Title:

Cohort profile: The Birmingham COPD Cohort Study

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Why was the cohort set up?

Chronic obstructive pulmonary disease (COPD) affects 5-10% of people worldwide (1), is rising in prevalence (2) and is the third most common cause of death (3). The annual burden of COPD regarding healthcare (mainly exacerbations resulting in emergency admissions) and societal (predominantly lost productivity) costs was estimated to be around $49.9billion in the USA (2010 prices (4)) and €48.4billion in the EU (2011 prices (5)). A substantial proportion of those with COPD are of working age, but there is some evidence that they have poorer employment history (6), higher rate of sickness absence (7) and poorer work performance (presenteeism) (8) compared to the general population.

There remains much uncertainty about the natural history of COPD (9, 10) and which interventions are effective in altering the course of early disease. Furthermore, up to 85% of cases (11-13) are undiagnosed; representing many with potentially unmet need. Partly in response to reports (14-16) highlighting the burden of COPD, extent of underdiagnosis and uncertainty about prognosis of early disease, expert reviews have highlighted a need for further longitudinal data (9, 10). However, established cohorts usually represent secondary care patients with more advanced disease, with short duration of follow up and, generally small samples (17-19). While large population cohorts have sometimes addressed questions relevant to COPD (20-28), limitations in outcome measures and quality of lung function testing provide insufficient data to inform the COPD arena. Importantly, there are no primary care COPD cohorts with case-found patients and few with patients representing the full range of disease severity, particularly those with mild to moderate disease, and diverse socioeconomic mix.

In recent years, several studies have also focused on patients reporting respiratory symptoms but who have normal lung function (former GOLD severity stage 0 (29)). The evidence on progression to COPD is limited and contradictory (23, 30, 31) and methods for assessing symptoms are inconsistent (23, 32). Thus there is also a paucity of evidence on the clinical relevance and natural history for this patient group.

Better understanding of natural history and prognostic factors is needed to facilitate consultations, and to inform management decisions and health service planning. Existing COPD prognostic indices (PI) mainly focus on predicting mortality risk (17, 33-36), though others were developed to predict additional outcomes such as exacerbations (37, 38), COPD-related hospitalisation (39), respiratory hospital attendance/admission (40), exacerbation or hospitalisation (41, 42). Only three indices (38, 41, 42) were derived in primary care populations despite this being where most COPD patients are managed, and most included patients with more severe established disease. No indices were developed in populations that included case-found patients. The methods and basis for selecting prognostic variables are rarely described, and the feasibility of obtaining all the required measures in non-specialist settings is not always considered. The paucity of evidence from the primary care setting as well as the other limitations suggests that further validation is required. Furthermore, the low discriminatory ability of most of the existing indices suggests that other important potential measures (e.g. co-morbidities, occupation or serum inflammatory markers) may need to be considered to improve prognostic prediction and usefulness of the indices.

Our prospective cohort study with an initial three-year follow up period, allows cross-sectional and longitudinal analyses. The aim is to identify the most appropriate COPD prognostic index for use in a

primary care population (with all cause hospitalisation as primary, and respiratory hospitalisation, exacerbations, primary care consultations and mortality as secondary outcomes), to examine factors associated with employment and work productivity among those with COPD of working age, to develop a platform to test novel interventions and to provide a data source for additional analyses of relevance to patient benefit.

Funding and ethical approval

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Who is in the cohort?

Patients were recruited from 71 General Practices (GP) across the West Midlands, UK and include three patient groups: those with diagnosed COPD according to GP records (prevalent cases), previously undiagnosed patients with respiratory symptoms and airflow obstruction confirmed by spirometry (incident cases) and symptomatic patients with normal lung function confirmed by spirometry ('symptomatic normals'). The latter two groups were identified through a linked case-finding trial (43).

To inform prognostic model development, we aimed to recruit 2000 patients. The sample size assumes that 25% of COPD patients will be hospitalised in the three-year period, a 30% loss-to-follow up and 12% three-year mortality.

Identifying potentially eligible patients

The process of identifying eligible patients differed according to the patient group. The sampling frame for the prevalent cases comprised patients aged 40 years and over, with diagnosed COPD. Standardised electronic searches were conducted in participating practices to identify patients on the COPD QoF register (COPD14). The resulting lists were screened by a clinician who excluded patients deemed unsuitable due to terminal illness, being housebound, inability to give informed consent and other adverse social factors (e.g. recent bereavement, alcohol dependency).

