Small airways obstruction and its risk factors in the Burden of Obstructive Lung Disease (BOLD) study: a multinational cross-sectional study

*Ben Knox-Brown, Jaymini Patel, James Potts, Rana Ahmed, Althea Aquart-Stewart, Hamid Hacene Cherkaski, Meriam Denguezli, Mohammed Elbiaze, Asma Elsony, Frits M E Franssen, Mohammed Al Ghobain, Imed Harrabi, Christer Janson, Rain Jõgi, Sanjay Juvekar, Herve Lawin, David Mannino, Kevin Mortimer, Asaad Ahmed Nafees, Rune Nielsen, Daniel Obaseki, Stefanni Nonna M Paraguas, Abdul Rashid, Li-Cher Loh, Sundeep Salvi, Terence Seemungal, Michael Studnicka, Wan C Tan, Emiel E F M Wouters, Cristina Barbara, Thorarinn Gislason, Kirthi Gunasekera, Peter Burney, Andre F S Amaral, for the BOLD Collaborative Research Group**

Summary

Background Small airways obstruction is a common feature of obstructive lung diseases. Research is scarce on small airways obstruction, its global prevalence, and risk factors. We aimed to estimate the prevalence of small airways obstruction, examine the associated risk factors, and compare the findings for two different spirometry parameters.

Methods The Burden of Obstructive Lung Disease study is a multinational cross-sectional study of 41 municipalities in 34 countries across all WHO regions. Adults aged 40 years or older who were not living in an institution were eligible to participate. To ensure a representative sample, participants were selected from a random sample of the population according to a predefined site-specific sampling strategy. We included participants' data in this study if they completed the core study questionnaire and had acceptable spirometry according to predefined quality criteria. We excluded participants with a contraindication for lung function testing. We defined small airways obstruction as either mean forced expiratory flow rate between 25% and 75% of the forced vital capacity ($FEF_{25–75}$) less than the lower limit of normal or forced expiratory volume in 3 s to forced vital capacity ratio (FEV_3/FVC ratio) less than the lower limit of normal. We estimated the prevalence of pre-bronchodilator (ie, before administration of 200 µg salbutamol) and post-bronchodilator (ie, after administration of 200 µg salbutamol) small airways obstruction for each site. To identify risk factors for small airways obstruction, we performed multivariable regression analyses within each site and pooled estimates using random-effects meta-analysis.

Findings 36 618 participants were recruited between Jan 2, 2003, and Dec 26, 2016. Data were collected from participants at recruitment. Of the recruited participants, 28 604 participants had acceptable spirometry and completed the core study questionnaire. Data were available for 26 443 participants for FEV_3/FVC ratio and 25 961 participants for $FEF_{25–75}$. Of the 26 443 participants included, 12 490 were men and 13 953 were women. Prevalence of pre-bronchodilator small airways obstruction ranged from 5% (34 of 624 participants) in Tartu, Estonia, to 34% (189 of 555 participants) in Mysore, India, for $FEF_{25–75}$, and for FEV_3/FVC ratio it ranged from 5% (31 of 684) in Riyadh, Saudi Arabia, to 31% (287 of 924) in Salzburg, Austria. Prevalence of post-bronchodilator small airways obstruction was universally lower. Risk factors significantly associated with FEV_3/FVC ratio less than the lower limit of normal included increasing age, low BMI, active and passive smoking, low level of education, working in a dusty job for more than 10 years, previous tuberculosis, and family history of chronic obstructive pulmonary disease. Results were similar for $FEF_{25–75}$, except for increasing age, which was associated with reduced odds of small airways obstruction.

Interpretation Despite the wide geographical variation, small airways obstruction is common and more prevalent than chronic airflow obstruction worldwide. Small airways obstruction shows the same risk factors as chronic airflow obstruction. However, further research is required to investigate whether small airways obstruction is also associated with respiratory symptoms and lung function decline.

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Introduction

The terms small airways obstruction, small airways dysfunction, and small airways disease are used interchangeably to describe a pathophysiology that occurs within airways of less than 2 mm diameter. Starting around the eighth generation of airway branching, the small airways contribute less than 10% to total airway resistance.[1] However, in asthma and chronic obstructive pulmonary disease, the small airways are the predominant site of resistance, and both diseases are

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*Members listed in appendix 11

National Heart and Lung Institute, Imperial College London, London, UK (B Knox-Brown MSc, J Patel PhD, J Potts BSc, Prof P Burney MD, A F S Amaral PhD); **Epidemiological Laboratory for Public Health, Research and Development, Khartoum, Sudan** (R Ahmed PhD, A Elsony PhD); **Department of Medicine, University of the West Indies, Mona, Jamaica** (A Aquart-Stewart FCCP); **Department of Pneumology,**

Faculty of Medicine Annaba, University Badji Mokhtar of Annaba, Annaba, Algeria (H H Cherkaski MD); **Faculté de Médecine Dentaire de Monastir, Université de Monastir, Monastir, Tunisia** (M Denguezli PhD); **Department of Respiratory Medicine, Faculty of Medicine, Mohammed Ben Abdellah University, University Hospital, Fes, Morocco** (Prof M Elbiaze MD); **Department of Respiratory Medicine, Maastricht University Medical Centre, Maastricht, Netherlands** (Prof F M E Franssen PhD, Prof E E F M Wouters MD); **Department of Research and Education, CIRO, Horn, Netherlands** (F M E Franssen); **King Abdullah International Medical Research Centre, King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia** (M Al Ghobain FCCP); **Ibn El Jazzar Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia** (I Harrabi MD); **Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden** (Prof C Janson PhD); **Lung Clinic, Tartu University Hospital, Tartu, Estonia** (R Jõgi PhD); **Vadu Rural Health Program, KEM Hospital Research Centre, Pune, India** (Prof S Juvekar PhD); **Unit of Teaching and Research in Occupational and Environmental Health, University of Abomey-Calavi, Cotonou, Benin** (H Lawin MD); **University of Kentucky, Lexington, KY, USA** (D Mannino MD); **COPD Foundation, Miami, FL, USA** (D Mannino); **University of Cambridge, Cambridge, UK** (Prof K Mortimer PhD); **Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK** (K Mortimer); **Department of Community Health Sciences, Aga Khan University, Karachi, Pakistan** (A A Nafees FCPS); **Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway** (R Nielsen PhD); **Department of Clinical Science, University of Bergen, Bergen, Norway** (R Nielsen); **Obafemi Awolowo**

Research in context

Evidence before this study

We searched PubMed and Web of Science from database inception to July 26, 2022. We used a combination of medical subject headings and text words related to selected spirometry parameters and derivations of the phrase small airways obstruction. Search terms included: ("$FEF_{25–75}$" OR "MMEF", OR "FEV_3/FVC" OR "FEF_{50}" OR "FEF_{75}") AND ("small airways obstruction" OR "small airways disease" OR "small airways dysfunction" OR "peripheral airway disease" OR "distal airways obstruction"). We screened titles and abstracts of search results to identify publications relevant to our study aims. Most population-based studies used the mean forced expiratory flow rate between 25% and 75% of the forced vital capacity ($FEF_{25–75}$) to assess small airways obstruction and there was no agreement regarding diagnostic criteria, with both percent predicted cutoffs and the lower limit of normal being used. Few studies reported prevalence of small airways obstruction as a primary outcome. Prevalence ranged from 7·5% to 45·9% and varied according to choice of spirometry parameter and world region. Prevalence estimates were generally higher for $FEF_{25–75}$ than forced expiratory volume in 3 s as a ratio of the forced vital capacity (FEV_3/FVC ratio). Only two population-based studies, both in China, provided prevalence estimates and also presented associated risk factors for small airways obstruction. Prevalence estimates were different between these studies (7·5% *vs* 43·5%). Risk factors for small airways obstruction reported by these two studies included smoking, low BMI, increasing age, female sex, use of solid fuels for cooking or heating, low level of education, family history of chronic obstructive pulmonary disease, and passive smoke exposure. No population-based data exist regarding the prevalence and risk factors for small airways obstruction outside of China.

Added value of this study

To the best of our knowledge, this is the first study to estimate the prevalence of small airways obstruction across several world regions using a standardised protocol. Additionally, we investigated the association of small airways obstruction with several potential risk factors and examined these associations across regions. Our study shows that there is considerable variation in the prevalence of small airways obstruction worldwide, with small airways obstruction generally more common than chronic airflow obstruction (forced expiratory volume in 1 s as a ratio of forced vital capacity less than the lower limit of normal). Additionally, we have shown that prevalence estimates vary depending on the choice of spirometry parameter and world region. We have also identified a strong association between $FEF_{25–75}$ and forced vital capacity, which could restrict its use in the assessment of small airways obstruction in comparison to FEV_3/FVC ratio. We found significant associations of small airways obstruction with both active and passive smoking, BMI, age, education level, working in a dusty job for longer than 10 years, a family history of chronic obstructive pulmonary disease, and a previous history of tuberculosis.

