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Incidence trends of airflow obstruction among European adults without asthma: a 20-year cohort study

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Investigating COPD trends may help healthcare providers to forecast future disease burden. We estimated sex- and smoking-specific incidence trends of pre-bronchodilator airflow obstruction (AO) among adults without asthma from 11 European countries within a 20-year follow-up (ECRHS and SAPALDIA cohorts). We also quantified the extent of misclassification in the definition based on pre-bronchodilator spirometry (using post-bronchodilator measurements from a subsample of subjects) and we used this information to estimate the incidence of post-bronchodilator AO (AO_{post-BD}), which is the primary characteristic of COPD. AO incidence was 4.4 (95% CI: 3.5–5.3) male and 3.8 (3.1–4.6) female cases/1,000/year. Among ever smokers (median pack-years: 20, males; 12, females), AO incidence significantly increased with ageing in men only [incidence rate ratio (IRR), 1-year increase: 1.05 (1.03–1.07)]. A strong exposure-response relationship with smoking was found both in males [IRR, 1-pack-year increase: 1.03 (1.02–1.04)] and females [1.03 (1.02–1.05)]. The positive predictive value of AO for AO_{post-BD} was 59.1% (52.0–66.2%) in men and 42.6% (35.1–50.1%) in women. AO_{post-BD} incidence was 2.6 (1.7–3.4) male and 1.6 (1.0–2.2) female cases/1,000/year. AO incidence was considerable in Europe and the sex-specific ageing-related increase among ever smokers was strongly related to cumulative tobacco exposure. AO_{post-BD} incidence is expected to be half of AO incidence.

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality worldwide¹, and it represents an important public health challenge, being both a preventable and treatable disease². Globally, the COPD burden is projected to increase in coming decades because of continued exposure to risk factors and ageing of the population³.

COPD is characterised by a progressive airflow obstruction that is not fully reversible⁴. According to the Global Initiative for Chronic Obstructive Lung Disease guidelines², the diagnosis of COPD requires post-bronchodilator

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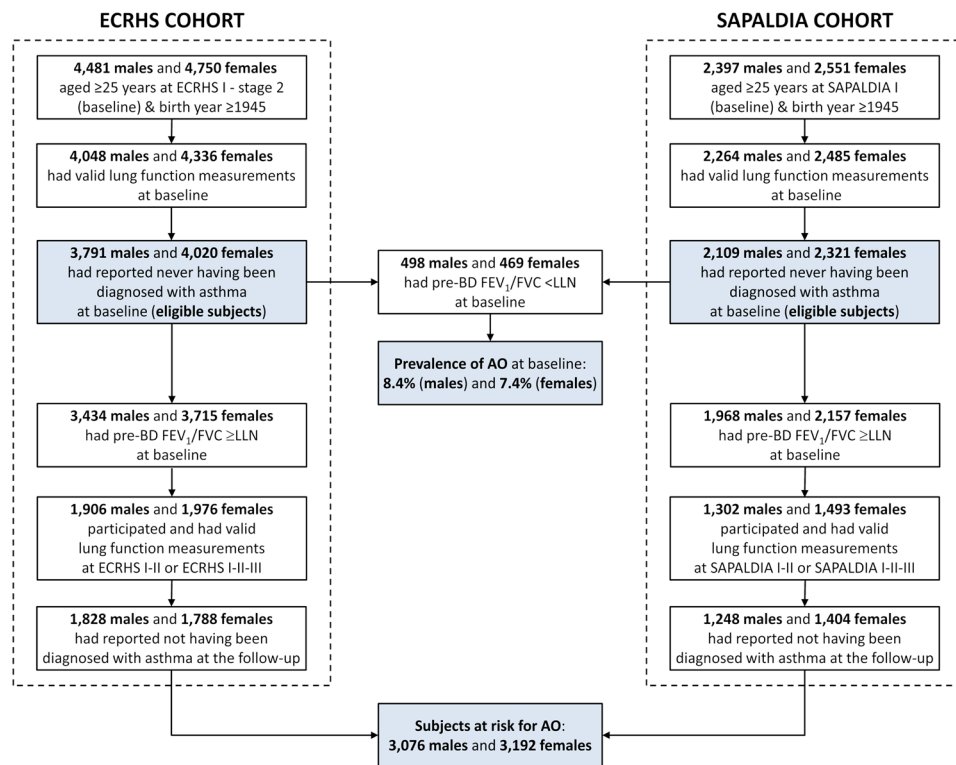


Figure 1. Selection of the subjects at risk for AO. Pre-BD: pre-bronchodilator.

spirometry, and the use of pre-bronchodilator measurements may lead to some misclassification of the disease⁵. However, post-bronchodilator spirometry has been adopted in epidemiological studies in recent years only.

