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Prognostic value of first-recorded breathlessness for future chronic respiratory and heart disease:

a cohort study using a UK national primary care database

Abstract

Background
Breathlessness is a common presentation in primary care.

Aim
To assess the long-term risk of diagnosed chronic obstructive pulmonary disease (COPD), asthma, ischaemic heart disease (IHD), and early mortality in patients with undiagnosed breathlessness.

Design and setting
Matched cohort study using data from the UK Clinical Practice Research Datalink.

Method
Adults with first-recorded breathlessness between 1997 and 2010 and no prior diagnostic or prescription record for IHD or a respiratory disease ('exposed' cohort) were matched to individuals with no record of breathlessness ('unexposed' cohort). Analyses were adjusted for sociodemographic and comorbidity characteristics.

Results
In total, 75 698 patients (the exposed cohort) were followed for a median of 6.1 years, and more than one-third subsequently received a diagnosis of COPD, asthma, or IHD. In those who remained undiagnosed after 6 months, there were increased long-term risks of all three diagnoses compared with those in the unexposed cohort. Adjusted hazard ratios for COPD ranged from 8.6 (95% confidence interval [CI] = 6.8 to 11.0) for >6–12 months after the index date to 2.8 (95% CI = 2.6 to 3.0) for >36 months after the index date; asthma, 11.7 (CI = 9.4 to 14.6) to 4.3 (CI = 3.9 to 4.6); and IHD, 3.0 (CI = 2.7 to 3.4) to 1.6 (CI = 1.5 to 1.7). Risk of a longer time to diagnosis remained higher in members of the exposed cohort who had no relevant prescription in the first 6 months; approximately half of all future diagnoses were made for such patients. Risk of early mortality (all cause and disease specific) was higher in members of the exposed cohort.

Conclusion
Breathlessness can be an indicator of developing COPD, asthma, and IHD, and is associated with early mortality. With careful assessment, appropriate intervention, and proactive follow-up and monitoring, there is the potential to improve identification at first presentation in primary care in those at high risk of future disease who present with this symptom.

Keywords
asthma; dyspnoea; electronic health records; general practice; heart disease; respiratory disease.

INTRODUCTION

Early diagnosis of chronic disease, with the possibility of early intervention, could deliver significant health benefits.[1–5] As examples, early recognition of chronic obstructive pulmonary disease (COPD) and intervention with smoking cessation could have major health benefits for the patient,[6–8] while timely intervention with appropriate medication in asthma alleviates symptoms and reduces emergency admissions in adolescents and adults.[9]

In UK primary care, health problems, including disease labels, are generally recorded using Read codes.[10] Primary care clinicians may record a symptom in medical records at a patient's first presentation if they are unsure of the underlying diagnosis or believe that the symptom represents a minor or self-limiting illness. The act of labelling a consultation with a symptom, rather than with the underlying (unknown) diagnosis, may affect the management and outcome of that patient. The use of a diagnostic record may flag up specific management strategies; for example, coding a patient as having heart failure or ischaemic heart disease (IHD) will mean clinicians are likely to initiate specific treatments and review patients in line with single-disease guidelines, and, in England, the Quality and Outcomes Framework (http://content.digital.nhs.uk/qof). However, early labelling of a disease may also lead to 'overdiagnosis' of disease in patients with symptoms that will resolve and, as such, may result in overinvestigation or overtreatment.

Breathlessness is a common respiratory symptom, but it may be an early indication of a chronic disease, such as COPD, asthma, or IHD. These are major public health concerns that have a substantial impact on quality of life and early mortality risk. It is not known what happens to those patients who present with initial breathlessness in primary care but are not given a diagnostic label for their symptom. The objectives of this study were to assess long-term risk of diagnosed COPD, asthma, and IHD, along with all-cause and disease-specific mortality, in patients with a newly recorded symptom in primary care of breathlessness, compared with patients without such a symptom.

METHOD

Database

This cohort study used data from the Clinical Practice Research Datalink (CPRD) service.[11] Diagnoses recorded by CPRD have been validated for a wide range of diseases, including respiratory and circulatory conditions.[12,13] For this study, included practices (n = 360), all from England, were those with links to the Hospital Episode Statistics (HES) database

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How this fits in

To the authors' knowledge, no study has yet identified what happens to patients who present with initial breathlessness in primary care but are not given a diagnostic label for their symptom. This study shows that the future disease burden of chronic obstructive pulmonary disease (COPD), asthma, and ischaemic heart disease (IHD) is high, and risk of early mortality is increased in patients presenting with undiagnosed breathlessness. In those who receive no relevant prescription in the first 6 months post-initial consultation, the increased risk of future diagnoses of COPD, asthma, and IHD remains; this may represent a missed opportunity for early management. These findings suggest a potential for more detailed investigation, monitoring, and early intervention among patients presenting with breathlessness; future studies need to establish whether this is feasible and cost-effective, and how to identify which patients would benefit.

and data on hospital inpatient information, neighbourhood deprivation (Index of Multiple Deprivation 2010 [IMD2010]), and mortality (via the Office for National Statistics [ONS]). Similar characteristics regarding patient demographics, years of follow-up, and prescribing behaviour have been shown in practices with and without such linkages.[14]

Study population

All individuals aged ≥18 years, whose first coded record of a breathlessness symptom was made between 1997 and 2010, were defined as being in the 'exposed' cohort. Prior to their first recorded code for breathlessness, patients included in this cohort had no diagnostic record of COPD, asthma, IHD, or other respiratory disease. Furthermore, patients had no prescription record of medications for COPD, asthma, or IHD in the 2 years prior to the first breathlessness symptom being recorded. The date of the first coded breathlessness symptom was defined as the index date.