A full description of the eligibility criteria for the case-finding trial was published previously (43). In brief, eligible patients were aged 40 to 79 who reported relevant respiratory symptoms on a screening questionnaire. Patients were subsequently invited to the Cohort study if, they had indicated willingness to be contacted about other studies.

Patient recruitment

Eligible patients were sent an invitation letter and study information sheet from their GP, with up to two reminders to non-responders. Interested patients were invited to an assessment visit at either

their General Practice or alternative local health centre, where informed consent was obtained (Figure 1).

[Figure 1 here]

Generalisability of cohort

Basic demographic data (sex, age and ethnicity) were obtained for all identified eligible patients from their primary care records (Table 1). Overall, those who consented to take part were more likely to be male and of White British ethnicity. Among prevalent cases, those who consented were slightly younger than other eligible patients, whereas the reverse was true for those identified through case-finding.

[Table 1 here]

Sample characteristics

Prevalent cases were older, more likely to be of White British ethnicity, less likely to be in paid employment and more deprived compared with the other two patient groups (Table 2). The observed differences may be due in part to the previously described eligibility criteria for the case-finding trial. Prevalent and incident cases were more likely to be male (61.6% and 61.0% respectively), but the sex-distribution was similar (52.8% male) in symptomatic normals. Incident cases had the highest proportion of current smokers (33.6%), compared with prevalent (28.3%) and symptomatic normals (19.4%). Only 10.4% of prevalent cases were never smokers compared with incident cases (14.7%) and symptomatic normals (19.1%).

[Table 2 here]

How often have they been followed up?

Patients receive six-monthly postal questionnaires (at 6, 12 18, 24, 30 months), with one reminder to non-responders. Follow-up study assessment visits (from March 2015) will be arranged three years after baseline, or as close as is feasible within the study period. We plan to apply for additional funding to extend the follow-up period beyond the initial three years.

What has been measured?

Baseline assessment visits, lasting an average of 90 minutes, were conducted by trained research assistants, using standardised protocols and recording data on a standardised Case Report Form. A high standard for spirometry training was achieved using a short modified programme modelled on the ARTP Spirometry course by the lung function unit at Queen Elizabeth Hospital Birmingham. Refresher training, quality monitoring and feedback were undertaken throughout the study. Research assistants were also trained in study-specific measures, phlebotomy and Good Clinical Practice (GCP).

Lung function was assessed using the ndd Easy One spirometer (ndd, Switzerland), before and 20 minutes after administration of 400 micrograms Salbutamol. A minimum of three and a maximum of eight blows pre-bronchodilator and six blows post-bronchodilator were permitted, or less if repeatability within 100mls was achieved, after which the best result was taken. Customised

software (MMiller) was used to ensure real-time display of volume-time and flow-volume graphs for quality assessment. At baseline, all traces were over-read and data for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were considered usable if they met ATS acceptability criteria and were reproducible to within 200 ml. A summary of prognostic, outcome and other variables assessed by either direct measurement or through questionnaires, is provided in Table 3. Height was measured to the nearest 0.1cm using a Leicester height monitor, and weight (to the nearest 0.1kg) and body fat were assessed using Tanita BC-420SMA body composition scale. Grip strength was measured to the nearest 1kg with a Saehan hydraulic hand dynamometer. Exercise capacity was assessed using the sit-to-stand test, which has been shown to be a valid alternative to the 6-minute walk test (44) and is more practical in primary care settings.

Data from occupational measures will contribute towards a nested study, to be reported separately.