Investigating how COPD rates could be affected by changes in major risk factors may help healthcare providers and decision makers to forecast the disease burden and to optimise clinical and public health strategies. In particular, tobacco smoking is the main preventable cause of COPD and it is still the most important health hazard in Europe⁶. Epidemiological tools for Health Impact Assessment⁷ are available to forecast changes in the COPD burden due to changes in a risk factor (e.g. the reduction in smoking after anti-tobacco interventions), but these tools need estimates of the COPD incidence and prevalence within a given population, among other information, as inputs.

In the present study, we evaluated incidence trends of pre-bronchodilator airflow obstruction (AO) by sex and lifetime smoking history, among adults without asthma. To fulfil this purpose, we analysed 20-year follow-up data from the European Community Respiratory Health Survey (ECRHS)^{8–10} and the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA)^{11–13}, and we identified AO using internally-derived equations of the lower limit of normal [LLN; 5th percentile of the distribution of the forced expiratory volume in 1 second (FEV₁) and the forced vital capacity (FVC) ratio in normal subjects]. In addition, we quantified the extent of misclassification in the definition based on pre-bronchodilator spirometry (using post-bronchodilator measurements from a subsample of our subjects) and we used this information to estimate the overall incidence of post-bronchodilator airflow obstruction (AO_{post-BD}), which is the primary characteristic of COPD.

Results

Main characteristics of the subjects. At baseline, 5,900 men and 6,341 women without diagnosed asthma from 32 centres located in 11 European countries (listed in Supplementary Table S1) participated in the ECRHS and SAPALDIA studies, and were eligible for the present study (Fig. 1). Among these individuals, the prevalence of AO was 8.4% in males and 7.4% in females. We identified 3,076 men and 3,192 women (mean age at baseline: 36 years), who had reported not having been diagnosed with asthma at the follow-up, as subjects at risk for AO and we included them in the analyses (Fig. 1 and Table 1). About 60% of these subjects participated and provided valid lung function measurements at all three examinations. The mean duration of the follow-up was 15 years (range: 1–20 years) for both sexes. Among those at risk for AO, 65.9% of men and 56.5% of women were ever smokers at baseline and/or during the follow-up. The median number of pack-years among male and female ever smokers was 20 and 12, respectively. The selection of the subjects at risk for AO and their main characteristics are reported separately for the ECRHS and SAPALDIA studies in Supplementary Tables S2 and S3. The main characteristics of the eligible subjects included or excluded from the analyses are described separately for the two cohorts in Supplementary Tables S4 and S5.

Incidence of AO. During the follow-up, 208 incident cases of AO out of a total of 45,536 person-years were identified among males, whereas the new cases were 194 out of a total of 48,135 person-years among females

	Males	Females
N° of subjects	3,076	3,192
Age at baseline (years), mean (range)	36 (25–48)	36 (25–47)
Subjects who participated and had valid lung function measurements at all examinations, %	59.5	60.6
Duration of the follow-up (years)*, mean (range)	15 (1–20)	15 (1–20)
Ever smokers at baseline and/or follow-up, %	65.9	56.5
N° of lifetime pack-years among ever smokers, median (IQR)	20 (9–34)	12 (4–23)
Pre-bronchodilator FEV₁/FVC(%), mean ± s.d.		
1 st examination (baseline)	79.8 ± 5.1	83.2 ± 5.2
2 nd examination	77.3 ± 5.6	78.8 ± 5.7
3 rd examination	75.2 ± 5.6	76.2 ± 5.2

Table 1. Main characteristics of the subjects at risk for AO. IQR: interquartile range; s.d.: standard deviation. *The end of the follow-up was the estimated calendar year of AO onset for the incident cases and the calendar year of the last examination for the remaining subjects.