Implications of all the available evidence

Our study has shown that small airways obstruction is common in the general population. We have corroborated previous findings and identified additional risk factors for small airways obstruction. However, we have identified that prevalence estimates and associations can vary depending on which spirometry parameter is used. Although further research is needed, it is likely that $FEF_{25–75}$ is unsuitable as a binary measure to classify the presence of small airways obstruction, due to its association with the forced vital capacity. FEV_3/FVC ratio is an alternative, with fewer limitations. The identification of a significant burden of small airways obstruction in several world regions has important implications for global health, especially considering the potential for isolated small airways obstruction to be used as a predictive marker of future obstructive lung disease. Future research should investigate whether small airways obstruction is associated with accelerated decline in lung function and increased symptom burden, especially in individuals with otherwise normal lung function.

associated with acute-on-chronic inflammation, mucus hypersecretion, and remodelling of the small airways.[2] In people with asthma, such changes have been associated with poor disease control, increased exacerbations, and decreased quality of life.[3] In people with chronic obstructive pulmonary disease, these changes have been shown to be associated with perceived effect of the disease on health status and increased gas trapping.[4,5]

There is no gold-standard method to non-invasively assess the small airways. Functional tests include spirometry, impulse oscillometry, body plethysmography, and nitrogen washout, and imaging includes high-resolution CT and hyperpolarised MRI.[6] Several spirometry parameters have been used to assess small airways obstruction, including the mean forced expiratory flow rate between 25% and 75% of the forced vital capacity ($FEF_{25–75}$)[7] and the forced expiratory volume in 3 s as a ratio of the forced vital capacity (FEV_3/FVC ratio).[8] In a review published in 2022, we found little consensus on the best spirometry parameter to use when measuring small airways obstruction.[9] Although $FEF_{25–75}$ is the most popular parameter, it is limited by high between-person variability,[10] whereas the FEV_3/FVC ratio is a more suitable alternative, but it is scarcely used.[11]

The rationale behind identifying small airways obstruction is its potential to act as a modifiable precursor to future obstructive lung disease.[12] In the only comprehensive population-based study in adults, Xiao and colleagues[13] estimated an overall prevalence of 43·5%, decreasing to 25·5% in adults with otherwise normal lung function (ie, isolated small airways obstruction). This study

showed that risk factors for small airways obstruction are shared with chronic obstructive pulmonary disease, suggesting that small airways obstruction is an early marker of obstructive lung disease.

To our knowledge, no study has attempted to estimate the prevalence of small airways obstruction and its associated risk factors across several world regions. Due to little research on this topic, substantial knowledge gaps still exist. Replication of previous findings and evaluation of the performance of different spirometry parameters are needed before small airways obstruction as an early marker for obstructive lung disease can be used for clinical and policy decision making. We aimed to estimate the prevalence of small airways obstruction, examine the associations of risk factors, and compare the findings for two different spirometry parameters in several world regions.

Methods

Study design and participants

The Burden of Obstructive Lung Disease (BOLD) study is a multinational cross-sectional study, and the protocol has been published elsewhere.[14] Briefly, adults aged 40 years or older who were not living in an institution were identified and recruited from 41 municipalities (most of which were urban) with populations larger than 150 000 people, across 34 countries in all WHO world regions. Participants were recruited from areas with meaningful administrative boundaries, using site-specific sampling strategies to randomly obtain representative samples of the populations. Site-specific sampling strategies included cluster sampling, stratified cluster sampling, stratified random sampling, random digit dialling, and simple random sampling. A participant's data were included in this study if they had completed the core study questionnaire and had acceptable spirometry according to predefined quality criteria.[15] Participants were excluded if they had a contraindication for lung function testing.

Ethical approval was obtained by each site from the local ethics committee, and written informed consent was obtained from every participant. All sites followed good clinical practice and local ethics regulations.

Procedures

Information on respiratory symptoms, health status, and exposure to potential risk factors was collected by trained fieldworkers, who administered standardised questionnaires translated into the local language. Lung function, including the forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), forced expiratory volume in 3 s (FEV_3), and $FEF_{25–75}$, was measured using the EasyOne Spirometer (ndd Medizintechnik, Zurich, Switzerland) before and 15 min after inhaled salbutamol (200 µg). Spirograms were centrally reviewed and assigned a quality score on the basis of acceptability and reproducibility criteria.[15] Data for sex were self-reported by study participants in the core questionnaire, with the options of male or female.

We defined small airways obstruction—pre-bronchodilator (ie, before administration of 200 µg salbutamol) and post-bronchodilator (ie, after administration of 200 µg salbutamol)—in two ways: $FEF_{25–75}$ less than the lower limit of normal (LLN) or FEV_3/FVC ratio less than the LLN. Salbutamol is used as a bronchodilator to establish whether the obstruction is reversible. Pre-bronchodilator estimates include individuals with reversible airflow obstruction (who no longer have a detectable abnormality after administration) and those with chronic airflow obstruction. Post-bronchodilator estimates reflect only individuals with chronic small airways obstruction. Both types of obstruction are important to investigate, because risk factors might differ. To calculate the LLN, we used sex-specific coefficients for age and height from reference equations for European Americans in the third US National Health and Nutrition Examination Survey (NHANES).[11,16] Additionally, we defined isolated small airways obstruction, in which the $FEF_{25–75}$ or FEV_3/FVC ratio was less than the LLN, with an FEV_1/FVC ratio equal to or greater than the LLN. We also defined airflow obstruction as pre-bronchodilator FEV_1/FVC ratio less than the LLN, chronic airflow obstruction as post-bronchodilator FEV_1/FVC ratio less than the LLN, and spirometric restriction as post-bronchodilator FVC less than the LLN.

We investigated potential risk factors, including age, categorised as 40–49 years, 50–59 years, 60–69 years, and 70 years or older; BMI, categorised as underweight (<18·5 kg/m²), healthy (18·5–24·9 kg/m²), overweight (25·0–30·0 kg/m²), and obese (>30·0 kg/m²); education, categorised as none, primary (ie, classified as grades 1–8 or 1–9 depending on site), secondary school (ie, classified as grades 9–12 or 10–12 depending on site), and technical or vocational college or university; pack-years of smoking, categorised as 1–5 pack-years, 6–15 pack-years, 16–25 pack-years, and more than 25 pack-years; smoking status, categorised as never, former, and current; passive smoking (ie, whether somebody else smoked in the participant's home in the past 2 weeks); previous history of tuberculosis diagnosis by a doctor; family history of chronic obstructive pulmonary disease (ie, mother, father, sister, or brother ever diagnosed with emphysema, chronic bronchitis, or chronic obstructive pulmonary disease by a doctor); dusty job (left to participant interpretation) for more than 10 years; and solid fuels for cooking or heating for more than 6 months in a lifetime.

Outcomes

The primary outcomes were the prevalence of pre-bronchodilator and post-bronchodilator small airways obstruction, defined by $FEF_{25–75}$ less than the LLN or FEV_3/FVC ratio less than the LLN; the associations of risk factors with small airways obstruction; and the difference

University, Ife, Nigeria (D Obaseki MD); **Philippine College of Chest Physicians, Quezon City, Philippines** (S N M Paraguas MD); **Philippine Heart Centre, Quezon City, Philippines** (S N M Paraguas); **RCSI and UCD Malaysia Campus, Penang, Malaysia** (A Rashid PhD, L-C Loh MD); **Pulmocare Research and Education Foundation, Pune, India** (S Salvi MD); **Symbiosis International (Deemed University), Pune, India** (S Salvi); **Faculty of Medical Sciences, University of the West Indies, Trinidad and Tobago** (Prof T Seemungal PhD); **University Clinic for Pneumology, Paracelsus Medical University Salzburg, Salzburg, Austria** (Prof M Studnicka MD); **Centre for Heart Lung Innovation, University of British Columbia, Vancouver, BC, Canada** (W C Tan MD); **Ludwig Boltzmann Institute for Lung Health, Vienna, Austria** (Prof E E F M Wouters); **Instituto de Saúde Ambiental, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal** (C Barbara PhD); **Serviço de Pneumologia, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal** (C Barbara); **Department of Sleep, Landspitali University Hospital, Reykjavik, Iceland** (Prof T Gislason PhD); **Faculty of Medicine, University of Iceland, Reykjavik, Iceland** (T Gislason); **Medical Research Institute, Central Chest Clinic, Colombo, Sri Lanka** (K Gunasekera MD)

Correspondence to:
Mr Ben Knox-Brown, National Heart and Lung Institute, Imperial College London, London SW3 6LR, UK
b.knox-brown20@imperial.ac.uk