[Table 3 here]

What has been found? Key findings and publications

Key findings:

While there is broad consensus that the Lower Limit of Normal (LLN) should be used instead of the fixed ratio ($FEV_1/FVC<70\%$) for defining airflow obstruction (AO) in epidemiological studies (45, 46), we present data for both criteria. Using the fixed ratio allows comparability with i) UK primary care practice in accordance to guidelines (47) and ii) other studies, which historically have used this definition. Our assessment visit spirometry confirmed AO in only 86.4% of prevalent cases using the fixed ratio criteria and 71.9% using LLN (Table 4). Lung function variability was also evident in patients recruited from the linked case-finding trial, even though spirometry in both studies was conducted by identically-trained researchers, using the same spirometers and protocols. At the Cohort baseline assessment, 81.2% of previously-defined incident cases and 14.0% of previously-defined symptomatic normals had AO (using the fixed ratio). The observed discrepancies may be explained in part by within-test reproducibility of FEV1 and FVC (repeatability) (48) and between-test variation in bronchodilator response (reversibility) (49); however among prevalent cases it could also indicate misdiagnosis, which will be explored in a subsequent paper.

The baseline characteristics of the prevalent, incident and symptomatic normal patients are summarised in Table 5. Compared with other groups, prevalent cases have more severe AO (23.6% versus 1.8% were GOLD stages 3-4), a higher rate of reporting chronic bronchitis (symptoms of cough and phlegm for as much as three consecutive months each year), wheeze, and severe dyspnoea (~⅔ reporting MRC grade 3-5, compared to ⅓ among other groups).

Prevalent cases also reported worse general (EQ5-D) and disease-specific (CAT) health-related quality of life. Compared with incident cases, those with prevalent COPD had lower exercise capacity, a higher frequency of exacerbations (defined as having a course of prescribed antibiotics or systemic steroids alone, or in combination (50)) over the previous year, and higher rates of all-cause and respiratory-related hospitalisations. However, the prevalence of major diagnosed co-morbidities (including diabetes, cardiovascular disease, osteoporosis, fractures, depression or peptic ulcers) did not differ between groups.

Overall, 4.2% of the cohort were underweight, and over a third were obese. The proportion underweight was greatest among prevalent cases (5.1%), whereas obesity was most common among the symptomatic normals (46.4%).

[Table 4 here]

Multivariable analyses adjusting for sex, age, smoking status and severity of AO, were undertaken to compare characteristics of prevalent and incident cases (Table 5). Incident cases were half as likely to report chronic cough and wheeze compared with prevalent cases, though no difference was found regarding chronic bronchitis or presence of co-morbidities. Incident cases were less likely to report severe dyspnoea (MRC grades 3-5), had higher generic and disease specific quality of life scores, higher BODE[1] index, indicating lower mortality risk and fewer all-cause and respiratory-related hospitalisations.

Restricting the analyses to patients with confirmed airway obstruction at the cohort baseline assessment for the prevalent and incident cases did not alter the direction of the findings, although the magnitude of effect altered slightly.

The above analysis confirms that incident cases identified through case-finding have less severe disease. Nevertheless, the majority (84%; 278/331) of incident cases have the potential to benefit from having been identified, if evidence-based interventions are administered. One third were current smokers and would benefit from intensive smoking cessation interventions. Over a third reported severe (MRC grade 3-5) dyspnoea, with potential to benefit from pulmonary rehabilitation (47) and over half reported symptoms of chronic cough, which can be responsive to pharmacotherapy (47). Longitudinal follow-up is needed to assess whether these potential benefits of early diagnosis are realised.

The data also highlight the need to explore the symptomatic normals that report comparable co-morbidities to other groups, and are similar to incident patients in respect of dyspnoea, CAT and EQ-5D scores as well as history of hospitalisations. Longitudinal analyses will determine whether symptomatic normals represent a pre-COPD stage, and if so, which factors affect future prognosis.

[Table 5 here]

Publications:

The study design and interim analyses have been presented at several international meetings including COPD8 in 2012, the Annual Congresses of the European Respiratory Society in 2013 (51) and 2014 (52), the World Conference of the International Primary Care Respiratory Group 2014 and the International Conference of the American Thoracic Society 2014 (53). Other print publications are in preparation.

What are the main strengths and weaknesses?

The inclusion of case-found patients provides the novel opportunity to characterise and follow a subgroup of previously undiagnosed COPD patients, many of whom have mild to moderate COPD and were under-represented in previous cohort studies.

[1] Calculated using sit-to-stand rather than 6-minute walk, due to space restrictions within GP surgeries

Establishing a large primary care COPD cohort and assessing a wide range of outcomes will enable us to test the external validity of existing prognostic indices (PI), and if necessary adapt or develop a new PI suitable for use in the primary care setting.

