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Cohort Profile

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Cohort Profile: Burden of Obstructive Lung Disease (BOLD) study

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Key Features

- The Burden of Obstructive Lung Disease (BOLD) study was established to assess the prevalence of chronic airflow obstruction, a key characteristic of chronic obstructive pulmonary disease, and its risk factors in adults (≥40 years) from general populations across the world.
- The baseline study was conducted between 2003 and 2016, in 41 sites across Africa, Asia, Europe, North America, the Caribbean and Oceania, and collected high-quality pre- and post-bronchodilator spirometry from 28 828 participants.
- The follow-up study was conducted between 2019 and 2021, in 18 sites across Africa, Asia, Europe and the Caribbean. At baseline, there were in these sites 12 502 participants with high-quality spirometry. A total of 6452 were followed up, with 5936 completing the study core questionnaire. Of these, 4044 also provided high-quality pre- and post-bronchodilator spirometry.
- On both occasions, the core questionnaire covered information on respiratory symptoms, doctor diagnoses, health care use, medication use and ealth status, as well as potential risk factors. Information on occupation, environmental exposures and diet was also collected.
- Collaborative research proposals and access to data requests should be submitted to Dr Andre F S Amaral [a.amaral@imperial.ac.uk]. For more information on the BOLD study, please visit [https://www.imperial.ac.uk/nhli/bold].

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Why was the cohort set up?

At the end of the 20th century, chronic obstructive pulmonary disease (COPD) was already considered a leading cause of morbidity and mortality.[1–3] Yet, little was known about its prevalence and aetiology, particularly in low- and middle-income countries (LMICs). This information is important to improve the understanding of the impact of the disease on quality of life and health care cost, as well as to identify ways to reduce its risk.

The Burden of Obstructive Lung Disease (BOLD) study was set up and launched across several regions of the world as a network of population-based surveys using a standardized protocol. The initial main aims of the study were to assess the worldwide prevalence of chronic airflow obstruction, which is a defining characteristic of COPD, and to identify its main risk factors. The main aims of the follow-up study were: (i) to quantify the rate of lung function decline during adulthood; (ii) to assess the risk factors associated with lung function decline; and (iii) to understand the relationship between lung function and mortality, particularly across different ethnic groups.

The baseline study was funded in part by a grant from the Wellcome Trust (085790/Z/08/Z), which supported the coordinating centre in London, UK, and in part by unrestricted educational grants from University of Kentucky, Aventis, Astra Zeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Merck, Novartis, Pfizer, Schering-Plough and Sepracor, which supported the initial coordinating centre in Portland, OR, USA. Additional support was provided to several sites in the baseline study (please see Funding for details). The follow-up study in LMICs was funded by the UK Medical Research Council (MR/R011192/1) and in European countries by AstraZeneca AB (ESR-17-13417).

Who is in the cohort?

The baseline study was conducted, between 2003 and 2016, in 41 sites in 34 countries across Africa, Asia, Europe, North America, the Caribbean and Oceania [https://www.imperial.ac.uk/nhli/bold] (Figure 1).[4] These were selected to represent most of the regions covered by the Global Burden of Disease Programme,[5] while over-representing larger regions such as South Asia and excluding Latin America, which had a separate study (PLATINO).[6] Participants were non-institutionalized adults, aged 40 years and over, recruited from the general population around sites with at least 150 000 inhabitants. Sampling varied across sites, with some using simple random sampling and others using either stratified random sampling or cluster sampling (Figure 1). For each site and participant, weights were derived to account for sampling design.

At baseline, 77 640 contact attempts were made to recruit participants to the study, but 28 901 were ineligible (either died before clinic/home visit or left catchment area or were under 40 years old or were institutionalized or were untraceable or could not be contacted). Of the 48 739 eligible people, 14 482 (29.7%) were non-responders (actively refused to participate or provided partial data) and 34 257 (70.3%) were responders (completed the core questionnaire and post-bronchodilator spirometry, regardless of quality control score) (Table 1). Overall, at baseline the proportions of males and smokers were slightly higher among responders, and the proportion of people with a diagnosis of respiratory disease was slightly higher among non-responders. Non-responders were also older (Table 2).