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	Total participants, n	Men, n (%)	Women, n (%)	Median age, years (IQR)	Median BMI (IQR)	Never smoked, n (%)	1–5 pack-years, n (%)	6–15 pack-years, n (%)	16–25 pack-years, n (%)	>25 pack-years, n (%)	Passive smoke exposure, n (%)	Post-primary education, n (%)	Dusty job for >10 years, n (%)	Use of solid fuels for cooking or heating, n (%)	Family history of chronic obstructive pulmonary disease, n (%)	Previous tuberculosis, n (%)
Tirana, Albania	939	467 (50%)	472 (50%)	53·0 (45·0–62·0)	27·6 (24·7–30·8)	595 (63%)	20 (2%)	58 (6%)	54 (6%)	212 (23%)	322 (34%)	562 (60%)	446 (47%)	937 (100%)	74 (8%)	8 (1%)
Annaba, Algeria	890	442 (50%)	448 (50%)	51·0 (44·0–59·0)	27·7 (24·4–32·0)	559 (63%)	34 (4%)	71 (8%)	73 (8%)	153 (17%)	103 (12%)	302 (34%)	198 (22%)	491 (55%)	52 (6%)	20 (2%)
Sydney, NSW, Australia	454	220 (48%)	234 (52%)	58·0 (48·5–68·0)	27·0 (24·2–30·8)	246 (54%)	40 (9%)	49 (11%)	40 (9%)	79 (17%)	48 (11%)	332 (73%)	75 (17%)	NR	86 (19%)	4 (1%)
Salzburg, Austria	1010	561 (56%)	449 (44%)	56·0 (48·0–65·0)	25·8 (23·7–28·5)	491 (49%)	71 (7%)	135 (13%)	111 (11%)	202 (20%)	213 (21%)	840 (83%)	160 (16%)	165 (16%)	63 (6%)	23 (2%)
Sémé-Kpodji, Benin	694	300 (43%)	394 (57%)	50·0 (44·0–57·0)	25·4 (22·3–29·9)	684 (99%)	2 (<1%)	6 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	67 (10%)	131 (19%)	668 (96%)	0	3 (<1%)
Limbe, Cameroon	284	170 (60%)	114 (40%)	50·0 (44·0–59·0)	25·5 (22·9–29·1)	228 (80%)	16 (6%)	22 (8%)	10 (4%)	8 (3%)	7 (2%)	70 (25%)	135 (48%)	239 (84%)	11 (4%)	3 (1%)
Vancouver, BC, Canada	655	258 (39%)	397 (61%)	54·0 (46·0–63·0)	25·7 (23·1–29·1)	346 (53%)	64 (10%)	80 (12%)	55 (8%)	110 (17%)	38 (6%)	608 (93%)	60 (9%)	110 (17%)	101 (15%)	22 (3%)
Guangzhou, China	382	191 (50%)	191 (50%)	53·0 (42·0–62·0)	23·4 (21·4–25·6)	213 (56%)	18 (5%)	35 (9%)	38 (10%)	78 (20%)	98 (26%)	167 (44%)	99 (26%)	378 (99%)	91 (24%)	15 (4%)
Tartu, Estonia	613	308 (50%)	305 (50%)	60·0 (50·0–70·0)	27·8 (24·8–31·3)	354 (58%)	50 (8%)	71 (12%)	57 (9%)	81 (13%)	88 (14%)	537 (88%)	103 (17%)	558 (91%)	51 (8%)	46 (8%)
Hannover, Germany	556	287 (52%)	269 (48%)	58·0 (49·0–66·0)	26·8 (24·1–29·8)	232 (42%)	53 (10%)	74 (13%)	62 (11%)	135 (24%)	105 (19%)	498 (90%)	65 (12%)	NR	69 (12%)	22 (4%)
Reykjavik, Iceland	598	318 (53%)	280 (47%)	54·0 (47·0–64·0)	27·2 (24·4–30·2)	265 (44%)	62 (10%)	78 (13%)	76 (13%)	117 (20%)	104 (17%)	454 (76%)	71 (12%)	112 (19%)	98 (16%)	31 (5%)
Mumbai, India	364	230 (63%)	134 (37%)	49·0 (43·0–57·5)	23·2 (21·1–26·4)	331 (91%)	5 (1%)	14 (4%)	8 (2%)	6 (2%)	4 (1%)	241 (66%)	15 (4%)	1 (<1%)	0	2 (1%)
Mysore, India	599	256 (43%)	343 (57%)	44·0 (42·0–48·0)	24·3 (22·5–26·5)	557 (93%)	8 (1%)	22 (4%)	9 (2%)	3 (1%)	0	388 (65%)	13 (2%)	509 (85%)	0	0
Pune, India	778	463 (60%)	315 (40%)	50·0 (45·0–59·0)	21·8 (19·1–24·3)	699 (90%)	52 (7%)	18 (2%)	5 (1%)	4 (1%)	85 (11%)	194 (25%)	45 (6%)	609 (78%)	36 (5%)	7 (1%)
Srinagar, India	755	412 (55%)	343 (45%)	47·5 (43·0–58·0)	21·8 (19·9–24·4)	668 (88%)	30 (4%)	41 (5%)	11 (1%)	5 (1%)	489 (65%)	97 (13%)	4 (1%)	755 (100%)	18 (2%)	3 (<1%)
Kingston, Jamaica	578	243 (42%)	335 (58%)	54·0 (47·0–64·0)	26·6 (22·6–32·0)	424 (73%)	44 (8%)	46 (8%)	33 (6%)	31 (5%)	91 (16%)	268 (46%)	169 (29%)	301 (52%)	9 (2%)	4 (1%)
Chui, Kyrgyzstan	858	270 (31%)	588 (69%)	52·0 (46·0–58·0)	28·1 (24·5–31·9)	632 (74%)	38 (4%)	44 (5%)	46 (5%)	98 (11%)	62 (7%)	689 (80%)	149 (17%)	765 (89%)	64 (7%)	11 (1%)
Naryn, Kyrgyzstan	820	315 (38%)	505 (62%)	52·0 (46·0–59·0)	26·6 (23·3–30·0)	647 (79%)	31 (4%)	50 (6%)	29 (4%)	63 (8%)	25 (3%)	552 (67%)	24 (3%)	816 (100%)	18 (2%)	6 (1%)

(Table 1 continues on next page)

	Total participants, n	Men, n (%)	Women, n (%)	Median age, years (IQR)	Median BMI (IQR)	Never smoked, n (%)	1–5 pack-years, n (%)	6–15 pack-years, n (%)	16–25 pack-years, n (%)	>25 pack-years, n (%)	Passive smoke exposure, n (%)	Post-primary education, n (%)	Dusty job for >10 years, n (%)	Use of solid fuels for cooking or heating, n (%)	Family history of chronic obstructive pulmonary disease, n (%)	Previous tuberculosis, n (%)
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Blantyre, Malawi	401	160 (40%)	241 (60%)	50·0 (44·0–58·0)	24·2 (20·1–28·4)	357 (89%)	20 (5%)	19 (5%)	2 (<1%)	3 (1%)	12 (3%)	51 (13%)	46 (11%)	347 (87%)	87 (22%)	22 (5%)
Chikwawa, Malawi	432	221 (51%)	211 (49%)	52·0 (45·0–62·0)	21·0 (19·2–23·5)	342 (79%)	40 (9%)	41 (9%)	2 (<1%)	7 (2%)	14 (3%)	5 (1%)	41 (9%)	432 (100%)	21 (5%)	17 (4%)
Penang, Malaysia	663	340 (51%)	323 (49%)	54·0 (46·0–63·0)	25·7 (23·1–28·6)	501 (76%)	20 (3%)	46 (7%)	26 (4%)	70 (11%)	170 (26%)	77 (12%)	145 (22%)	486 (73%)	34 (5%)	0
Fes, Morocco	767	354 (46%)	413 (54%)	54·0 (48·0–60·0)	27·5 (24·1–31·1)	574 (75%)	25 (3%)	50 (7%)	35 (5%)	83 (11%)	106 (14%)	117 (15%)	213 (28%)	385 (50%)	77 (10%)	13 (2%)
Maastricht, Netherlands	589	300 (51%)	289 (49%)	57·0 (49·0–55·0)	27·0 (24·7–29·7)	231 (39%)	50 (8%)	88 (15%)	72 (12%)	148 (25%)	116 (20%)	359 (61%)	64 (11%)	157 (27%)	122 (21%)	8 (1%)
Ife, Nigeria	882	345 (39%)	537 (61%)	53·5 (45·0–64·0)	24·5 (21·4–28·3)	817 (93%)	39 (4%)	16 (2%)	6 (1%)	4 (<1%)	15 (2%)	356 (40%)	127 (14%)	603 (68%)	4 (<1%)	4 (<1%)
Bergen, Norway	541	261 (48%)	280 (52%)	58·0 (49·0–70·0)	26·2 (23·5–28·7)	210 (39%)	41 (8%)	114 (21%)	90 (17%)	86 (16%)	122 (23%)	435 (80%)	129 (24%)	NR	101 (19%)	1 (<1%)
Karachi, Pakistan	574	259 (45%)	315 (55%)	50·0 (45·0–57·0)	26·3 (22·7–29·7)	465 (81%)	18 (3%)	29 (5%)	20 (3%)	42 (7%)	75 (13%)	178 (31%)	109 (19%)	402 (70%)	82 (14%)	3 (1%)
Manila, Philippines	729	302 (41%)	427 (59%)	50·0 (44·0–58·0)	24·5 (21·7–27·5)	394 (54%)	76 (10%)	105 (14%)	55 (8%)	99 (14%)	358 (49%)	428 (59%)	170 (23%)	305 (42%)	44 (6%)	59 (8%)
Nampicuan and Talugtug, Philippines	722	356 (49%)	366 (51%)	52·0 (46·0–61·0)	21·1 (19·0–23·6)	365 (51%)	41 (6%)	90 (12%)	88 (12%)	138 (19%)	334 (46%)	324 (45%)	110 (15%)	713 (99%)	22 (3%)	26 (4%)
Krakow, Poland	423	212 (50%)	211 (50%)	53·0 (46·0–53·0)	27·2 (24·6–30·5)	177 (42%)	22 (5%)	63 (15%)	55 (13%)	106 (25%)	177 (42%)	254 (60%)	#VALUE!	402 (95%)	77 (18%)	13 (3%)
Lisbon, Portugal	683	317 (46%)	366 (54%)	64·0 (55·0–72·0)	27·6 (25·0–31·1)	429 (63%)	37 (5%)	41 (6%)	34 (5%)	142 (21%)	107 (16%)	212 (31%)	268 (39%)	359 (53%)	170 (25%)	32 (5%)
Riyadh, Saudi Arabia	700	375 (54%)	325 (46%)	49·0 (44·0–55·0)	30·7 (27·2–34·3)	533 (76%)	23 (3%)	45 (6%)	40 (6%)	59 (8%)	37 (5%)	345 (49%)	71 (10%)	270 (39%)	24 (3%)	14 (2%)
Uitsig and Ravensmead, South Africa	647	242 (37%)	405 (63%)	52·0 (45·0–61·0)	27·2 (22·0–32·1)	252 (39%)	63 (10%)	173 (27%)	70 (11%)	89 (14%)	325 (50%)	161 (25%)	160 (25%)	302 (47%)	95 (15%)	95 (15%)
Colombo, Sri Lanka	1020	457 (45%)	563 (55%)	53·0 (46·0–60·0)	24·2 (20·9–27·1)	852 (84%)	64 (6%)	74 (7%)	20 (2%)	10 (1%)	86 (8%)	213 (21%)	234 (23%)	704 (69%)	29 (3%)	8 (1%)
Gezeira, Sudan	578	299 (52%)	279 (48%)	51·0 (45·0–60·0)	25·7 (21·6–29·5)	462 (80%)	36 (6%)	46 (8%)	20 (3%)	14 (2%)	70 (12%)	142 (25%)	88 (15%)	350 (61%)	56 (10%)	3 (1%)