	Males	Females
Overall incidence rate		
N° of incident cases	208	194
person-years at risk	45,536	48,135
cases/1,000/year (95% CI)	4.4 (3.5–5.3)	3.8 (3.1–4.6)
Incidence rate among never smokers		
N° of incident cases	39	61
person-years at risk	16,094	21,451
cases/1,000/year (95% CI)	2.3 (1.5–3.2)	2.7 (1.9–3.4)
Incidence rate among ever smokers		
N° of incident cases	168	133
person-years at risk	29,368	26,657
cases/1,000/year (95% CI)	5.5 (4.3–6.6)	4.8 (3.8–5.8)

Table 2. Incidence of AO.

(Table 2). The overall incidence rate (IR) of AO in subjects aged 25–64 was 4.4 cases/1,000/year [95% confidence interval (95% CI: 3.5–5.3)] for males and 3.8 (3.1–4.6) for females. The incidence of AO was higher for ever smokers compared to never smokers in both men [incidence rate ratio (IRR) for smoking (95% CI): 2.34 (1.65–3.32)] and women [1.78 (1.31–2.42)]. These estimates are reported separately for the ECRHS and SAPALDIA studies in Supplementary Table S6.

Trends in the incidence of AO. The incidence of AO greatly increased with ageing in men [IRR per 1-year increase (95% CI): 1.04 (1.02–1.06)], whereas a less steep, and statistically non-significant increase was observed in women [1.01 (0.99–1.03)] (Fig. 2). Among ever smokers, a positive trend in AO incidence was found in men as age increased [1.05 (1.03–1.07)], whereas this age trend was less steep and did not reach statistical significance in women [1.02 (0.99–1.04)] (Fig. 3). In addition, a strong exposure-response relationship was found between lifetime pack-years and AO incidence for both males [IRR per 1-pack-year increase (95% CI): 1.03 (1.02–1.04)] and females [1.03 (1.02–1.05)] (Fig. 4). Among never smokers, no age trend in AO incidence was observed for either men [IRR per 1-year increase (95% CI): 1.00 (0.96–1.03)] or women [1.00 (0.97–1.03)] (Fig. 3).

Incidence of AO_{post-BD}. The positive predictive value of AO for AO_{post-BD} was 59.1% (95% CI: 52.0–66.2%) among the 212 men and 42.6% (35.1–50.1%) among the 184 women with AO and valid post-bronchodilator spirometry at the 3rd examination. Based on these figures, the estimated IR of AO_{post-BD} was 2.6 (95% CI: 1.7–3.4) cases/1,000/year in males and 1.6 (1.0–2.2) cases/1,000/year in females.

Discussion

This 20-year follow-up study of two large, population-based, European cohorts of young adults without asthma provided estimates of the incidence of AO over time. This information was used to evaluate the incidence of AO_{post-BD}. We found a considerable incidence of AO, quantified as 4.4 male and 3.8 female cases/1,000/year. AO incidence increased with ageing and these trends seem to be largely attributable to active smoking. The exposure-response relationship between lifetime pack-years and AO incidence could possibly be stronger in females. The incidence of AO was also high (2.3 male and 2.7 female cases/1,000/year) among lifetime non-smokers. The expected incidence of AO_{post-BD} was 2.6 and 1.6 cases/1,000/year for males and females, respectively.

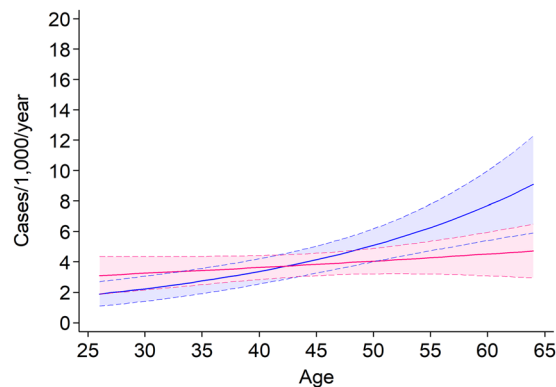


Figure 2. Age trends in AO incidence among males (blue line) and females (red line). Dotted lines represent the 95% confidence limits.