In total, high-quality post-bronchodilator spirometry data are available for 28 828 participants (52.6% females, 47.4% males). The mean age of participants was 55 years, the mean body mass index (BMI) was 26.7 kg/m^2, 39.8% had ever smoked and 25.8% had higher education. The mean post-bronchodilator FVC (forced vital capacity) was 3.24 L and the mean post-bronchodilator FEV_1 (forced expiratory volume in one second)/FVC was 77.7%. Table 3 shows the distribution of these characteristics by sex.

How often have they been followed up?

The follow-up study was planned for 23 sites, but it was not feasible in five sites due to the COVID-19 pandemic.

Figure 1. Burden of Obstructive Lung Disease (BOLD) study sites

Table 1. Numbers of contact attempts, ineligible people, non-responders, responders, response rate and cooperation rate in each Burden of Obstructive Lung Disease cohort site at baseline and at follow-up

Site	Baseline[a]						Follow-up[b]					
	Invites	Ineligible	Non-responders	Responders	Response rate, %	Cooperation rate, %	Invites	Ineligible (dead)	Non-responders	Responders	Response rate, %	Cooperation rate, %
Albania (Tirana)	1200	24	190	986	82	84	—	—	—	—	—	—
Algeria (Annaba)	969	0	52	917	95	95	—	—	—	—	—	—
Australia (Sydney)	2488	738	1165	585	24	33	—	—	—	—	—	—
Austria (Salzburg)	2200	192	659	1349	61	67	—	—	—	—	—	—
Benin (Sèmè-Kpodji)	900	22	28	850	94	97	706	84 (14)	505	117	17	19
Cameroon (Limbe)	719	24	262	433	60	62	—	—	—	—	—	—
Canada (Vancouver)	2434	659	919	856	35	48	—	—	—	—	—	—
China (Guangzhou)	690	0	88	602	87	87	—	—	—	—	—	—
England (London)	4467	2540	1230	697	16	36	—	—	—	—	—	—
Estonia (Tartu)	1440	482	300	658	46	69	619	219 (219)	1	399	64	100
Germany (Hannover)	2546	1092	741	713	28	49	—	—	—	—	—	—
Iceland (Reykjavik)	1000	94	146	760	76	84	757	260 (187)	119	378	50	76
India (Kashmir)	1100	17	130	953	87	88	771	660 (18)	22	89	12	80
India (Mumbai)	1857	1069	273	515	28	65	—	—	—	—	—	—
India (Mysore)	945	73	147	725	77	83	607	57 (23)	13	537	88	98
India (Pune)	1438	0	50	1388	97	97	851	146 (103)	11	694	82	98
Jamaica	907	19	93	795	88	90	594	356 (10)	141	97	16	41
Kyrgyzstan (Chui)	1226	151	5	1070	87	100	894	316 (42)	108	470	53	81
Kyrgyzstan (Naryn)	1202	92	5	1105	92	100	865	162 (47)	79	624	72	89
Malawi (Blantyre)	760	67	108	585	77	84	—	—	—	—	—	—
Malawi (Chikwawa)	982	153	1	828	84	100	448	69 (28)	5	374	85	99
Malaysia (Penang)	1218	407	98	713	59	88	—	—	—	—	—	—
Morocco (Fes)	985	0	19	966	98	98	770	571 (2)	134	65	9	33
Netherlands (Maastricht)	1341	198	513	630	47	55	—	—	—	—	—	—
Nigeria (Ile-Ife)	1704	504	52	1148	67	96	884	405 (56)	17	462	52	96
Norway (Bergen)	1130	133	290	707	63	71	661	198 (139)	165	298	45	64
Pakistan (Karachi)	3172	2116	4	1052	33	100	616	227 (51)	130	259	42	67
Philippines (Manila)	1397	1	478	918	66	66	—	—	—	—	—	—
Philippines (Nampicuan-Talugtug)	1177	28	158	991	84	86	727	198 (116)	57	472	65	89
Poland (Krakow)	769	39	127	603	78	83	—	—	—	—	—	—
Portugal (Lisbon)	7123	4348	2030	745	10	27	—	—	—	—	—	—
Saudi Arabia (Riyadh)	866	0	82	784	91	91	—	—	—	—	—	—
S. Africa (Uitsig & Ravensmead)	1378	110	377	891	65	70	—	—	—	—	—	—
Sri Lanka	1406	12	214	1180	84	85	—	—	—	—	—	—
Sudan (Gezeira)	1361	315	212	834	61	80	—	—	—	—	—	—
Sudan (Khartoum)	698	2	101	595	85	85	520	450 (2)	13	57	11	81
Sweden (Uppsala)	998	31	379	588	59	63	551	106 (52)	170	275	50	62
Trinidad & Tobago	1424	0	37	1387	97	97	—	—	—	—	—	—
Tunisia (Sousse)	799	17	65	717	90	92	661	332 (46)	60	269	41	82
Turkey (Adana)	2077	45	1157	875	42	43	—	—	—	—	—	—
USA (Lexington, KY)	15 147	13 087	1497	563	4	27	—	—	—	—	—	—