(Table 1 continues on next page)

	Total participants, n	Men, n (%)	Women, n (%)	Median age, years (IQR)	Median BMI (IQR)	Never smoked, n (%)	1–5 pack-years, n (%)	6–15 pack-years, n (%)	16–25 pack-years, n (%)	>25 pack-years, n (%)	Passive smoke exposure, n (%)	Post-primary education, n (%)	Dusty job for >10 years, n (%)	Use of solid fuels for cooking or heating, n (%)	Family history of chronic obstructive pulmonary disease, n (%)	Previous tuberculosis, n (%)
(Continued from previous page)																
Khartoum, Sudan	446	265 (59%)	181 (41%)	52·5 (45·0–60·0)	25·5 (22·1–29·4)	354 (79%)	22 (5%)	31 (7%)	20 (4%)	19 (4%)	35 (8%)	144 (32%)	52 (12%)	367 (82%)	8 (2%)	5 (1%)
Uppsala, Sweden	459	237 (52%)	222 (48%)	58·0 (50·0–65·0)	26·2 (23·7–29·0)	224 (49%)	47 (10%)	74 (16%)	45 (10%)	69 (15%)	25 (5%)	349 (76%)	80 (17%)	NR	58 (13%)	5 (1%)
Port of Spain, Trinidad and Tobago	1085	434 (40%)	651 (60%)	52·5 (45·0–61·0)	27·7 (24·2–31·9)	806 (74%)	48 (4%)	80 (7%)	66 (6%)	85 (8%)	248 (23%)	575 (53%)	214 (20%)	508 (47%)	42 (4%)	0
Sousse, Tunisia	661	309 (47%)	352 (53%)	52·0 (46·0–58·0)	28·6 (25·2–32·9)	409 (62%)	14 (2%)	35 (5%)	65 (10%)	138 (21%)	243 (37%)	264 (40%)	234 (35%)	308 (47%)	42 (6%)	0
Adana, Türkiye	610	290 (48%)	320 (52%)	51·0 (44·0–60·0)	29·3 (25·8–32·5)	282 (46%)	55 (9%)	58 (10%)	60 (10%)	155 (25%)	335 (55%)	89 (15%)	205 (34%)	590 (97%)	66 (11%)	17 (3%)
London, UK	575	271 (47%)	304 (53%)	58·0 (49·0–57·0)	26·4 (23·6–29·7)	233 (41%)	54 (9%)	90 (16%)	54 (9%)	144 (25%)	95 (17%)	528 (92%)	80 (14%)	354 (62%)	94 (16%)	11 (2%)
Lexington, KY, USA	429	173 (40%)	256 (60%)	55·0 (49·0–63·0)	29·3 (25·9–34·2)	180 (42%)	20 (5%)	24 (6%)	34 (8%)	171 (40%)	129 (30%)	349 (81%)	125 (29%)	300 (70%)	179 (42%)	6 (1%)

Total participants is the number of participants included in at least one prevalence estimate. Pack-years were calculated by number of cigarettes smoked per day divided by 20 and multiplied by years of smoking. Passive smoking was defined as somebody else smoking in the participant's home in the past 2 weeks. Use of solid fuels for cooking or heating was defined as more than 6 months of use in a lifetime. Family history of chronic obstructive pulmonary disorder was defined as mother, father, sister, or brother ever diagnosed with emphysema, chronic bronchitis, or chronic obstructive pulmonary disorder by a doctor. Previous tuberculosis was defined as tuberculosis ever diagnosed by a doctor. Centres are listed alphabetically by country.

Table 1: **Participant characteristics from the 41 sites of the BOLD study with good quality spirometry measuring small airway obstruction**

between the two small airways obstruction parameters. These outcomes were assessed in participants with acceptable spirometry according to predefined criteria, excluding participants for whom data were missing for FEV_3/FVC ratio or $FEF_{25–75}$. Secondary outcomes included prevalence of isolated small airways obstruction and risk factors for isolated small airways obstruction, which were assessed by exclusion of participants with established airflow obstruction (FEV_1/FVC ratio <LLN). We also examined agreement between parameters.

Statistical analysis

We estimated the prevalence of pre-bronchodilator and post-bronchodilator small airways obstruction for each study site, allowing for sampling weights and stratification or clustering at each site. We evaluated the concordance of the two parameters to define small airways obstruction using the Cohen's κ coefficient. We used multivariable logistic regression to assess the association of small airways obstruction with risk factors in each site and then pooled estimates using random-effects meta-analysis.[17] I^2 was used to summarise heterogeneity. Heterogeneity was considered significant if the p values from the χ^2 test were less than 0·05. We also regressed $FEF_{25–75}$ (L/s) and FEV_3/FVC ratio (%), as continuous proxies for small airways obstruction, against the same potential risk factors. We included and mutually adjusted for all risk factors in the regression models for each site. The model for $FEF_{25–75}$ was additionally adjusted for FVC (L), because they are correlated.[10] In secondary analyses, we re-ran the models, excluding participants with established airflow obstruction (FEV_1/FVC ratio <LLN). All analyses were performed using Stata version 17 and corrected for sampling weights.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

36 618 participants were recruited between Jan 2, 2003, and Dec 26, 2016. We collected data for participants at recruitment. A total of 28 604 participants had acceptable spirometry and completed the core study questionnaire. Due to missing or unreliable data, 2161 participants were excluded for FEV_3/FVC ratio and 2643 participants were excluded for $FEF_{25–75}$. Data were available for 26 443 participants for FEV_3/FVC ratio and 25 961 participants for $FEF_{25–75}$.

The baseline characteristics of the participants included in the study are shown in table 1. There were slightly more women than men (12 490 men and 13 953 women), and overall mean age ranged from 46·8 years to 63·4 years across sites. The proportion of people who had ever smoked varied considerably from 1% (ten of 694 participants) in Sémé-Kpodji, Benin, to 61% (394 of 647 participants) in Uitsig and Ravensmead,

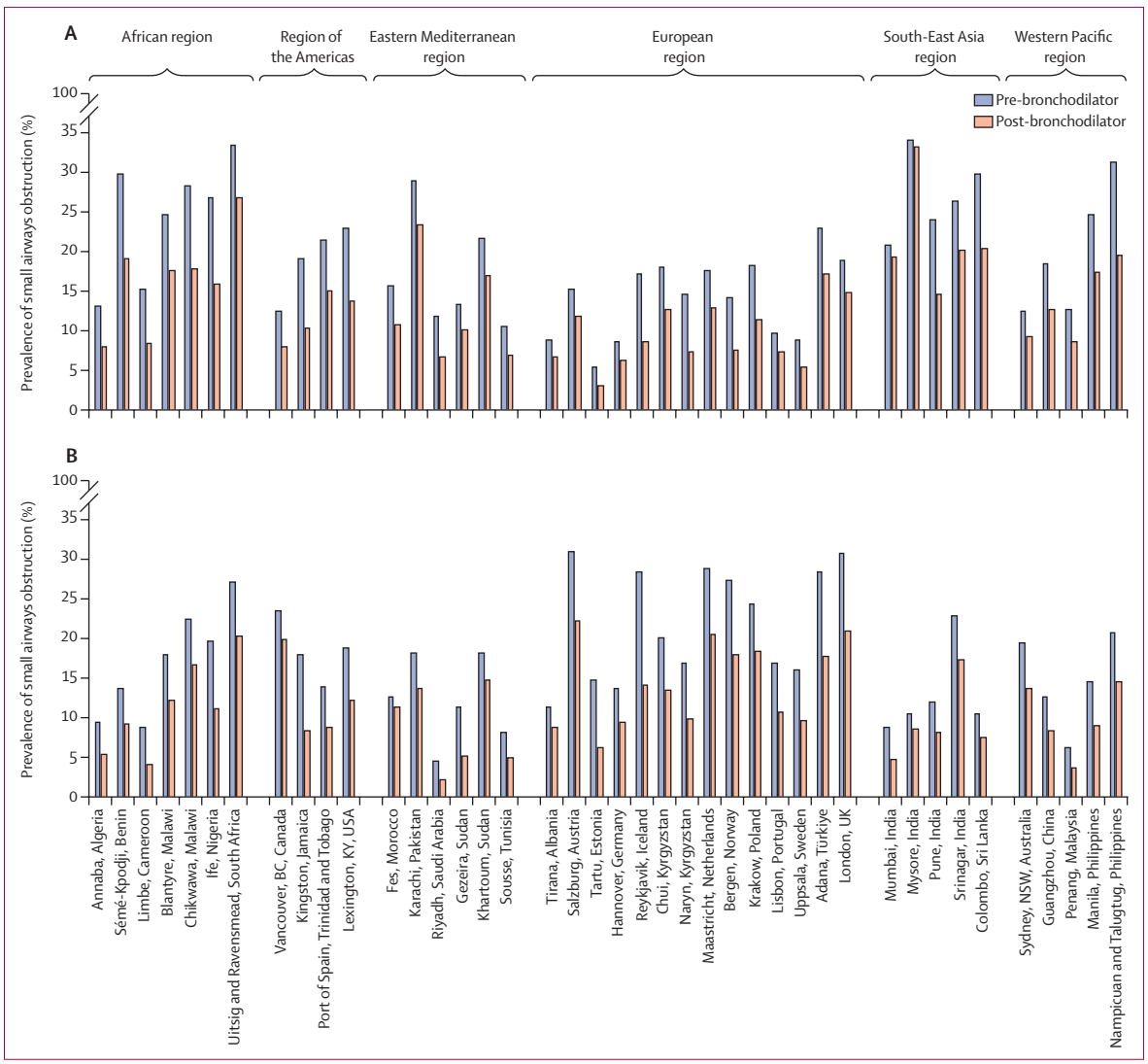

Figure: **Prevalence estimates of small airways obstruction for each study site, stratified by WHO region**
(A) Prevalence as estimated by mean forced expiratory flow rate between 25% and 75% of the forced vital capacity less than the lower limit of normal. (B) Prevalence as estimated by ratio of forced expiratory volume in 3 s to forced vital capacity less than the lower limit of normal.