A further strength is the inclusion of symptomatic patients with normal lung function. Longitudinal data on this patient group may identify modifiable factors affecting progression. As with other chronic diseases, early detection and management of such patients may prevent or delay progression of the condition.

Conducting the study assessments within General Practices was a pre-requisite, due to the administration of Salbutamol to assess reversibility. Unfortunately this requirement precluded housebound patients from participating, who may have had more severe COPD. Thus the findings are likely to be more relevant to an ambulatory primary care COPD population, with predominantly mild to moderate disease.

Despite the setting, ethnic diversity within our cohort was limited. Although a translated cover sheet was enclosed at initial invitation, lack of resources prohibited use of multiple recruitment strategies, such as snowball sampling, peer researchers and contact with key community leaders (54), which may have boosted recruitment of those for whom English was not their first language.

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

The data are held by the BLISS research team at the University of Birmingham. Copies of the questionnaires, measurement procedures and administrative processes are available on request, through our website (www.birmingham.ac.uk/bliss). Copies of published and in-press papers will also be available on the website. Potential collaborators should contact the programme manager or the principal investigators in the first instance, before completing a formal New Research Proposal pro forma (see website for details). Proposals are assessed for feasibility, potential overlap with ongoing work and cost to participants. Successful collaborations to date include projects between research team members and others with complementary skills both within and external to the University of Birmingham (see website for details) and hosting of post-graduate research students. We very much welcome new opportunities for collaboration.

Birmingham COPD Cohort study profile in a nutshell:

- This is the first primary care based cohort of COPD patients including both existing and case-found patients, as well as those with chronic respiratory symptoms and normal lung function
- This prospective cohort study will identify the most appropriate prognostic index for use in a primary care COPD population, which best predicts risk of hospital admission
- A total of 2302 patients aged 40 and above were recruited from 71 General Practices across the West Midlands, UK and include: those with diagnosed COPD, previously undiagnosed patients with respiratory symptoms and airflow obstruction confirmed by spirometry and symptomatic patients with normal lung function confirmed by spirometry.
- Clinical assessments were conducted at baseline (2012-2014) and three-year follow-up, with postal questionnaires completed at six-monthly intervals. 2107 patients remained eligible on commencement of follow-up assessments.

- Data collected includes spirometry, physiological and anthropometric measures, as well as biological samples, self-completed questionnaires and linkage to health and social care data.
- We welcome new opportunities for collaboration and copies of the questionnaires, measurement procedures and administrative processes are available on request, through our website.

Author contributions

PA and DAF are co-PIs for the BLISS programme, which was conceived in consultation with REJ, KKC, JGA and RAS, and with BGC, AJD, SG, KJ, SJ, JLM, MRM, RDR, WSS and AMT as co-investigators. PA led the Cohort study, REJ the TargetCOPD trial, and JGA the occupational sub-cohort. AE oversaw programme management, MRM and BGC oversaw spirometry training and quality control, RDR and JLM advised on statistical aspects, KK oversaw data collection for occupational measures, WSS advised on measurements to aid labour economic analysis, AMT advised on biological sample collection protocols and management, HB contributed to data management for symptomatic normals. APD recruited the General Practices, supervised data collection and conducted the data analysis. APD and PA drafted the manuscript with contribution from REJ. PA had responsibility for the final content. All authors reviewed and approved the final submission.

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Figure 1: Flowchart summarising patient recruitment and assessment for the Birmingham COPD Cohort Study