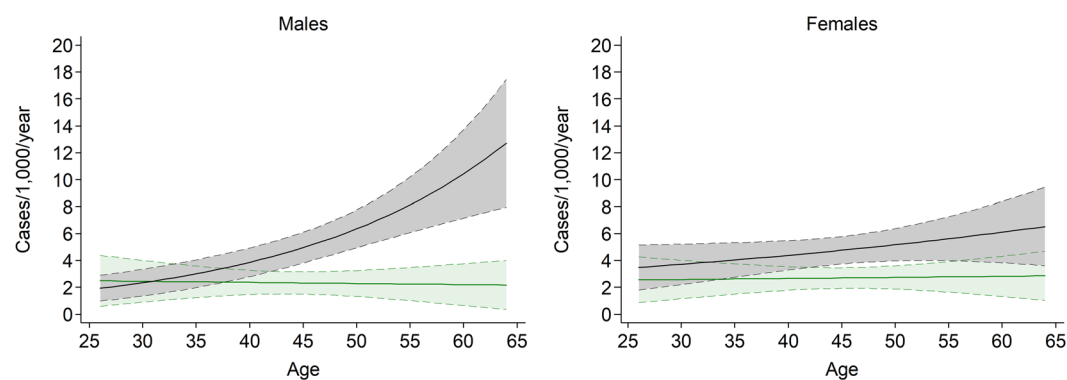


Figure 3. Age trends in AO incidence among ever smokers (black line) and never smokers (green line), according to sex. Dotted lines represent the 95% confidence limits.

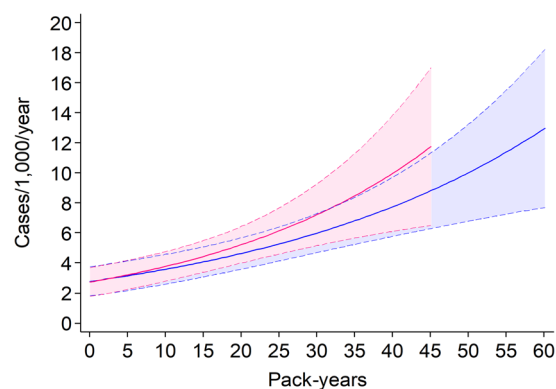


Figure 4. Relationship between AO incidence and lifetime pack-years among male ever smokers (blue line) and female ever smokers (red line). Dotted lines represent the 95% confidence limits.

Few spirometry-based studies have investigated the incidence of AO in large cohorts with long follow-up periods in Europe^{14,15}. Our estimates of the overall incidence of AO are consistent with earlier results from the ECRHS I and II data¹⁴, in which the incidence of pre-bronchodilator $FEV_1/FVC < 70\%$ over 9 years was 3.2 and 2.4 cases/1,000/year in men and women aged 20–54, respectively. The present analyses add further and stronger evidence that AO is a major health problem in adults¹⁶, especially in males¹⁵. In respect to the previous analysis of the ECRHS data¹⁴, the longer follow-up and the inclusion of the SAPALDIA cohort in the present study (with the consequent higher sample size) enabled us to investigate incidence trends across all ages of adulthood. As a result, we found an increase of AO incidence up to 64 years in both sexes, even if this increase was less steep and did not reach statistical significance in women.

The higher incidence of AO with ageing is well known, even if it is unclear whether ageing-related biological mechanisms lead to COPD or if age reflects the accumulation of exposures during a lifetime¹⁷. In our study, we found that the incidence of AO increased with ageing among ever smokers only, which supports the concept that age reflects cumulative exposures (especially tobacco smoking) throughout life. Therefore, in the present analyses, the higher incidence of AO in men could be due to both the higher percentage of ever smokers and the higher level of tobacco exposure (pack-years) in the male cohort.