South Africa, as did cumulative smoking (ie, pack-years) and passive smoking exposure. The proportion of participants educated above primary level also varied drastically. Having a family history of chronic obstructive pulmonary disease was most common in Lexington, KY, USA, and a previous history of tuberculosis was most prevalent in Uitsig and Ravensmead, South Africa. The proportion of participants working in a dusty job for more than 10 years was lowest in Srinagar, India, and highest in Tirana, Albania. Spirometry results for each study site are summarised in appendix 11 (pp 1–2).

Prevalence estimates for small airways obstruction are shown in appendix 11 (p 6). The prevalence of pre-bronchodilator small airways obstruction ranged from 5% (34 of 624 participants) in Tartu, Estonia, to 34% (189 of 555 participants) in Mysore, India, for $FEF_{25–75}$ less than the LLN (figure A). For FEV_1/FVC ratio less than the LLN, prevalence estimates ranged from 5% (31 of 684 participants) in Riyadh, Saudi Arabia, to 31% (287 of 924 participants) in Salzburg, Austria (figure B). Post-bronchodilator estimates were universally lower than pre-bronchodilator estimates. Compared with other regions, prevalence estimates were generally higher for European sites for FEV_1/FVC ratio less than the LLN but lower for European sites for $FEF_{25–75}$ less than the LLN. The κ coefficient ranged from 0·41 to 0·54 across regions (appendix 11 pp 3–5). When stratifying by sex, prevalence estimates appeared similar for $FEF_{25–75}$ less than the LLN but higher in men for the FEV_1/FVC ratio less than the LLN (appendix 11 pp 7–8).

In people with pre-bronchodilator small airways obstruction, 66% (2821 of 4294) of participants for

FEV_3/FVC ratio less than the LLN and 53% (2657 of 4967) of participants for $FEF_{25–75}$ less than the LLN also had airflow obstruction. For FEV_3/FVC ratio less than the LLN, 15% (641 of 4177) of participants with small airways obstruction and both pre-bronchodilator and post-bronchodilator measurements had reversible airflow obstruction, and for $FEF_{25–75}$ less than the LLN, 18% (787 of 4469) of participants with both pre-bronchodilator and post-bronchodilator measurements had reversibility according to the American Thoracic Society and European Respiratory Society definition.[18] Additionally, 18% (736 of 4205) of participants with small airways obstruction for FEV_3/FVC ratio less than the LLN, in whom FVC was measured post-bronchodilator, and 41% (1861 of 4514) of participants with small airways obstruction for $FEF_{25–75}$ less than the LLN, in whom FVC was measured post-bronchodilator, also had spirometric restriction. Participants with small airways obstruction with $FEF_{25–75}$ less than the LLN had a lower FVC and higher FEV_1/FVC ratio than participants with small airways obstruction using FEV_3/FVC ratio less than the LLN (table 2).

Pre-bronchodilator small airways obstruction was significantly associated with sex, age, BMI, current and former smoking, pack-years of smoking, working in a dusty job for more than 10 years, family history of chronic obstructive pulmonary disease, and previous tuberculosis. Notably, previous tuberculosis was associated with small airways obstruction mostly in Uitsig and Ravensmead, South Africa, Tartu, Estonia, and Manila, Phillipines, where tuberculosis was most prevalent, and working in a dusty job for more than 10 years was associated with small airways obstruction mostly in the Western Pacific region, especially in Manila, Philippines, and Penang, Malaysia (data not shown). For both $FEF_{25–75}$ less than the LLN (table 3) and FEV_3/FVC ratio less than the LLN (table 4) the magnitude of these associations was similar, except for increasing age, which was associated with increased odds of small airways obstruction for FEV_3/FVC ratio less than the LLN and decreased odds of small airways obstruction for $FEF_{25–75}$ less than the LLN. A 1 L increase in FVC was significantly associated with reduced odds of small airways obstruction for $FEF_{25–75}$ less than the LLN (odds ratio [OR] 0·28, 95% CI 0·24–0·33). Post-bronchodilator small airways obstruction was also associated with passive smoking (FEV_3/FVC ratio less than the LLN only) and low level of education (ie, none to primary education). Female sex was associated with reduced odds of small airways obstruction in the logistic regression but was not significantly associated with the continuous measure $FEF_{25–75}$. Additionally, low BMI was associated with increased odds of post-bronchodilator small airways obstruction for FEV_3/FVC ratio less than the LLN but not significantly associated with the FEV_3/FVC ratio as a continuous measure. The association between increasing age and reduced odds of small airways obstruction for $FEF_{25–75}$ less than the LLN was not supported by the results of the linear regression. Otherwise, results of the linear and logistic regression analyses showed a similar pattern (table 3, 4; appendix 11 pp 9–12).

There was moderate heterogeneity across sites for the association of small airways obstruction (defined as $FEF_{25–75}$<LLN) with sex, age, current and former smoking, pack-years of smoking, and low level of education (ie, none to primary education). Heterogeneity was generally lower for associations with small airways obstruction defined as FEV_3/FVC ratio less than the LLN. Post-bronchodilator associations showed lower heterogeneity across sites than pre-bronchodilator associations (table 3 and 4).

Secondary analyses excluding participants with established airflow obstruction (FEV_1/FVC ratio <LLN) showed universally lower prevalence estimates than the main analyses, which included these participants (appendix 11 pp 6, 13). Pre-bronchodilator, prevalence of an isolated small airways obstruction for $FEF_{25–75}$ less than the LLN ranged from 1% (seven of 507) of participants in Tartu, Estonia, to 27% (132 of 491) of participants in Mysore, India, and for FEV_3/FVC ratio less than the LLN from 1% (eight of 646) of participants in Riyadh, Saudi Arabia, to 14% (95 of 697) of participants in Salzburg, Austria. Post-bronchodilator estimates were lower. The κ coefficient ranged from 0·13 to 0·25, indicating fair agreement between parameters (appendix 11 p 5). Risk factors associated with isolated

	Small airways obstruction		Isolated small airways obstruction	
	$FEF_{25–75}$ (<LLN)	FEV_3/FVC (<LLN)	$FEF_{25–75}$ (<LLN and FEV_1/FVC ≥LLN)	FEV_3/FVC (<LLN and FEV_1/FVC ≥LLN)
Pre-bronchodilator				
Total participants with small airways obstruction, n	4967	4294	2120	1459
FEV_1, L	1·9 (0·6)	2·01 (0·8)	1·9 (0·5)	2·5 (0·8)
FEV_3, L	2·4 (0·8)	2·6 (1·0)	2·3 (0·7)	2·8 (1·0)
FVC, L	2·8 (1·0)	3·2 (1·1)	2·6 (0·8)	3·5 (1·1)
FEV_1/FVC	66·5 (10·0)	63·3 (10·1)	74·0 (3·8)	71·9 (5·7)
$FEF_{25–75}$, L/s	1·1 (0·6)	1·1 (0·7)	1·3 (0·4)	1·6 (0·7)
FEV_3/FVC	84·0 (8·0)	78·9 (11·0)	88·8 (4·3)	80·6 (14·9)
Post-bronchodilator				
Total participants with small airways obstruction, n	3529	3044	1624	949
FEV_1, L	1·8 (0·6)	2·0 (0·8)	1·9 (0·5)	2·5 (0·8)
FEV_3, L	2·3 (0·8)	2·6 (1·0)	2·2 (0·7)	2·9 (1·1)
FVC, L	2·7 (0·9)	3·3 (1·1)	2·5 (0·8)	3·6 (1·1)
FEV_1/FVC	66·1 (10·8)	62·0 (10·8)	74·4 (4·1)	71·7 (6·5)
$FEF_{25–75}$, L/s	1·1 (0·5)	1·1 (0·7)	1·3 (0·4)	1·6 (0·7)
FEV_3/FVC	83·9 (8·5)	78·1 (11·7)	89·5 (3·9)	79·7 (17·2)

Data are mean (SD) unless otherwise stated. FEV_1=forced expiratory volume in 1 s. FEV_3=forced expiratory volume in 3 s. FVC=forced vital capacity. $FEF_{25–75}$=mean forced expiratory flow rate between 25% and 75% of the FVC. FEV_3/FVC=FEV_3 as a ratio of the FVC. FEV_1/FVC=FEV_1 as a ratio of the FVC. LLN=lower limit of normal given age and sex using reference equations from the National Health and Nutrition Examination Survey.[11,16]

Table 2: **Summary spirometry results for BOLD participants with small airways obstruction**

small airways obstruction for both $FEF_{25–75}$ less than the LLN and FEV_3/FVC ratio less than the LLN were similar to those of small airways obstruction (appendix 11 pp 14–17).