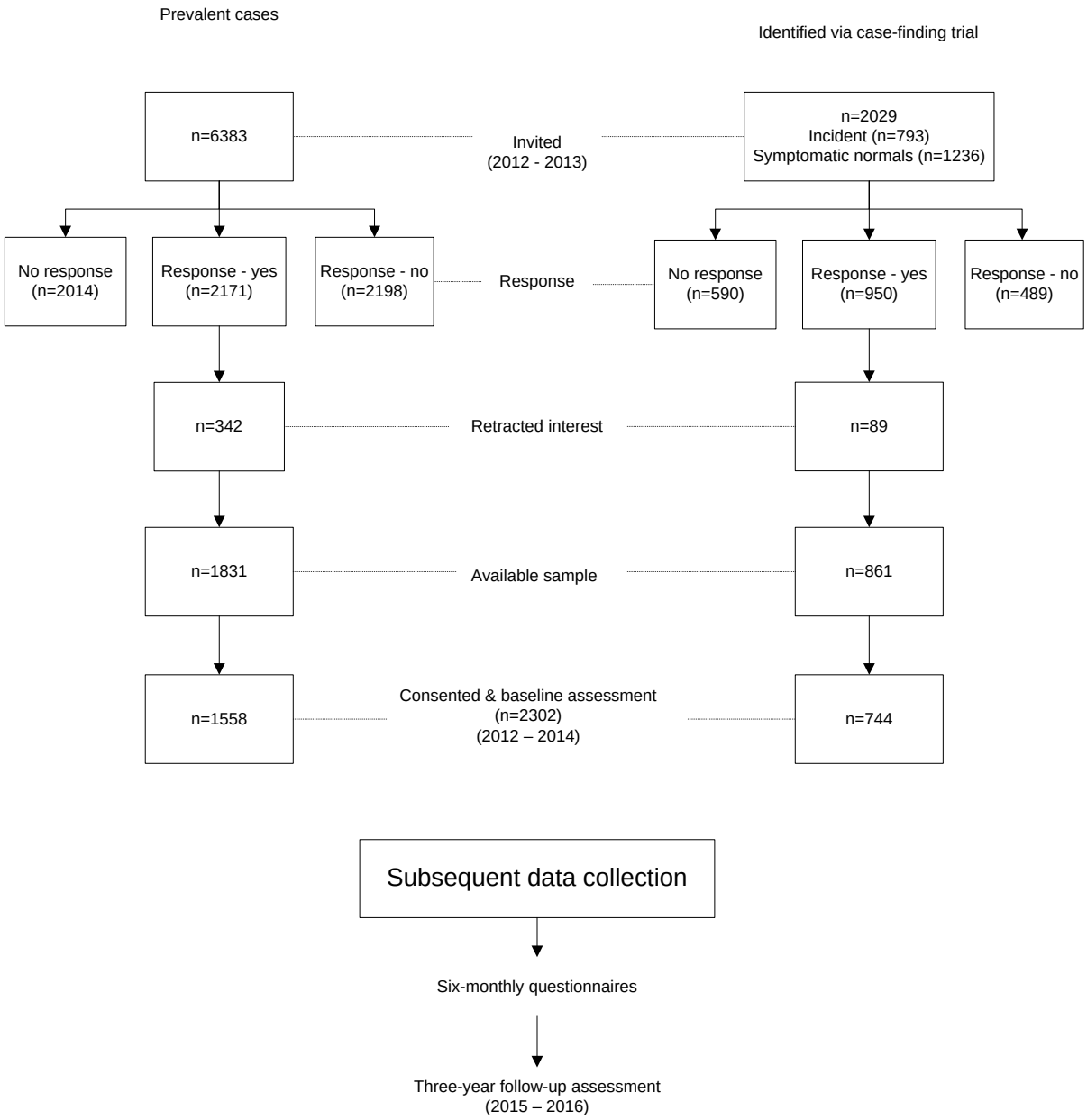

Table 1: Demographic characteristics of cohort participants from primary care records, comparing consented with non-consented patients

	Prevalent cases		**Incident cases & symptomatic normal patients (symptomatic patients identified through case-finding)**	
	Consented participants (n=1558)	**Eligible, not consented (n=4825)**	**Consented participants (n=744)**	**Eligible, not consented (n=1285)**
Age – mean (SD)	69.0 (9.4)	69.8 (11.0)	62.3 (9.6)	59.2 (10.9)
Age categories – n (%)				
40-49yrs	55 (3.5)	212 (4.4)	97 (13.0)	330 (25.7)
50-59yrs	188 (12.1)	721 (14.9)	182 (24.5)	340 (26.5)
60-69yrs	596 (38.3)	1445 (30.0)	273 (36.7)	360 (28.0)
70-79yrs	522 (33.5)	1521 (31.5)	192 (25.8)	255 (19.8)
80-89yrs	191 (12.3)	837 (17.4)	n/a*	n/a*
90yrs+	6 (0.4)	89 (1.8)	n/a*	n/a*
Sex				
Male	959 (61.6)	2415 (50.1)	417 (56.1)	667 (51.9)
Female	599 (38.5)	2410 (50.0)	327 (44.0)	618 (48.1)
Ethnicity				