We found that female smokers reached the same level of AO incidence at a lower number of pack-years than male smokers, even if our study included a limited number of heavy smokers. Other studies have suggested that women may be at a greater risk of smoking-induced lung function impairment for the same level of exposure as men¹⁸. This may be related to a sex-specific predisposition for smoking-related lung damage or a dose-dependent effect due to smaller airways in women, with each cigarette smoked representing a proportionally greater exposure. It has been hypothesised that oestrogens could potentiate the oxidative stress due to smoking exposure, contributing to airway remodelling^{19,20}. Sørheim and colleagues have also found that a greater lung function reduction and a more severe COPD was more common among female patients with a low smoking exposure²¹.

Current trends in smoking habits may have a complex effect on future trends in AO incidence. During the past decades, smoking initiation rates reduced or levelled off among late adolescents and young adults²², and smoking cessation rates increased²³ across Europe. However, after 1990, smoking initiation rates markedly increased among early adolescents in different European regions²². In addition, subjects who start smoking before the age of 16 may be less likely to quit than those who start later²³. Accordingly, we can speculate an increase in AO incidence during the next decades across Europe among the individuals who were in their early adolescence after the Nineties.

The high incidence of AO among never smokers, which was relatively constant with ageing, supports previous evidence that COPD also generates a substantial burden in the population not exposed to active smoking^{24,25}. Early life insults, such as tobacco exposure *in utero* and childhood, low birth weight and childhood lung infections, may increase the risk of COPD²⁶. Occupational exposures to chemicals, dust or fumes²⁷, indoor exposure to biomass fuels²⁸, outdoor air pollution²⁹, chronic asthma³⁰ and alpha-1-antitrypsin deficiency³¹ may also increase the risk of COPD in subjects who have never smoked.

The positive predictive value of AO for $AO_{\text{post-BD}}$ was lower in women than in men in our sample, which could be explained by differences among the subjects with AO. As reported by Sawalha and colleagues⁵, we also found that the percentage of ever smokers (79.7% vs 73.4%), the median number of lifetime pack-years (25 vs 20), and the percentage of subjects with productive cough (21.0% vs 14.5%), factors that may predict the occurrence of COPD¹⁴, were higher in men than in women with AO and valid post-bronchodilator spirometry at the 3rd examination. In addition, our estimates of the positive predictive value (59.1% in males and 42.6% in females) were lower than the figure obtained by Schermer and colleagues (74.7% in both sexes) when the fixed cut-off definition of AO was used⁴. The fixed cut-off criterion leads to a substantial over-diagnosis of AO in middle-aged and elderly subjects⁴ and, consequently, to a higher positive predictive value.

We found that the expected overall incidence of $AO_{\text{post-BD}}$ was half of the incidence of AO. We acknowledge that the expected incidence of $AO_{\text{post-BD}}$ could still be an overestimate of the incidence of COPD in Europe, as $AO_{\text{post-BD}}$ cases may include a non-negligible proportion of asymptomatic never smokers³² who would likely not be diagnosed with COPD in a clinical setting².

The present study has several strengths. Firstly, it relies on the long follow-up of two large population-based cohorts of adults without asthma. In addition, the young age of our subjects at baseline enabled us to investigate AO in the early phases of COPD, which is crucial in identifying the group of individuals who could benefit from preventive interventions. The exclusion of the individuals who had reported a diagnosis of asthma at baseline or at the follow-up should have limited the bias due to the asthma-COPD misclassification. Asthma and COPD have a different aetiology, characteristics and clinical course³³, and $AO_{\text{post-BD}}$ in adulthood (even in smokers) should not be considered as COPD without giving consideration to earlier asthma³⁴. However, among the incident cases of AO at the 2nd examination, 61.3% of males and 66.7% of females had either AO or key indicators of COPD² or they reported a physician diagnosis of COPD at the 3rd examination (detailed description available in the Supplementary Information, page 7). This result suggests that a subgroup of AO cases in the present study could be patients with undiagnosed asthma. Further, the inclusion in the analyses of two large cohorts of subjects from 11 countries should have increased the generalizability of our results to the European population. Lastly, the computation of the LLN equations within our cohorts, by taking the heterogeneity of the spirometric measurements among centres into account³⁵, should have reduced the misclassification due to the use of predictive equations generated from other populations³⁶.

