table 2). In those with isolated SAO, the median CRP was higher in those who developed

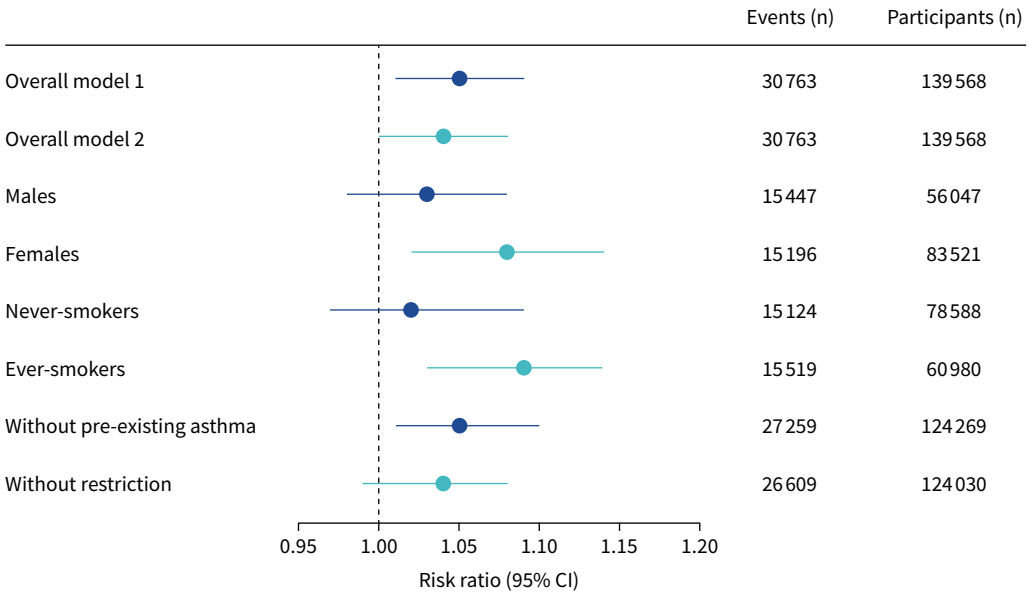

FIGURE 2 Risk of cardiovascular disease associated with isolated small airways obstruction. Model 1: mixed effects quasi-Poisson regression model adjusted for age (years), sex (male, female), ethnicity (White, non-White), body mass index ($kg \cdot m^{-2}$), smoking status (never-smoker, ex-smoker, current smoker), Townsend deprivation index and assessment centre (as a random variable). Model 2: mixed effects quasi-Poisson regression models adjusted for age (years), sex (male, female), ethnicity (White, non-White), body mass index ($kg \cdot m^{-2}$), smoking status (never-smoker, ex-smoker, current smoker), pack-years of smoking, Townsend deprivation index and assessment centre (as a random variable).

TABLE 2 Generalised linear log link regression model testing association between isolated small airways obstruction (SAO) and C-reactive protein (CRP)

	Log scale coefficient (95% CI)	p-value	Interpretation
Overall			
Unadjusted	0.04 (0.00–0.07)	0.029	4% increase in CRP in those with isolated SAO
Adjusted[#]	0.09 (0.05–0.11)	<0.001	9% increase in CRP in those with isolated SAO
Never-smokers			
Adjusted[¶]	0.02 (−0.03–0.06)	0.474	Not associated

[#]: adjusted for age (years), ethnicity (White, non-White), body mass index ($kg \cdot m^{-2}$) and smoking status (never-smoker, ex-smoker, current smoker); [¶]: adjusted for age (years), ethnicity (White, non-White) and body mass index ($kg \cdot m^{-2}$).

CVD than in those who did not; however, there was no association with CVD diagnosis when adjusted for confounders (risk ratio 1.01 (95% CI 1.00–1.02)) (supplementary table S10).

Discussion

In this large longitudinal study of adults, we show that people with isolated SAO are 1.05 times as likely to have a future CVD diagnosis compared to people without SAO. This translates into a 1 percentage point higher risk over 9 years.

Whilst consistent with previous studies using cross-sectional [4] and mortality [5] data, our study is the first to show the extent to which isolated SAO relates to incidence of CVD.

Spirometric isolated SAO alone is not a recognised clinical disease and as such the optimal management is unclear. Further, this population is likely heterogenous and the cause of isolated SAO, or associated respiratory condition, may alter the susceptibility of developing CVD. For example, isolated SAO may reflect a period on the continuum to airways obstruction and COPD; however, not all will develop obstruction [1, 2, 7]. When we excluded those who developed airflow obstruction during follow-up from our analysis, we found the relationship between isolated SAO and CVD persisted, suggesting the increased CVD risk is established prior to the onset of fixed obstruction. Isolated SAO is common in asthma; however, there has been some debate regarding the relationship between asthma and CVD [18–20]. When we excluded those with a pre-existing diagnosis of asthma the association between isolated SAO and incident CVD remained. Therefore, there is an effect of isolated SAO on CVD diagnosis irrespective of pre-existing asthma.

Multiple studies have shown the association between low lung volumes, or restriction, and CVD [21–24]. This may reflect the effect of early life on lung development, lung health and the association with comorbidities. In our sensitivity analysis when we excluded those with restriction, we found that the risk ratio remained similar, although not statistically significant. This may be because restriction has a stronger effect on CVD development than isolated SAO.

We compared the risk of incident CVD in those with isolated SAO defined by FEV_3/FEV_6 and $FEF_{25–75\%}$. Whilst the $FEF_{25–75\%}$ group had a higher risk, the confidence intervals were wide, likely reflecting the smaller number of participants. $FEF_{25–75\%}$ is a better predictor for the future development of obstruction than FEV_3/FVC [2] and, especially given the $FEF_{25–75\%}$ group had more participants with reduced FEV_1 than the FEV_3/FEV_6 group, the $FEF_{25–75\%}$ group may represent a group of more "advanced" isolated SAO. However, the *post hoc* analysis (supplementary table S7) showed similar effect sizes.