White British	1120 (71.9)	3287 (68.1)	477 (64.1)	788 (61.3)
Mixed	3 (0.2)	14 (0.3)	5 (0.7)	12 (0.9)
Asian	17 (1.1)	85 (1.8)	23 (3.1)	73 (5.7)
African/Caribbean	5 (0.3)	42 (0.9)	13 (1.8)	32 (2.5)
Other	43 (2.8)	149 (3.1)	4 (0.5)	12 (0.9)
Unclear/missing	370 (23.8)	1248 (25.9)	222 (29.8)	368 (28.6)

* Upper age limit of 79 years due to eligibility for the case-finding trial

Table 2: Baseline self-reported demographics for whole cohort, then split by patient group

	All cohort (n=2302)	**Prevalent (n=1558)**	**Incident (n=331)**	**Symptomatic normal LF (n=413)**
Age – mean (SD)	67.3 (9.9)	69.2 (9.4)	65.3 (8.7)	61.8 (10.0)
Age categories – n (%)				
40-49yrs	128 (5.6)	50 (3.2)	19 (5.7)	59 (14.3)
50-59yrs	362 (15.7)	183 (11.8)	69 (20.9)	110 (26.6)
60-69yrs	851 (37.0)	586 (37.6)	127 (38.4)	138 (33.4)
70-79yrs	749 (32.5)	530 (34.0)	115 (34.7)	104 (25.2)
80-89yrs	206 (9.0)	203 (13.0)	1 (0.3)[††]	2 (0.5)[††]
90yrs+	6 (0.3)	6 (0.4)	-	-
Sex – n (%) male	1379 (59.9)	959 (61.6)	202 (61.0)	218 (52.8)
Ethnicity – n (%)				
White British	2034 (88.4)	1391 (89.3)	291 (87.9)	352 (85.3)
Mixed	13 (0.6)	5 (0.3)	2 (0.6)	6 (1.5)
Asian	53 (2.3)	28 (1.8)	8 (2.4)	17 (4.1)
African/Caribbean	23 (1.0)	10 (0.6)	4 (1.2)	9 (2.2)
Other	1 (0.04)	-	-	1 (0.2)
No clear answer/missing	178 (7.7)	124 (8.0)	26 (7.9)	28 (6.8)
Employment – n (%)				
In work	503 (22.1)	248 (16.1)	98 (30.0)	157 (38.5)
Not in work	1776 (77.9)	1296 (83.9)	229 (70.0)	251 (61.5)
Deprivation quintiles[†] – n (%)				
Quintile 1	569 (24.7)	411 (26.4)	73 (22.1)	85 (20.6)
Quintile 2	581 (25.2)	404 (25.9)	78 (23.6)	99 (24.0)
Quintile 3	450 (19.6)	261 (16.8)	88 (26.6)	101 (24.5)
Quintile 4	389 (16.9)	280 (18.0)	49 (14.8)	60 (14.5)

Quintile 5	313 (13.6)	202 (13.0)	43 (13.0)	68 (16.5)
Smoking status – n (%)				
Current	583 (27.4)	404 (28.3)	103 (33.6)	76 (19.4)
Ex	1276 (60.0)	876 (61.3)	159 (51.8)	241 (61.5)
Never	268 (12.6)	148 (10.4)	45 (14.7)	75 (19.1)

[†]Based on the Index of Multiple Deprivation (IMD) 2010; with higher quintiles indicating less deprivation. Quintiles based on data for the West Midlands, UK

[††]Patients had their 80th birthday between the Cohort invitation and baseline assessment