Discussion

To the best of our knowledge, this is the first large population-based study to investigate the prevalence of small airways obstruction and its risk factors across several world regions. Our study shows that there is considerable variation in the prevalence of small airways obstruction worldwide, and that small airways obstruction is generally more common than airflow obstruction and chronic airflow obstruction. Additionally, we have shown that prevalence estimates vary depending on the choice of spirometry parameter. Overall, we found significant associations between small airways obstruction and both active and passive tobacco smoking, BMI, age, education level, working in a dusty job for longer than 10 years, family history of chronic obstructive pulmonary disease,

	Pre-bronchodilator small airways obstruction (FEF_{25-75} <LLN)			Pre-bronchodilator FEF_{25-75} (L/s)			Post-bronchodilator small airways obstruction (FEF_{25-75} <LLN)			Post-bronchodilator FEF_{25-75} (L/s)		
	OR (95% CI)	I^2, %	χ^2 heterogeneity p value	Regression coefficient (95% CI)*	I^2, %	χ^2 heterogeneity p value	OR (95% CI)	I^2, %	χ^2 heterogeneity p value	Regression coefficient (95% CI)*	I^2, %	χ^2 heterogeneity p value
Female	0·51 (0·43 to 0·59)	50·0%	<0·0001	–0·03 (–0·09 to 0·02)	72·2%	<0·0001	0·49 (0·41 to 0·59)	42·8%	0·0020	–0·07 (–0·13 to –0·02)	74·0%	<0·0001
Age												
40–49 years	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
50–59 years	0·69 (0·61 to 0·79)	47·0%	0·0010	–0·30 (–0·34 to –0·25)	53·8%	<0·0001	0·84 (0·73 to 0·97)	48·8%	<0·0001	–0·37 (–0·40 to –0·33)	47·1%	<0·0001
60–69 years	0·39 (0·32 to 0·46)	50·1%	<0·0001	–0·59 (–0·63 to –0·54)	50·3%	<0·0001	0·59 (0·48 to 0·70)	51·5%	<0·0001	–0·71 (–0·76 to –0·66)	63·6%	<0·0001
≥70 years	0·08 (0·05 to 0·11)	52·1%	<0·0001	–0·80 (–0·88 to –0·73)	71·3%	<0·0001	0·15 (0·11 to 0·21)	45·0%	0·0030	–0·95 (–1·04 to –0·85)	78·8%	<0·0001
BMI, kg/m²												
<18·5	1·57 (1·28 to 1·91)	12·7%	0·16	–0·03 (–0·11 to 0·05)	49·3%	0·0010	1·83 (1·46 to 2·30)	20·0%	0·31	–0·10 (–0·18 to –0·01)	64·2%	<0·0001
18·5–24·9	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
25·0–30·0	0·78 (0·70 to 0·91)	40·0%	0·0050	0·13 (0·10 to 0·15)	31·6%	0·042	0·83 (0·73 to 0·93)	14·7%	0·37	0·13 (0·09 to 0·16)	41·3%	0·0030
>30·0	0·71 (0·61 to 0·82)	34·0%	0·037	0·19 (0·15 to 0·23)	55·4%	<0·0001	0·78 (0·66 to 0·90)	27·7%	0·092	0·19 (0·15 to 0·24)	43·7%	0·0020
Smoking status												
Never	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
Current	2·80 (2·30 to 3·41)	62·0%	<0·0001	–0·27 (–0·33 to –0·21)	65·8%	<0·0001	2·48 (2·02 to 3·07)	44·0%	0·0030	–0·31 (–0·38 to –0·24)	73·7%	<0·0001
Former	2·03 (1·79 to 2·30)	3·2%	0·39	–0·15 (–0·21 to –0·08)	72·1%	<0·0001	1·70 (1·37 to 2·14)	60·4%	<0·0001	–0·18 (–0·27 to –0·09)	86·4%	<0·0001
Smoking history												
Never	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
1–5 pack-years	1·40 (1·14 to 1·70)	0·0%	0·61	–0·05 (–0·12 to 0·01)	57·8%	<0·0001	1·36 (1·02 to 1·81)	40·6%	0·018	–0·06 (–0·14 to 0·03)	81·4%	<0·0001
6–15 pack-years	1·62 (1·35 to 1·94)	14·7%	0·23	–0·15 (–0·20 to –0·10)	33·6%	0·028	1·71 (1·40 to 2·08)	11·0%	0·46	–0·15 (–0·21 to –0·10)	39·0%	<0·0001
16–25 pack-years	2·41 (1·93 to 3·00)	31·5%	0·018	–0·29 (–0·37 to –0·21)	65·7%	<0·0001	2·59 (2·07 to 3·25)	28·3%	0·11	–0·28 (–0·38 to –0·18)	78·0%	<0·0001
>25 pack-years	2·80 (2·26 to 3·46)	46·5%	0·0010	–0·40 (–0·46 to –0·34)	53·3%	<0·0001	3·63 (2·89 to 4·55)	36·6%	0·036	–0·48 (–0·55 to –0·42)	50·5%	<0·0001
Passive smoking†	1·02 (0·92 to 1·13)	0·0%	0·60	–0·07 (–0·12 to –0·01)	73·3%	<0·0001	1·09 (0·98 to 1·22)	0·0%	0·62	–0·08 (–0·12 to –0·03)	56·4%	<0·0001
Education level												
None to primary	1·06 (0·92 to 1·21)	7·0%	0·33	–0·05 (–0·09 to –0·00)	52·7%	<0·0001	1·25 (1·03 to 1·52)	40·9%	0·0050	–0·07 (–0·11 to –0·02)	52·4%	<0·0001
Secondary	0·96 (0·84 to 1·10)	0·0%	0·25	0·00 (–0·04 to 0·04)	47·5%	<0·0001	1·04 (0·87 to 1·25)	25·8%	0·099	–0·01 (–0·06 to 0·04)	51·0%	0·0010
Tertiary†	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..

(Table 3 continues on next page)

	Pre-bronchodilator small airways obstruction (FEF_{25-75} <LLN)			Pre-bronchodilator FEF_{25-75} (L/s)			Post-bronchodilator small airways obstruction (FEF_{25-75} <LLN)			Post-bronchodilator FEF_{25-75} (L/s)		
	OR (95% CI)	I^2, %	χ^2 heterogeneity p value	Regression coefficient (95% CI)*	I^2, %	χ^2 heterogeneity p value	OR (95% CI)	I^2, %	χ^2 heterogeneity p value	Regression coefficient (95% CI)*	I^2, %	χ^2 heterogeneity p value
(Continued from previous page)												
Dusty job for >10 years	1·23 (1·08 to 1·39)	19·7%	0·20	−0·07 (−0·10 to −0·05)	2·0%	0·56	1·23 (1·09 to 1·39)	0·0%	0·56	−0·07 (−0·10 to −0·03)	13·9%	0·20
Solid fuels for cooking or heating for >6 months in a lifetime	1·00 (0·88 to 1·13)	16·8%	0·12	0·02 (−0·09 to 0·12)	93·0%	<0·0001	1·07 (0·92 to 1·24)	27·7%	0·028	0·01 (−0·12 to 0·14)	94·4%	<0·0001
Family history of chronic obstructive pulmonary disease§	1·27 (1·08 to 1·50)	21·5%	0·21	−0·08 (−0·12 to −0·05)	4·6%	0·19	1·41 (1·20 to 1·65)	2·2%	0·65	−0·09 (−0·13 to −0·05)	2·3%	0·054
Ever diagnosed with tuberculosis by a doctor	2·05 (1·42 to 2·95)	48·0%	<0·0001	−0·28 (−0·34 to −0·10)	78·7%	<0·0001	2·73 (2·08 to 3·59)	11·6%	0·32	−0·27 (−0·39 to −0·14)	72·5%	<0·0001

Presence of small airways obstruction was defined as FEF_{25-75} <LLN, given age, sex, and height using European American reference equations from the National Health and Nutrition Examination Survey.[11,16] Pack-years were calculated by number of cigarettes smoked per day divided by 20 and multiplied by years of smoking. Risk factors were identified a priori. We attempted to include all risk factors in the regression models for each centre for small airways obstruction. However, on occasion the exposed group for solid fuel use, family history of chronic obstructive pulmonary disease, and previous history of tuberculosis were small and did not include any participants with small airways obstruction. In these instances, the effect of the risk factor was not estimated for that site. Likewise, for solid fuel use, some sites reported usage close to or at 100%. In these instances, sites were excluded due to perfect prediction of success. Information on solid fuel use was not collected for Australia, Germany, Norway, and Sweden. No participants with previous history of tuberculosis were identified for Tunisia, Trinidad and Tobago, Malaysia, and Mysore, India. No instances of family history of chronic obstructive pulmonary disease were identified for Mumbai, India, and Benin. OR=odds ratio. FEF_{25-75}=mean forced expiratory flow between 25% and 75% of the forced vital capacity. FEV_1/FVC=forced expiratory volume in 1 s as a ratio of the forced vital capacity. LLN=lower limit of normal. *Negative regression coefficient indicates a reduction in FEF_{25-75} (ie, worsened lung function). †Defined as somebody else smoking in the participant's home in the past 2 weeks. ‡Classified as technical or vocational college or university. §Mother, father, sister, or brother ever diagnosed with emphysema, chronic bronchitis, or chronic obstructive pulmonary disease by a doctor.