The main limitation of the present study is the lack of post-bronchodilator spirometry at all examinations, which did not enable us to directly estimate the incidence of $AO_{\text{post-BD}}$ and to confirm the presence of $AO_{\text{post-BD}}$ in subsequent spirometry tests^{37,38}. In addition, having measured lung function only at three time points over 20 years could have affected the estimates of the incidence trends, as we could only predict the year of AO onset between two examinations. Further, only 60% of the subjects in our cohorts participated and had valid lung function measurements at all examinations, and attrition could have influenced our findings and limited their generalizability to some extent. However, in males, the overall IR of AO estimated from the subsample of subjects with data from all the examinations was comparable with the figure obtained from the whole cohort (4.5 vs 4.4 cases/1,000/year), whereas a lower value was found in females (3.0 vs 3.8 cases/1,000/year). The percentage of ever smokers was lower among the eligible subjects included in the study than among those excluded, for both cohorts and sexes (Supplementary Tables S4 and S5). Accordingly, we speculate that AO incidence could be underestimated in our analyses as a consequence of the lower percentage of ever smokers among the study subjects. Lastly, we acknowledge that ever smoking should be subdivided into current or past exposures, and that these two categories should be further subdivided based on pack-years (and time since smoking cessation for quitters), in order

to better assess the impact of current and past smoking on AO incidence trends. Unfortunately, these analyses would require a high number of incident cases to obtain stable results.

In conclusion, the incidence of AO was considerable over 20 years among European adults without asthma, who were followed up between ages 25 and 64. The ageing-related increase in AO incidence among ever smokers was strongly related to cumulative tobacco exposure, which seems to largely explain the different age trends for men and women. The exposure-response relationship between lifetime pack-years and AO incidence could possibly be stronger in females. Although the incidence of AO was relatively constant with age, it was high even among lifetime non-smokers, which supports the fact that COPD also represents a substantial burden in the population not exposed to active smoking. The incidence of $AO_{\text{post-BD}}$ is expected to be half of the incidence of AO and the extent of misclassification (when using pre-bronchodilator as opposed to post-bronchodilator spirometry) was higher in women.

Methods

Study design. The ECRHS and SAPALDIA studies share a comparable research protocol with information collected at three examinations. ECRHS (www.ecrhs.org) is an international, population-based, cohort study on respiratory health on random samples of subjects aged 20–44 years in 1991–1993 (ECRHS I; 1st examination)⁸. Each participant was sent a brief screening questionnaire (stage 1) and, from those who responded, a 20% random sample was invited to undergo a more detailed clinical examination (stage 2). The participants in the ECRHS I - stage 2 were followed up in 1998–2002 (ECRHS II; 2nd examination)⁹ and in 2010–2013 (ECRHS III; 3rd examination)¹⁰. SAPALDIA (www.sapaldia.ch/en/) is a Swiss, population-based, cohort study on the long-term health effects of air pollutants in subjects aged 18–60 years in 1991, who were randomly selected from local registries of inhabitants to undergo standardized clinical tests (SAPALDIA I; 1st examination)^{11,39}. The participants in SAPALDIA I were re-examined in the clinical centres in 2001–2003 (SAPALDIA II; 2nd examination)¹² and in 2010–2011 (SAPALDIA III; 3rd examination)¹³.

The subjects in both the ECRHS and SAPALDIA studies underwent a detailed clinical interview and pre-bronchodilator spirometry at each examination, and post-bronchodilator spirometry was also measured at the last follow-up contact. The maximum FEV_1 and the maximum FVC from at least two technically satisfactory manoeuvres were measured according to the American Thoracic Society criteria for repeatability^{39,40}. Biomedin, Jaeger Masterscope, SensorMedics or Vitalograph spirometers were used at the 1st and 2nd examinations, whereas NDD EasyOne was used in almost all centres at the 3rd examination (see Supplementary Table S1). In both the studies, the lung function measurements were corrected for the change in spirometer, according to Bridevaux and colleagues⁴¹.