Table 3: Prognostic and outcome measures

Phase	Measures and example questionnaires
Baseline assessment (2012-2014)	**Spirometry:** pre- and post-bronchodilator, 400µg Salbutamol via large volume spacer **Anthropometry:** height, weight, bioimpedance, arm span, waist/hip/neck circumference **Physiology:** sit-to-stand test, hand grip strength, blood pressure, heart rate, oxygen saturation, breathlessness on exertion (BORG scale) **Blood samples:** DNA, serum and plasma aliquots stored at -80°C **Self-completed questionnaires:** demographics, lifestyle, home environment, HRQoL (e.g. SGRQ-C (55), EQ-5D 5L (56), CAT (57), MRC (58)), general health, exacerbations, health care usage, exercise (IPAQ – short (59)), physician-diagnosed medical conditions (comorbidities), depression (PHQ-9 (60)) **Interviewer-led questionnaire:** current medications, occupational history, presenteeism (SPS-6 (61), WPAI (62))
Six-monthly questionnaires (2012-2015)	**Self-completed questionnaire only:** lifestyle, home environment, HRQoL (e.g. SGRQ-C, EQ-5D 5L, CAT, MRC), general health, exacerbations, health care usage, exercise (IPAQ - short), medical conditions, depression (PHQ-9), medications, occupation, presenteeism (SPS-6)
Follow-up assessment (2015-2016)	**Spirometry:** 400µg Salbutamol via large volume spacer, post-bronchodilator **Anthropometry:** height, weight, bioimpedance, arm span, waist circumference **Physiology:** sit-to-stand test, hand grip strength, oxygen saturation, breathlessness on exertion (BORG scale) **Self-completed questionnaires:** demographics, lifestyle, home environment, HRQoL (e.g. SGRQ-C, EQ-5D 5L, CAT, MRC), general health, exacerbations, health care usage, exercise (IPAQ - short), medical conditions, depression (PHQ-9), medications, occupation
Routine data (2015-2016)	**General Practitioner records:** co-morbidities, test results, referrals, medication **HSCIC data:** deaths and hospital episodes since 2012

HRQoL = health-related quality of life, SGRQ-C = St George's Respiratory Questionnaire-Short, EQ-5D 5L = EuroQol 5 dimensions 5-level version, CAT = COPD Assessment Test, MRC = Medical Research Council Dyspnoea Scale, IPAQ – short = International Physical Activity Questionnaire, PHQ-9 = Patient Health Questionnaire, SPS-6 = Stanford Presenteeism Scale, WPAI = Work Productivity and Activity Impairment Questionnaire, HSCIC = Health and Social Care Information Centre

Table 4: Baseline airway obstruction for whole cohort, then split by patient group

	All cohort (n=2302)	**Prevalent (n=1558)**	**Incident (n=331)**	**Symptomatic normal LF (n=413)**
Airway obstruction – LLN (GLI)	1259 (57.5)	1059 (71.9)	181 (56.7)	19 (4.8)
Airways obstruction – FR	1587 (72.4)	1272 (86.4)	259 (81.2)	56 (14.0)
GOLD stage if <FR – n (%)				
1 (FEV_1 ≥ 80% pred)	515 (32.5)	311 (24.5)	160 (61.8)	44 (78.6)
2 (50-79%)	766 (48.3)	661 (52.0)	94 (36.3)	11 (19.6)
3 (30-49%)	260 (16.4)	254 (20.0)	5 (1.9)	1 (1.8)
4 (<30%)	46 (2.9)	46 (3.6)	-	-

LLN = lower limit of normal, GLI = Global Lungs Initiative, GOLD = Global Initiative for chronic Obstructive Lung Disease, FR = fixed ratio (FEV_1/FVC), FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity
Lower Limit of Normal (LLN) is defined as the lowest 5^{th} percentile of predicted FEV1 values for a healthy population
Fixed Ratio is defined as FEV_1/FVC <0.70

Table 5: Characteristics and health care use of cohort participants at baseline, comparing prevalent, incident and symptomatic normals