Table 3: **Adjusted pooled estimates of effects of risk factors on small airways obstruction, using FEF_{25-75} <LLN, and on FEF_{25-75}**

	Pre-bronchodilator small airways obstruction (FEV_1/FVC <LLN)			Pre-bronchodilator % FEV_1/FVC			Post-bronchodilator small airways obstruction (FEV_1/FVC <LLN)			Post-bronchodilator % FEV_1/FVC		
	OR (95% CI)	I^2, %	χ^2 heterogeneity p value	Regression coefficient (95% CI)*	I^2, %	χ^2 heterogeneity p value	OR (95% CI)	I^2, %	χ^2 heterogeneity p value	Regression coefficient (95% CI)*	I^2, %	χ^2 heterogeneity p value
Female	0·85 (0·74 to 0·98)	48·0	<0·0001	0·32 (0·06 to 0·58)	59·3	<0·0001	0·83 (0·72 to 0·95)	29·8	0·030	0·56 (0·35 to 0·78)	51·9	<0·0001
Age												
40–49 years	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
50–59 years	1·37 (1·20 to 1·56)	36·3	0·026	−1·83 (−2·10 to −1·56)	73·2	<0·0001	1·68 (1·44 to 1·96)	34·3	0·022	−1·80 (−2·03 to −1·57)	70·1	<0·0001
60–69 years	2·00 (1·74 to 2·29)	30·1	0·052	−3·75 (−4·02 to −3·48)	45·4	0·0010	2·49 (2·01 to 2·98)	48·3	<0·0001	−3·75 (−4·03 to −3·47)	57·7	<0·0001
≥70 years	2·47 (2·12 to 2·88)	14·4	0·17	−5·65 (−6·24 to −5·01)	74·6	<0·0001	3·29 (2·74 to 3·94)	22·8	0·049	−5·58 (−6·16 to −5·01)	75·6	<0·0001
BMI, kg/m²												
<18·5	1·55 (1·25 to 1·92)	16·9	0·34	−0·87 (−2·51 to 0·77)	93·7	<0·0001	1·79 (1·43 to 2·25)	18·2	0·50	−0·82 (−2·55 to 0·84)	93·7	<0·0001
18·5–24·9	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
25·0–30·0	0·85 (0·78 to 0·94)	0·0	0·54	0·33 (0·15 to 0·52)	22·8	0·10	0·82 (0·73 to 0·92)	9·2	0·56	0·41 (0·21 to 0·60)	38·2	0·0090
>30·0	0·70 (0·62 to 0·79)	2·7	0·72	0·72 (0·43 to 1·00)	57·9	<0·0001	0·64 (0·54 to 0·75)	17·2	0·37	0·81 (0·56 to 1·06)	49·3	0·0010
Smoking status												
Never	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
Current	2·17 (1·82 to 2·61)	51·0	<0·0001	−1·59 (−1·97 to −1·20)	69·3	<0·0001	2·87 (2·32 to 3·57)	56·9	<0·0001	−1·74 (−2·10 to 1·38)	66·3	<0·0001
Former	1·80 (1·56 to 2·08)	27·9	0·028	−1·60 (−2·29 to −0·92)	89·7	<0·0001	1·95 (1·66 to 2·30)	32·4	0·0090	−1·62 (−2·31 to −0·93)	91·4	<0·0001

(Table 4 continues on next page)

	Pre-bronchodilator small airways obstruction (FEV_3/FVC <LLN)			Pre-bronchodilator % FEV_3/FVC			Post-bronchodilator small airways obstruction (FEV_3/FVC <LLN)			Post-bronchodilator % FEV_3/FVC		
	OR (95% CI)	I^2, %	χ^2 heterogeneity p value	Regression coefficient (95% CI)*	I^2, %	χ^2 heterogeneity p value	OR (95% CI)	I^2, %	χ^2 heterogeneity p value	Regression coefficient (95% CI)*	I^2, %	χ^2 heterogeneity p value
(Continued from previous page)												
Smoking history												
Never	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
1–5 pack-years	1·26 (1·03 to 1·52)	15·6	0·20	–0·37 (–0·72 to –0·03)	36·7	0·012	1·53 (1·26 to 1·87)	2·4	0·30	–0·43 (–0·70 to –0·15)	32·9	0·012
6–15 pack-years	1·76 (1·52 to 2·03)	0·0	0·66	–0·91 (–1·23 to –0·60)	36·3	0·021	1·84 (1·55 to 2·19)	8·1	0·12	–1·02 (–1·33 to –0·71)	42·9	0·0070
16–25 pack-years	2·13 (1·79 to 2·54)	16·7	0·29	–1·34 (–1·86 to –0·82)	70·7	<0·0001	2·36 (1·93 to 2·89)	20·8	0·13	–1·25 (–1·68 to –0·82)	65·7	<0·0001
>25 pack-years	2·96 (2·57 to 3·40)	8·2	0·45	–2·69 (–3·22 to –2·16)	68·5	<0·0001	3·74 (3·09 to 4·50)	35·9	0·016	–2·74 (–3·18 to –2·30)	53·9	<0·0001
Passive smoking†	1·00 (0·90 to 1·12)	0·0	0·62	–0·33 (–0·67 to 0·01)	69·2	<0·0001	1·20 (1·06 to 1·35)	0·0	0·91	–0·22 (–0·46 to 0·02)	51·4	<0·0001
Education level												
None to primary	1·13 (0·99 to 1·29)	13·9	0·15	–0·40 (–0·70 to –0·10)	49·6	<0·0001	1·41 (1·20 to 1·66)	9·7	0·64	–0·45 (–0·75 to –0·16)	59·7	<0·0001
Secondary	1·05 (0·93 to 1·19)	3·1	0·41	0·17 (–0·21 to 0·25)	33·8	0·023	1·19 (1·02 to 1·38)	0·0	0·69	–0·03 (–0·27 to 0·21)	48·0	0·0010
Tertiary†	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..	1 (ref)	..	..
Dusty job for >10 years	1·17 (1·05 to 1·30)	0·0	0·81	–0·46 (–0·69 to –0·25)	23·3	0·19	1·26 (1·10 to 1·44)	23·0	0·057	–0·48 (–0·72 to –0·24)	47·4	0·0010
Solid fuels for cooking or heating for >6 months in a lifetime	1·07 (0·92 to 1·24)	42·4	0·0030	–0·15 (–0·43 to 0·12)	58·1	<0·0001	1·05 (0·90 to 1·23)	25·3	0·049	–0·14 (–0·44 to 0·17)	70·0	<0·0001
Family history of chronic obstructive pulmonary disease§	1·30 (1·11 to 1·53)	23·7	0·21	–0·45 (–0·76 to –0·13)	36·6	0·0020	1·25 (1·01 to 1·55)	41·4	0·0080	–0·44 (–0·78 to –0·11)	51·1	<0·0001
Ever diagnosed with tuberculosis by a doctor	1·94 (1·46 to 2·59)	0·0	0·59	–0·98 (–1·85 to –0·11)	80·2	<0·0001	2·11 (1·48 to 3·01)	49·8	0·0010	–0·85 (–1·68 to –0·03)	75·4	<0·0001

Presence of small airways obstruction was defined as FEV_3/FVC <LLN, given age and sex using European American reference equations from the National Health and Nutrition Examination Survey.[11,16] Pack-years were calculated by number of cigarettes smoked per day divided by 20 and multiplied by years of smoking. Risk factors were identified a priori. We attempted to include all risk factors in the regression models for each centre for small airways obstruction. However, on occasion the exposed group for solid fuel use, family history of chronic obstructive pulmonary disease, and previous history of tuberculosis was small and did not include any participants with small airways obstruction. In these instances, the effect of the risk factor was not estimated for that site. Likewise, for solid fuel use, some sites reported usage close to or at 100%. In these instances, sites were excluded due to perfect prediction of success. Information on solid fuel use not collected for Australia, Germany, Norway, and Sweden. No participants with a history of tuberculosis were identified for Tunisia, Trinidad and Tobago, Malaysia, and Mysore, India. No instances of family history of chronic obstructive pulmonary disease were identified for Mumbai, India, and Benin. OR=odds ratio. FEV_3/FVC=forced expiratory volume in 3 s as a ratio of the forced vital capacity. FEV_1/FVC=forced expiratory volume in 1 s as a ratio of the forced vital capacity. LLN=lower limit of normal. *Negative regression coefficient indicates a reduction in FEV_3/FVC (ie, worsened lung function). †Defined as somebody else smoking in the participant's home in the past 2 weeks. ‡Classified as technical or vocational college or university. §Mother, father, sister, or brother ever diagnosed with emphysema, chronic bronchitis, or chronic obstructive pulmonary disease by a doctor.

Table 4: **Adjusted pooled estimates of effects of risk factors on small airways obstruction, using FEV_3/FVC <LLN, and on FEV_3/FVC**

and previous tuberculosis but not for use of solid fuels for cooking and heating.

Due to absence of a gold standard, we used both $FEF_{25–75}$ and FEV_3/FVC ratio to estimate the prevalence of small airways obstruction. In this study, we found that a 1 L increase in FVC was associated with significantly reduced odds of small airways obstruction when using $FEF_{25–75}$ less than the LLN. Normal reference ranges for $FEF_{25–75}$ are affected by variability in both expiratory flows and FVC, which leads to large reference intervals around predicted values.[10] Due to this variability, $FEF_{25–75}$ less than the LLN has been shown at extremes of age to incorrectly classify the presence of airflow obstruction.[11] FEV_3/FVC ratio does not have the same limitations as $FEF_{25–75}$, as it accounts for variation in the FVC and therefore has a more acceptable between-person coefficient of variation.