Selection of the subjects and definitions. The *eligible subjects* (Fig. 1) were those who:

- were at least 25 years old in the ECRHS - stage 2 or SAPALDIA I, in order to exclude those who may still not have reached the plateau phase of lung function growth at baseline⁴²;
- were born in 1945 or later, in order to have the same age range in the ECRHS and SAPALDIA cohorts;
- had provided valid lung function measurements at baseline;
- had reported never having been diagnosed with asthma at baseline.

The *subjects at risk for AO* (Fig. 1) were the eligible participants who:

- had pre-bronchodilator $FEV_1/FVC \geq LLN$ at baseline (internally-derived LLN equations were computed, which take the variation in the spirometric measurements due to differences among centres into account^{35,43}; detailed description available in the Supplementary Information, pages 3–4);
- had provided valid lung function measurements during at least two consecutive examinations (ECRHS/SAPALDIA I-II or ECRHS/SAPALDIA I-II-III);
- had reported not having been diagnosed with asthma at the follow-up.

The subjects at risk who had pre-bronchodilator $FEV_1/FVC < LLN$ at one of the follow-up contacts were considered to be *incident cases of AO*. For each new case, the year of age at AO onset was estimated by linear interpolation, (i) assuming that the decline in FEV_1/FVC between two examinations was constant and (ii) taking into account the change in the LLN cut-off with ageing (detailed description available in the Supplementary Information, page 5). Based on these assumptions, we obtained the year of age when the FEV_1/FVC had reached a level below the LLN for each individual. The end of the follow-up was the calendar year of AO onset (obtained by summing the estimated year of age at onset to the birth year) for the incident cases, and the calendar year of the last examination for the remaining subjects.

Smoking was classified as “*never*” (i.e. never smoking at baseline and follow-up) and “*ever*” (i.e. past or current smoking at baseline or follow-up). Lifetime pack-years were quantified at the end of the follow-up.

Statistical analyses. The ECRHS and SAPALDIA data were pooled to estimate the IRs of AO and their trends, within age 25–64 years during 1991–2011. Data pooling was justified due to the fact that the AO rates were similar in the two studies for both sexes (see Supplementary Table S6). Age was right-censored at 64 years in order to avoid data sparseness, whereas the time period was right-censored at 2011 in order to analyse the data from the same period for both the studies. The sex-specific pooled datasets were reshaped by age to estimate AO incidence (detailed description available in the Supplementary Information, page 6).

Incidence of AO. The overall IRs of AO were computed separately in males and females using two-level Poisson models (subject = level 1 unit; centre = level 2 unit). All the models had log person-years as the offset, a random intercept term at level 2 and study (0 = ECRHS, 1 = SAPALDIA) as a fixed effect. The smoking-specific IRs of AO were estimated adding smoke (ever vs never) and the smoke \times study interaction term to the fixed part of the models. All the rates were obtained by setting the indicator of the study equal to the proportion of person-years in SAPALDIA (0.44 for males and 0.46 for females), in order to account for the different overall time at risk in the two cohorts.

Trends in the incidence of AO. Age trends in AO incidence were estimated separately in males and females using two-level Poisson models with log person-years as the offset, a random intercept term at level 2 and age, study and the age \times study interaction term as fixed effects. Age was included as a linear factor in the models since higher degree polynomials or spline interpolations did not improve goodness-of-fit. Age trends were computed according to smoking history adding smoke and the age \times smoke interaction term to the fixed part of the models. Lastly, AO incidence was evaluated according to lifetime pack-years among ever smokers, using sex-specific reshaped datasets by pack-years and two-level Poisson models with pack-years, study and the pack-years \times study interaction term as fixed effects. The number of pack-years was right-censored at 60 for men and 45 for women to avoid data sparseness.

Incidence of $AO_{\text{post-BD}}$. The expected IR of $AO_{\text{post-BD}}$ (post-bronchodilator $FEV_1/FVC < LLN$) was estimated from the overall IR of AO, separately in men and women. Firstly, the positive predictive value of AO for $AO_{\text{post-BD}}$ was computed for each sex among those with pre-bronchodilator $FEV_1/FVC \geq LLN$ and valid post-bronchodilator lung function measurements in the ECRHS/SAPALDIA III. Secondly, the expected IR of $AO_{\text{post-BD}}$ was obtained as the product of the sex-specific estimates of the AO rate and the positive predictive value. The 95% confidence interval of the $AO_{\text{post-BD}}$ rate was computed by using the delta method and assuming that the sex-specific estimates of the AO rate and of the positive predictive value have a perfect positive correlation.