[a] At baseline: ineligible people were those who died before clinic/home visit, who left the catchment area, who were under 40 years old, who were institutionalized, who were untraceable or who could not be contacted. Non-responders were those who actively refused to participate and those who provided partial data. Responders were those who completed the core questionnaire and post-bronchodilator spirometry, regardless of quality control score. Response rate was defined as the number of responders divided by the number of invites or attempts to contact potential participants. Cooperation rate was defined as the number of responders divided by the number of responders plus the number of non-responders.

[b] At follow-up: invites (attempts to contact) were made to those who responded at baseline and had useable spirometry. Ineligible people were those who died between baseline and follow-up, who left the catchment area, who were untraceable or who could not be contacted. Non-responders were those who actively refused to participate and those who provided partial data. Responders were those who completed the core questionnaire. Response rate was defined as the number of responders divided by the number of invites or attempts to contact potential participants. Cooperation rate was defined as the number of responders divided by the number of responders plus the number of non-responders.

Table 2. Selected characteristics comparing non-responders and responders at baseline in the Burden of Obstructive Lung Disease cohort

	All 41 sites		18 sites with follow-up data	
	Non-responders ($n = 14\,482$)	Responders ($n = 34\,257$)	Non-responders ($n = 1973$)	Responders ($n = 15\,896$)
Sex, %				
Male	44.3	46.7	46.0	45.2
Female	55.7	53.3	54.0	54.8
Age (years), mean (SD)	62 (15)	55 (11)	58 (14)	55 (12)
Ever smokers,[a] %	35.2	37.9	34.0	32.1
Doctor-diagnosed asthma, emphysema, chronic bronchitis or chronic obstructive pulmonary disease,[b] %	12.7	10.6	7.8	7.9
Other comorbid conditions,[c] %	33.8	33.4	32.8	29.7

Sites names ($n = 41$): Albania (Tirana); Algeria (Annaba); Australia (Sydney); Austria (Salzburg); **Benin (Sèmè-Kpodji)**; Cameroon (Limbe); Canada (Vancouver); China (Guangzhou); England (London); **Estonia (Tartu)**; Germany (Hannover); **Iceland (Reykjavik)**; **India (Kashmir)**; India (Mumbai); **India (Mysore)**; **India (Pune)**; **Jamaica**; **Kyrgyzstan (Chui)**; **Kyrgyzstan (Naryn)**; Malawi (Blantyre); **Malawi (Chikwawa)**; Malaysia (Penang); **Morocco (Fes)**; Netherlands (Maastricht); **Nigeria (Ile-Ife)**; **Norway (Bergen)**; **Pakistan (Karachi)**; Philippines (Manila); **Philippines (Nampicuan-Talugtug)**; Poland (Krakow); Portugal (Lisbon); Saudi Arabia (Riyadh); S. Africa (Uitsig & Ravensmead); Sri Lanka; Sudan (Gezeira); **Sudan (Khartoum)**; **Sweden (Uppsala)**; Trinidad & Tobago; **Tunisia (Sousse)**; Turkey (Adana); USA (Lexington, KY). Sites in bold type have follow-up data ($n = 18$).

[a] Missing for 11 194 non-responders (41 sites); missing for 1164 non-responders (18 sites).