We defined small airways obstruction as $FEF_{25–75}$ or FEV_3/FVC ratio less than the LLN according to the NHANES reference equations.[11,16] The LLN is more appropriate than arbitrary percent predicted cutoffs, which are prone to misclassification of obstructive lung disease.[19] $FEF_{25–75}$ is particularly prone to misclassification, for which the LLN as a percentage of the predicted normal value decreases substantially with increasing age.[16] We chose to use the NHANES reference equations for European Americans, because prevalence estimates for chronic airflow obstruction have been shown to be

similar regardless of whether ethnicity is considered.[20] We did not use the Global Lung Initiative equations, as they do not include reference values for FEV_3/FVC ratio.[10]

There was moderate agreement between $FEF_{25–75}$ and FEV_3/FVC ratio less than the LLN in the classification of small airways obstruction. Prevalence estimates were generally higher for $FEF_{25–75}$ less than the LLN than FEV_3/FVC ratio less than the LLN, especially in sites with a higher prevalence of spirometric restriction and a younger population. Xiao and colleagues[13] reported the prevalence of small airways obstruction as 42·7% in the central south region of China. By contrast, we estimated prevalence of pre-bronchodilator small airways obstruction to be 18% (65 of 351 participants) for the BOLD study site of Guangzhou, China, in the same region. This disagreement is likely to be explained by different diagnostic criteria. Xiao and colleagues[13] used two of $FEF_{25–75}$, mean forced expiratory flow rate at 50% of the FVC, or mean forced expiratory flow rate at 75% of the FVC of less than 65% predicted, whereas we used the more conservative $FEF_{25–75}$ less than the LLN. They also presented prevalence estimates according to a range of criteria. For $FEF_{25–75}$ less than the LLN, they reported an estimate of 23·1%, and for FEV_3/FVC ratio less than the LLN, they reported an estimate of 13·6%, which are both far more similar to our estimates. These differing results show that appropriate selection of diagnostic criteria is essential for comparison of results from different studies. For FEV_3/FVC ratio less than the LLN, Hansen and colleagues[21] estimated prevalence of small airways obstruction to be 16·3% in the NHANES study population; in comparison, we estimated pre-bronchodilator prevalence to be 19% (71 of 375 participants) for Lexington, KY, USA.

Two previous studies have investigated potential risk factors for small airways obstruction in general populations of adults, both based in Chinese populations.[13,22] We found cigarette smoking to be the strongest risk factor associated with small airways obstruction, with a clear dose–response relationship. This finding agrees with both previous publications. We also found passive smoke exposure to be a risk factor for small airways obstruction; however, this finding was only for post-bronchodilator FEV_3/FVC ratio less than the LLN. The association was weaker than previously reported,[13,22] probably due to different definitions for passive smoking.

We found inconsistent results for the association of small airways obstruction with sex. Female sex was associated with reduced odds of small airways obstruction for both pre-bronchodilator and post-bronchodilator $FEF_{25–75}$ and FEV_3/FVC ratio less than the LLN. However, results of the multivariable linear regression were inconclusive. By contrast, Xiao and colleagues[13] reported a strong association between female sex and increased odds of small airways obstruction. An increased risk is logical, as women have smaller conducting airways than men, and animal studies have shown a link between oestrogen receptors and increased damage to the small airways in female smokers.[23] Due to these conflicting findings, it is difficult to draw conclusions as to the true association of small airways obstruction with sex. We were unable to investigate further as stratification of our samples by sex led to small subgroups being excluded.

In agreement with Xiao and colleagues,[13] we found increasing age to be associated with increased odds of pre-bronchodilator and post-bronchodilator small airways obstruction for FEV_3/FVC ratio less than the LLN. With normal ageing, there is a reduction in the number of small airways, contributing to an age-related decline in lung function.[24] Despite reference equations accounting for age, we found a residual effect of ageing, probably representing cumulative exposure to unmeasured risk factors and any measurement error. The association of increasing age with reduced odds of small airways obstruction for $FEF_{25–75}$ less than the LLN was not unexpected. Xiao and colleagues[13] reported that prevalence of small airways obstruction peaked between the ages of 40–49 years and declined thereafter.[13] Despite this pattern, they still showed increased odds of small airways obstruction with increasing age, probably due to their using a younger reference group (ie, 20–29 years) than ours (ie, 40–49 years). A potential explanation for our finding is the large between-person variation in healthy populations for $FEF_{25–75}$, which appears to be exacerbated at extremes of age.[11]

The association of high BMI with reduced odds of pre-bronchodilator and post-brochodilator small airways obstruction in our study for both $FEF_{25–75}$ and FEV_3/FVC ratio less than the LLN is similar to other studies of small airways obstruction and chronic obstructive pulmonary disease.[13,25] Chen and colleagues[22] reported increased odds of small airways obstruction for a high waist circumference. However, BMI does not account for body-fat distribution, so we could not investigate this association. It is well known that low BMI is associated with chronic airflow obstruction.[26] We found that low BMI was associated with increased odds of small airways obstruction for both parameters, which supports previous findings for small airways obstruction.[13] However, due to a low number of participants in the low BMI group, we cannot provide reliable support for this association.

Low education level was associated with increased odds of post-bronchodilator small airways obstruction for both $FEF_{25–75}$ and FEV_3/FVC ratio less than the LLN. This finding was previously seen for chronic airflow obstruction in the BOLD study population[25] and for small airways obstruction in the study by Xiao and colleagues.[13] In high-income countries, low level of education is associated with adverse health behaviours,[27] which potentially explains the increased risk of small airways obstruction in some populations. We also found an association between having first degree relatives with chronic obstructive pulmonary disease and increased risk of pre-bronchodilator and post-bronchodilator small airways obstruction for both $FEF_{25–75}$ and

FEV_3/FVC ratio less than the LLN. Xiao and colleagues[13] reported a similar association for parental history of chronic obstructive pulmonary disease and, although genetic susceptibility is a factor in obstructive lung diseases, this association is subject to recall bias and should be interpreted with care. Additionally, previous diagnosis of tuberculosis was associated with increased risk of pre-bronchodilator and post-bronchodilator small airways obstruction for both $FEF_{25–75}$ and FEV_3/FVC ratio less than the LLN. This association was stronger in places where tuberculosis is more common. Xiao and colleagues[13] did not report evidence of this association. However, one study showed that 63% of patients in their post-tuberculosis treatment period have small airways obstruction according to $FEF_{25–75}$.[28] It is not clear whether airflow obstruction is down to pathological changes relating to tuberculosis or to associated risk factors, such as smoking.

We found that working in a dusty job for longer than 10 years was associated with increased risk of pre-bronchodilator and post-bronchodilator small airways obstruction for both $FEF_{25–75}$ and FEV_3/FVC ratio less than the LLN. Associations were strongest in the Western Pacific region, especially in Manila, Philippines, and Penang, Malaysia. Previous studies have shown how dust in the workplace is associated with both asthma and chronic obstructive pulmonary disease,[29] which could explain the associations in our study. Further studies are needed to support this association, especially as type of dust exposure was not considered. There was no evidence of association between the use of solid fuels for cooking and heating and small airways obstruction. This null finding was consistent across study sites and contrasts with Xiao and colleagues' findings,[13] which could in part be explained by our different definitions of exposure, with their study looking at acute exposure and our study looking at exposure over the lifetime. Our finding agrees with what has previously been shown in the BOLD study population for chronic airflow obstruction.[30]

Our secondary analysis found that, worldwide, isolated small airways obstruction in $FEF_{25–75}$ or FEV_3/FVC ratio is fairly common. Similar to Xiao and colleagues,[13] we found significant associations with common risk factors for obstructive lung disease. This finding has important clinical implications, as we have identified many individuals with small airways obstruction who would be classified as healthy according to traditional measurement indices. A potential explanation is that damage to the small airways occurs early in the disease process. Therefore, the higher prevalence of small airways obstruction in this study than for traditional airflow obstruction reflects the inclusion of individuals with early airflow obstruction who might progress to chronic airflow obstruction in later life.[8,12] Only studies in smokers and hospital-based populations have suggested a link between small airways obstruction and subsequent chronic obstructive pulmonary disease,[8,12] and further studies, preferably longitudinal, in general populations are needed.

Our study has several strengths, including a wide geographical coverage of representative populations, large sample size, and quality-assured spirometry. We also used the LLN to define atypical results, which is widely accepted to be more appropriate than percent predicted cutoffs. Our study also has limitations, including the absence of a gold-standard parameter to assess small airways obstruction. Although this study sheds some light on the appropriateness of parameters, there is still much debate on whether they truly assess the small airways. The choice of spirometry reference equations was also limited by an absence of up-to-date equations for FEV_3/FVC ratio. Finally, although the associations of small airways obstruction with our identified risk factors are biologically plausible, our cross-sectional study design means that we could not directly investigate causality.

In conclusion, we have shown that small airways obstruction is common in the general population. We have provided support for the findings of Xiao and colleagues[13] and identified several preventable risk factors. We have shown that $FEF_{25–75}$ and FEV_3/FVC ratio cannot be used interchangeably to assess small airways obstruction, and due to its considerable limitations, $FEF_{25–75}$ should be used with caution. Future research should investigate whether isolated small airways obstruction is associated with accelerated decline in lung function, development of airway obstruction, and symptom burden before the assessment of small airways obstruction is included in clinical and policy decision making.

Contributors

BK-B and AFSA conceived the study. Under the supervision of AFSA, BK-B performed data analysis and prepared the initial draft with input from PB. JPa assisted with the preparation of the database. All authors contributed to further drafting and final approval of the paper. AFSA and JPa accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DM declares being a consultant to and receiving royalties from GlaxoSmithKline, AstraZeneca, and the COPD Foundation (royalty payments are up to date) and acting as an expert witness for Schlesinger Law Firm, outside of the submitted work. RN reports grants and personal fees from AstraZeneca and GlaxoSmithKline and grants from Boehringer Ingelheim and Novartis, outside of the submitted work. All other authors declare no competing interests.

Data sharing

De-identified participant data and questionnaires may be shared, after publication, on a collaborative basis upon reasonable request made to Dr Amaral (a.amaral@imperial.ac.uk). Requesting researchers will be required to submit an analysis plan.

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