Susceptibility for CVD may also be affected by sex. Sex at birth influences CVD, and obstructive lung disease risk, and we found a difference in risk ratio when stratifying by sex. In our study, females with isolated SAO were more likely to develop CVD than males with isolated SAO. Males tend to have a higher prevalence of CVD [25, 26], although the incidence rate in females increases post-menopause. In addition, in those with isolated SAO, males are more likely to develop fixed airflow obstruction than females [2] and COPD is more common in males than females. Interestingly, the risk of cardiovascular death is higher in females with isolated SAO (compared to females without isolated SAO) than males with isolated SAO (compared to males without isolated SAO) [5]. Females may be more susceptible to some of the harmful effects of tobacco smoking as female smokers have a higher risk of acute coronary syndrome

compared to male smokers [27]. Thus, the risk of CVD associated with isolated SAO, and the attributable risk of smoking, may not be homogenous across sexes and this requires further exploration.

Relative to studies exploring the mechanism of the relationship between COPD and CVD [8, 28–32], CVD development among those with isolated SAO has drawn less attention. Shared risk factors, notably tobacco smoking, is one explanation for heightened CVD development in those with COPD. However, many studies exploring the link between COPD and CVD have not fully accounted for the possible confounding effect of tobacco smoking [30]. In addition, studies have shown never-smokers with COPD are not at increased risk of CVD [22, 33]. However, ever-smokers with COPD have much higher rates of obstructive coronary artery disease than ever-smokers without COPD [34]. Whilst smoking may account for some of the increased CVD risk in those with COPD, the relationship between COPD and CVD is complex [32].

We show that the risk of CVD attributed to isolated SAO was present when adjusting for smoking status and pack-years. To examine whether this association could be explained by residual confounding by smoking, we stratified the analysis by smoking status. We found that isolated SAO results in greater risk of CVD among smokers but not among never-smokers. This suggests that the relationship between isolated SAO and CVD incidence is driven by smoking. However, we did not find statistical support to clearly state that smoking modifies the relationship between isolated SAO and CVD.

Systemic inflammation is a likely contributor to the increase in CVD in those with COPD, and people with COPD have increased airway inflammation [35] and higher circulating levels of CRP than controls [36]. We showed that isolated SAO, compared to those without, was associated with a 9% increase in CRP, although this association was not present in never-smokers. We found no association between CRP and CVD diagnosis in those with isolated SAO. The median CRP for those with isolated SAO in our study was lower than those with COPD [36]; CRP was measured only once at baseline, and this may explain our findings. We show CRP is associated with isolated SAO; however, this does not suggest CRP is implicated in the development of isolated SAO or CVD. Testing other markers of inflammation such as interleukin-6 and assessing for longitudinal changes in inflammation in those with isolated SAO alongside lung function changes would help elucidate the impact of inflammation in the pathway.

Besides being the first to use longitudinal data to show the incidence of CVD in those with isolated SAO, a strength of our study is the large sample size of over 139 000 participants. Our inclusion of only good quality spirometry data ensures we have robust measures to define isolated SAO status. In addition, we used multiple data sources linked to the UK Biobank to identify CVD diagnosis.

One limitation is that the UK Biobank is not representative of the UK population [37] and, whilst this does not preclude causal inference [38], the findings are most applicable to middle-aged, predominantly White European populations. To be confident of the generalisability of our findings, validation in other populations, including of non-European ancestry, would be beneficial. As with all studies in this area, there is no universally agreed gold standard test for identifying isolated SAO, and different methods deliver differing prevalence estimates [2, 39]. This makes comparing studies using different methodologies challenging. We chose FEV_3/FEV_6 to minimise the risk of misclassification bias due to inaccurate measurement of FVC. We used longitudinal data to establish temporality; notwithstanding, whilst unlikely, reverse causation is possible. Finally, it is not clear whether those who developed obstruction did so before or after developing CVD and therefore these data should be interpreted with caution.

In summary, we show that isolated SAO confers a modest increased risk of future CVD. Isolated SAO is a heterogenous condition, with various causes, and for some it will progress to obstruction. The CVD risk profile in this cohort is also heterogenous, and smoking may drive much of this risk. Isolated SAO is not a recognised diagnosis and as such does not prompt a proven management strategy. We suggest future studies aim to elucidate the mechanisms of increased CVD risk in this group and how best this risk can be managed.

Provenance: Submitted article, peer reviewed.

Ethics statement: The UK Biobank has ethics approval from the North West – Haydock Research Ethics Committee (21/NW/0157) and all participants provided written consent.

Conflict of interest: S. Bartlett-Pestell reports support for attending meetings from Chiesi. V. Quintero Santofimio, J. Potts, E. Fuertes and A.F.S. Amaral report no conflicts of interest. J.P. Allinson reports grants from Asthma+Lung

UK; payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca and Chiesi; support for attending meetings from AstraZeneca; and leadership roles with the American Thoracic Society and the Global Lung Function Initiative. J.A. Wedzicha reports grants from AstraZeneca, Boehringer, Chiesi, GSK, Novartis and Genentech; consultancy fees from AstraZeneca, Epiendo, Gilead, GSK, Empiricio, Sanofi, Roche, Altesa, Pfizer and NEATstix; payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, GSK, Boehringer, Recipharm, Novartis, Roche and Sanofi; and participation on a data safety monitoring board for Virtus.

Support statement: No funding declared.

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