[b] Missing for 4487 non-responders (41 sites); missing for 767 non-responders (18 sites).

Table 3. Selected characteristics of the Burden of Obstructive Lung Disease cohort participants who completed the core questionnaire and had provided useable spirometry at baseline (41 sites; $n = 28\,828$)

Characteristic	Male ($n = 13\,659$)	Female ($n = 15\,169$)
Age (years), mean (SD)	55.1 (11.0)	54.2 (10.9)
Body mass index (kg/m^2), mean (SD)	25.7 (4.9)	27.6 (7.1)
Ever smokers, %	59.2	22.4
Higher education, %	24.2	25.3
Post-bronchodilator FVC (L), mean (SD)	3.82 (0.98)	2.72 (0.71)
Post-bronchodilator FEV1/FVC (%), mean (SD)	76.4 (9.4)	78.8 (7.9)

FEV_1 (forced expiratory volume in one second); FVC, forced vital capacity; SD, standard deviation.

Participants from the BOLD baseline study were followed up once, between 2019 and 2021, in 14 sites in LMICs and four sites in Northern Europe, with a median follow-up time of 8.4 years. At follow-up, 12 502 individuals who had completed the core questionnaire, and had provided acceptable and repeatable lung function measurements at baseline, were invited to participate. The number of participants who completed the core questionnaire was 5936, and of these 4044 were able to perform spirometry and provided high-quality post-bronchodilator measurements for at least one lung function parameter (Figure 2). Slightly more than half of these participants were females (55.6%), the mean age was 61 years, the mean BMI was 26.5 kg/m^2 and 30.7% had ever smoked. Table 4 shows the distribution of these characteristics by sex for participants who were followed up and had high-quality lung function data.

Among participants lost to follow-up, 1155 had died, 3658 had migrated or were unreachable and 1237 refused to participate. To explore reasons for not being able to participate in the follow-up, we investigated potential explanatory variables (sex, age, BMI, smoking status, education level, self-reported doctor diagnosis of cardiovascular disease, self-reported doctor diagnosis of diabetes, a history of tuberculosis, dyspnoea, chronic cough, chronic phlegm and wheezing) using logistic regression within each site and then pooling together estimates using random effects meta-analysis. Older participants, current smokers and those with lower BMI were more likely to be lost to follow-up (Table 5). Based on this information, we calculated inverse probability weights to correct for loss-to-follow up in future analyses.[7,8]

What has been measured?

In both surveys, participants were asked to answer a set of standardized questionnaires and undergo a series of measurements. The questionnaires were translated into the local language of each site, back-translated to English and checked for accuracy before administration by trained staff. Questionnaires were developed to obtain information about respiratory symptoms, respiratory and cardiometabolic diagnoses, health care use, medication use, activity limitation and health status, as well as about potential risk factors, including tobacco smoking, occupational and environmental exposures and diet (Table 6). In addition, measurements of several anthropometric parameters, blood pressure and pulse rate (M2 Basic, Omron), and lung function were taken. Lung function testing was performed using a spirometer (EasyOne, ndd Medizintechnik AG), before and after the administration of 200 μg of salbutamol via an inhalation spacer (Able, Clement Clarke International). All spirometry curves were checked centrally at the BOLD Operations Centre, and to be considered useable, tests had to include at least three acceptable curves (no hesitation, complete blow, no artefact affecting lung function readings), with the two best blows being within 200 mL of each other. Prior to the start of the surveys, study site staff underwent a 1-week intensive training which covered consenting, questionnaire data collection, spirometry testing