The statistical analyses were carried out using STATA 15 (StataCorp, College Station, TX).

Ethics statement. Ethics approval was obtained by all centres from the appropriate ethics committees in ECRHS [Antwerp City and Antwerp South: Adviescommissie Medische Ethiek UZA-UA (CME); Tartu: Research Ethics Committee of the University of Tartu, Estland (N° 209T-17); French centres: Comité de protection des personnes, Sud V Est (N° 2011-A00013-38); German centres: Ethik-Kommission der Bayerischen Landesärztekammer (N° 10015); Reykjavik: National Biotech Committee of Iceland (NBCI) (N° VSNb2011090016/03.11); Pavia: Fondazione IRCCS Policlinico ‘San Matteo’ (N° P-20110024215); Turin: Comitato Etico dell’Azienda Sanitaria Locale TO/2 di Torino (N° 569/09/08); Verona: Comitato Etico per la Sperimentazione dell’Azienda Ospedaliera Istituti Ospitalieri di Verona (N° 1393); Bergen: Universitetet i Bergen, Regional komité for medisinsk og helsefaglig forskningsetikk, Vest-Norge (REK Vest) (N° 2010/759); Albacete: Comité de Ética e Investigación de Complejo Hospitalario de Albacete (N° 04/09); Barcelona: Comité Ético de Investigación Clínica del Instituto Municipal de Asistencia Sanitaria, Barcelona, Spain (N° PS09/00716); Galdakao: Comité Ético de Investigación del Hospital de Galdakao, Spain (N° 20101104); Huelva: Comisión de Investigación del Hospital Juan Ramón Jiménez de Huelva (N° 20090417); Oviedo: Comité Ético de Investigación Clínica Regional, Hospital Universitario Central de Asturias (N° 20110415); Swedish centres: Ethics Committee at the Medical Faculty, Uppsala University (N° 1999/313 and 2010/068); Basel: Swiss Academy of Medical Sciences and the ethics committee of Basel (N° PV123/00,157/00); UK centres: NRES Committee London - Stanmore (REC Reference 11/LO/0965 IRAS number 70769)] and in SAPALDIA [Swiss Academy of Medical Sciences and the regional committees for each study centre; ethics approval is coordinated by the lead ethical agency EKNZ in Basel, Switzerland]. In both the studies, written informed consent was obtained from the participants and all experiments were performed in accordance with relevant guidelines and regulations.

Data availability

Due to data protection reasons, the datasets analysed in the present study cannot be made publicly available. The datasets are available to interested researchers from the corresponding author on reasonable request.

Received: 23 September 2019; Accepted: 13 February 2020;

Published online: 26 February 2020

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Acknowledgements

The present analyses are part of the ALEC Study (www.alecstudy.org). The ALEC project leader is Deborah Jarvis. The manuscript was done with ALEC Workpackage 6 led by Cosetta Minelli. Other Workpackage leaders in ALEC are Cecilie Svanes, John Henderson (University of Bristol, Bristol, UK), Judith Garcia-Aymerich [ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain] and Nicole Probst-Hensch. ALEC has received funding from the European Union's Horizon 2020 research and innovation programme [Grant Agreement No. 633212]. The co-ordination of the ECRHS was supported by the European Commission (phases 1 and 2) and the Medical Research Council (phase 3). The SAPALDIA cohort was funded by The State Secretariat for Education, Research and Innovation (SERI), Switzerland. The principal investigators and team

members of the ECRHS and SAPALDIA studies, and the national funders who supported data collection in the ECRHS and SAPALDIA studies are listed in the appendix available in the Supplementary Information.

Author contributions

S.A., L.C. and A.M. conceived the study. S.A. designed the study and drafted the analysis plan and the first version of the manuscript. L.C., S.A. and G.P. performed the statistical analysis. All the authors contributed in the collection of data in/from the original studies, discussion of the statistical analysis plan and interpretation of study results. All the authors critically reviewed and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41598-020-60478-5>.

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