	All cohort (n=2302)	**Prevalent (n=1558)**	**Incident (n=331)**	**Symptomatic normal LF (n=413)**	**Adjusted odds ratio (95% CI); p value[¥]**
Chronic cough – n (%) yes	1273 (56.9)	944 (62.4)	157 (48.6)	172 (42.6)	0.53 (0.41, 0.69); <0.001
Chronic phlegm – n (%) yes	978 (43.7)	747 (49.4)	116 (35.9)	115 (28.5)	0.56 (0.43, 0.74); <0.001
Chronic cough / chronic phlegm – n (%) yes	1340 (59.9)	991 (65.5)	167 (51.7)	182 (45.1)	0.53 (0.40, 0.69); <0.001
Wheeze – n (%) yes	1490 (66.7)	1111 (73.5)	194 (60.1)	185 (46.3)	0.50 (0.38, 0.66); <0.001
MRC dyspnoea – n (%)					0.42 (0.32, 0.55); <0.001
Grade 1-2	1013 (46.8)	551 (37.8)	206 (64.8)	256 (65.6)	
Grade 3-5	1154 (53.2)	908 (62.2)	112 (35.2)	134 (34.4)	
Asthma – n (%) yes	881 (39.9)	617 (46.0)	87 (28.8)	107 (27.5)	0.40 (0.30, 0.54); <0.001
Cardiovascular disease – n (%) yes	1239 (59.2)	871 (62.5)	171 (55.2)	197 (50.8)	0.93 (0.71, 1.23); 0.62
Co-morbidities – n (%)					0.90 (0.67, 1.20); 0.46[α]
None	598 (26.0)	401 (25.7)	92 (27.8)	105 (25.4)	
1	767 (33.3)	511 (32.8)	114 (34.4)	142 (34.4)	
2	558 (24.2)	370 (23.8)	81 (24.5)	107 (25.9)	
3 or more	379 (16.5)	276 (17.7)	44 (13.3)	59 (14.3)	

Exacerbations – n (%)					0.25 (0.19, 0.34); <0.001[α]
None	1126 (52.0)	574 (39.4)	234 (74.5)	318 (81.1)	
1	377 (17.4)	293 (20.1)	45 (14.3)	39 (10.0)	
2	305 (14.1)	262 (18.0)	21 (6.7)	22 (5.6)	
3 or more	356 (16.5)	329 (22.6)	14 (4.5)	13 (3.3)	
Weight status – n (%)					0.95 (0.45, 20.2); 0.89[α]
Underweight (BMI<20)	90 (4.2)	76 (5.1)	9 (3.1)	5 (1.3)	
Healthy (20-25)	465 (21.5)	346 (23.2)	62 (21.3)	57 (15.0)	
Overweight (25-30)	823 (38.1)	571 (38.3)	111 (38.1)	141 (37.2)	
Obese (30+)	784 (36.3)	499 (33.5)	109 (37.5)	176 (46.4)	
BODE[††] score – n (%)					0.44 (0.32, 0.60); <0.001[α]
0-2	732 (44.2)	361 (32.4)	158 (66.1)	213 (70.3)	
3-4	480 (29.0)	356 (31.9)	65 (27.2)	59 (19.5)	
5-6	297 (17.9)	252 (22.6)	16 (6.7)	29 (9.6)	
7-10	148 (8.9)	146 (13.1)	-	2 (0.7)	
All-cause hospitalisations in previous 12 months – n (%) yes	315 (14.7)	251 (17.4)	29 (9.3)	35 (8.9)	0.64 (0.42, 0.99); <0.05
Respiratory hospitalisations in	114 (5.3)	103 (7.0)	3 (1.0)	8 (2.0)	0.24 (0.07, 0.77); <0.05

previous 12 months – n (%) yes					
	All cohort (n=2302)	**Prevalent (n=1558)**	**Incident (n=331)**	**Symptomatic normal LF (n=413)**	**Adjusted mean difference (95% CI); p value[¥]**
CAT score – mean (SD)	18.0 (8.8)	20.0 (8.8)	14.4 (7.41)	14.1 (7.7)	-4.5 (-5.74, -3.30); <0.001
EQ-5D 5L score – mean (SD)	0.72 (0.2)	0.69 (0.2)	0.78 (0.2)	0.75 (0.2)	0.07 (0.04, 0.10); <0.001
Sit-to-Stand test – mean (SD)	19.3 (6.8)	18.0 (6.1)	21.6 (6.9)	21.9 (7.8)	2.3 (1.49, 3.20); <0.001

[††] Calculated using sit-to-stand rather than 6-minute walk, due to space restrictions within GP surgeries

[¥] Regression models compared prevalent and incident cases only, adjusting for sex, age, smoking status and disease severity

[α] Dependent variable treated as binary outcome (co-morbidities = none / 1 or more, exacerbations = none / 1 or more, weight status = underweight/not underweight, BODE = 0-2 / 3-10)