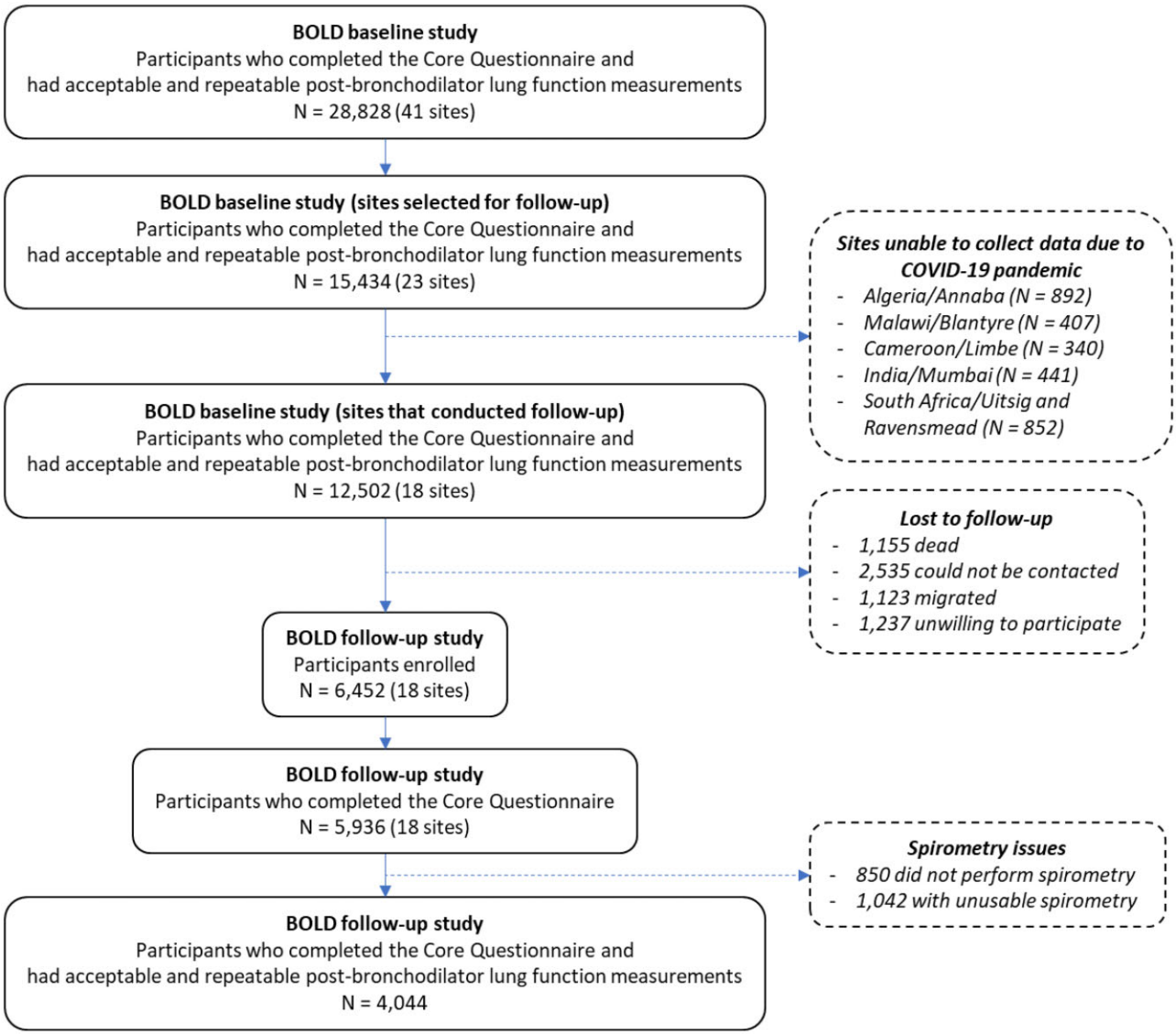

Figure 2. Selection of participants in the Burden of Obstructive Lung Disease (BOLD) cohort

Table 4. Selected characteristics of the Burden of Obstructive Lung Disease cohort participants who completed the core questionnaire and had provided useable spirometry both at baseline and follow-up ($n = 4044$)

	Baseline		Follow-up	
Characteristics	Male ($n = 1802$)	Female ($n = 2242$)	Male ($n = 1802$)	Female ($n = 2242$)
Age (years), mean (SD)	52.1 (9.3)	51.2 (9.1)	61.5 (10.1)	60.0 (10.0)
Body mass index (kg/m^2), mean (SD)	25.0 (4.5)	26.1 (5.7)	25.7 (5.0)	27.2 (5.7)
Ever smokers, %	47.8	15.5	49.2	15.9
Higher education, %	27.6	31.6	27.6	31.6
Post-bronchodilator FVC (L), mean (SD)	3.87 (0.99)	2.73 (0.70)	3.54 (0.91)	2.51 (0.64)
Post-bronchodilator FEV1/FVC (%), mean (SD)	77.9 (7.5)	79.7 (6.9)	75.9 (8.3)	78.2 (7.1)

FEV_1 (forced expiratory volume in one second); FVC, forced vital capacity; SD, standard deviation.

and quality control, anthropometry measurements and data transfer.

What has it found? Key findings and publications

BOLD has published extensively on the prevalence and aetiology of chronic airflow obstruction. By April 2023, there were 102 publications in peer-reviewed journals [https://www.imperial.ac.uk/nhli/bold/publications]. Here we highlight the main findings from this study to date.

i) The prevalence of chronic airflow obstruction varies widely across world regions but is, on average, slightly lower in LMICs and more common among males (11.2%) than among females (8.6%). Among males, the

Table 5. Pooled odds ratio (OR) and 95% confidence interval (CI) of being lost to follow-up

Variable	Adjusted OR (95% CI)[a]	Heterogeneity	
		I^2 (%)	P^b
Sex			
Male	(ref)	—	—
Female	1.03 (0.80–1.32)	78.8	<0.001
Age (years)	1.03 (1.01–1.04)	85.2	<0.001
Body mass index (kg/m^2)	0.98 (0.97–0.99)	24.7	0.2
Smoking status			
Current	(ref)	—	—
Former	0.86 (0.65–1.13)	40.1	0.06
Never	0.75 (0.63–0.89)	13.4	0.4
Education level			
Tertiary	(ref)	—	—
Secondary	0.93 (0.82–1.07)	1.2	0.2
None to primary	1.05 (0.86–1.29)	36.2	0.06
Doctor diagnosis			
Cardiovascular disease	1.21 (0.92–1.58)	45.9	0.04
Diabetes	0.81 (0.56–1.19)	53.3	0.03
Tuberculosis	0.90 (0.55–1.48)	37.7	0.05
Respiratory symptoms			
Dyspnoea	0.94 (0.73–1.21)	46.7	0.02
Chronic cough	0.98 (0.75–1.23)	36.7	0.03
Chronic phlegm	0.89 (0.65–1.20)	44.6	0.009
Wheeze	1.02 (0.87–1.20)	0.0	0.8

[a] Adjusted simultaneously for all variables in the table.
[b] *P*-value from chi square test for heterogeneity across sites.

prevalence of chronic airflow obstruction ranges from 3.5% in Riyadh (Saudi Arabia) to 23.2% in Uitsig and Ravensmead (South Africa), and among females from 2% in Sousse (Tunisia) to 19.4% in Salzburg (Austria).[4]; The main risk factors for chronic airflow obstruction are tobacco smoking (both active and passive), which accounts for approximately 46% of the prevalence in males and 26% in females. The next most important risk factors are a poor education level and poverty, followed by a history of tuberculosis (where tuberculosis is common), a low BMI and exposure to dust in the workplace for more than 10 years.[4,9–12]

ii) Ambient particulate matter and the use of solid fuels for cooking and heating are unlikely to explain a substantial amount of the prevalence of chronic airflow obstruction. These findings are equally true for males and females.[13,14]

iii) The prevalence of small airways obstruction in the presence of what is usually considered normal lung function (i.e. isolated small airways obstruction) is common in general populations across the world. In addition, the main risk factors for isolated small airways obstruction are the same as for chronic airflow obstruction, suggesting that the former has the potential to predict the latter.[15]

iv) There is a large proportion of people with low forced vital capacity (FVC), suggestive of low lung volumes, in

Table 6. Information collected in the Burden of Obstructive Lung Disease cohort at baseline and follow-up

Information	Baseline	Follow-up
Core questionnaire		
Smoking status/history	Yes	Yes
Respiratory symptoms (cough, sputum, wheezing, shortness of breath)	Yes	Yes
Respiratory diagnoses (asthma, emphysema, chronic bronchitis, COPD)	Yes	Yes
Cardiometabolic diagnoses (cardiovascular disease, hypertension, diabetes)	Yes	Yes
History of tuberculosis	Yes	Yes
Health care use	Yes	Yes
Medication use (respiratory)	Yes	Yes
Quality of life (mental and physical health)	Yes	Yes
Physical activity	No	Yes
Sleep	No	Yes
Occupational questionnaire		
High-risk jobs	Yes	Yes
Job history	No	Yes
Job exposure matrix linkage	No	Yes
Environmental questionnaire		
Solid fuel use	Yes	Yes
Pesticide use	No	Yes
Proximity to road	No	Yes
GPS coordinates (home)[a]	No	Yes
Food frequency questionnaire[a]	Yes	Yes
Physical measurements		
Spirometry	Pre- and post-bronchodilator	Pre- and post-bronchodilator
Anthropometry	Standing height, weight	Standing height, weight, ulna length, fibula length, waist circumference, hip circumference, neck circumference
Cardiovascular disease markers	No	Blood pressure, pulse rate

COPD, chronic obstructive pulmonary disease; GPS, global positioning system.
[a] Some sites only.

LMICs, particularly in sub-Saharan Africa. In addition, this low FVC is associated with cardiometabolic diseases (i.e. cardiovascular disease, hypertension and diabetes)[16] and cardiometabolic risk factors.[17]

What are the main strengths and weaknesses?

The BOLD study has brought together a strong and widespread international collaboration to address the epidemiology of COPD and is today a reference in the field of chronic respiratory diseases. In addition, this study has had an important impact on capacity building and promotion of equity and inclusion across the study sites.

The main strengths of the BOLD study are the:

i) broad coverage of world regions and ethnic groups;
ii) large sample of representative population-based data;
iii) use of a standardized protocol, including the same questionnaires and same model of spirometers to test lung function, across study sites;
iv) centralized training and certification of interviewers and spirometry technicians. The quality of the data was monitored throughout the study, and re-training of staff was carried out if necessary;
v) high quality of pre- and post-bronchodilator lung function measurements, with centralized quality control and assessment of all spirometry curves. In the follow-up study, we also developed and implemented an algorithm to monitor lung function data collection and provide feedback to spirometry technicians in 'real-time'.

The main weaknesses are the:

i) self-reported doctor diagnoses of COPD, asthma, heart disease, hypertension and diabetes, which are subject to recall bias and local diagnostic guidelines and patterns;
ii) limited data on causes of death in sites located in LMICs;
iii) except for four sites in Northern Europe, the lack of biological samples, including DNA samples, for investigation of biological mechanisms. These will be sought in the next wave of the study.

To compensate for non-response at baseline and at follow-up, we derived weights for respondents to the core questionnaire. However, we cannot dismiss the possibility of bias in our estimates due to unmeasured factors.

Can I get hold of the data? Where can I find out more?

The study data are not freely accessible. However, proposals for collaboration will be considered. Requests should be directed to the project lead, Dr Andre F S Amaral [a.amaral@imperial.ac.uk].

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Ethics approval

All sites received approval from their local ethics committee, the follow-up study was also approved by Imperial College London Research Ethics Committee (ref. 17IC4272), and participants provided informed consent.

Data availability

See Can I get hold of the data? above.

Author contributions

A.F.S.A. drafted the manuscript. J.Po. and B.K.B. conducted data analysis. All authors reviewed and contributed to the final version of the manuscript.

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Conflict of interest

D.M. is a consultant to GlaxoSmithKline, AstraZeneca and Up-to-Date, a shareholder of GlaxoSmithKline, and an expert witness on behalf of people suing the tobacco industry. T.S. has received honoraria from AstraZeneca, GlaxoSmithKline and Boehringer Ingelheim for lecturing and attendance at advisory boards over the past 3 years, and has published research with GlaxoSmithKline in the past year. W.C.T. reports grants from Canadian Institute of Heath Research (CIHR/Rx&D Collaborative Research Program Operating Grants 93326) with industry partners Astra Zeneca Canada, Boehringer-Ingelheim Canada, GlaxoSmithKline Canada, Merck, Novartis Pharma Canada, Nycomed Canada, Pfizer Canada, during the conduct of the CanCOLD study; personal fees from GlaxoSmithKline, Canada, and from Astrazeneca, Canada, outside the submitted work.

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