Members of the 'unexposed' cohort were matched to individuals in the exposed cohort 1:1 by year of birth, sex, and practice. Individuals in the unexposed cohort had:

- no prior recorded breathlessness symptom;
- no prior diagnosis of COPD, asthma, IHD, or other respiratory disease; and
- no prescription record of medications for COPD, asthma, or IHD for the 2 years prior to the index date of their matched patient from the exposed cohort.

Those in the unexposed cohort were given the same index date as their matched exposed cohort patient.

The matched cohorts were followed from the index date until 31 March 2014 or the date they no longer contributed to CPRD (for example, because of death, leaving the practice, or the practice leaving CPRD), whichever was earlier.

Outcomes

New diagnoses of COPD, asthma, and IHD were defined as the first recording of these conditions in either CPRD or the linked hospital inpatient data in the follow-up period; each was analysed separately so that a patient could have multiple outcomes. COPD, asthma, and IHD (including heart failure) were identified using Read codes that were mapped to *International Classification of Diseases (10th revision)*[15] codes in the linked HES dataset to enable outcome identification from inpatient hospital information as well as primary care. Read codes used are available at https://www.keele.ac.uk/mrr following registration.

Mortality information, including date and cause, was obtained from the linked ONS data. COPD- and IHD-related mortality, as well as all-cause mortality, were determined. Asthma-related mortality was not studied because of its rarity.

Covariates

Covariates thought to be potentially related to both the recording of exposure symptoms and outcomes were:

- year of index date;
- age;
- sex;
- geographical region;
- smoking status;
- alcohol consumption;
- body mass index (BMI);
- level of neighbourhood deprivation;
- other recorded respiratory symptoms (cough, sputum);
- recorded inflammatory conditions (rheumatoid arthritis, gout, polymyalgia rheumatica, inflammatory bowel disease, systemic lupus erythematosus, spondyloarthritis);
- common mental health disorders (depression, anxiety);
- diabetes;
- non-specific chest pain;

- musculoskeletal pain; and
- total number of comorbid conditions.

Smoking and alcohol information were classified as 'ever smoked/drunk alcohol', 'never', or 'missing', based on data recorded prior to the index date. The 'missing' category was included to maximise the numbers in the analysis. The BMI value used was the most recent record before index date and was grouped into '<25 kg/m^2', '≥25 kg/m^2' (overweight), or 'missing'. Neighbourhood deprivation level was calculated using the IMD 2010, a weighted measure of deprivation across seven domains for geographical areas (income deprivation; employment deprivation; education, skills, and training deprivation; health deprivation and disability; crime; barriers to housing and services; and living environment deprivation);[16] this was categorised based on quintile score (1 = least deprived, 5 = most deprived).

Cough, sputum, and specific comorbidities were defined through Read codes extracted from patients' consultation records in the 2-year period prior to the index date. The total number of prescriptions for drugs recorded under different sections of the *British National Formulary*[17] in the 2-year period prior to the index date was used as a surrogate measure of the number of comorbid conditions at baseline; this has been shown to be as predictive of health outcomes as more complicated comorbidity measures.[18]

Primary care management

As a measure of primary care management, prescribed medications for COPD, asthma, and IHD in the first 6 months after the index date (and before any relevant diagnosis) were identified. A 6-month period was thought to be a sufficient timeframe to ensure that a diagnosis resulting from the initial symptom presentation found its way into the record; this allowed for relevant investigations to be undertaken. Medications relevant to COPD, asthma, and IHD were identified via consensus of two researchers who are academic primary care physicians. Two lists were compiled:

- drugs used only for the management of COPD, asthma, or IHD (the narrow list); and
- drugs used for COPD, asthma, or IHD and possibly used in other conditions (the broad list).

It was not possible to determine separate medication lists for COPD and asthma as these conditions often coexist in the same patient.[19,20] When identifying the study cohorts, the narrow list was used to exclude individuals whose records indicated evidence of COPD, asthma, or IHD before the index date. The broad list was used to determine whether patients in the exposed cohort received medications relevant to COPD, asthma, or IHD after the index date; as such, the broad list generates a conservative estimate of patients who did not receive any relevant management. Medication lists are available at https://www.keele.ac.uk/mrr following registration.

Statistical analysis

The rates of new diagnoses of COPD, asthma, and IHD, and all-cause and disease-specific mortality per 10 000 person-years at risk, were determined in both the exposed and unexposed cohorts, stratified by time from the index date.

The first 6 months after the index date were defined as the diagnostic window. The risk of future diagnosis was expected to vary by length of time from the index date, and so the follow-up time from >6 months onwards was split into three periods:

- >6–12 months;
- >12–36 months; and
- >36 months after index date in those with no diagnosis by the start of the relevant period.

Cox proportional-hazards regression was used to produce both unadjusted and adjusted hazard ratios (HRs) for each of the three disease outcomes separately, estimating the excess risk of each outcome diagnosis associated with a first presentation of the symptom of breathlessness. The validity of the proportional-hazards assumption was tested using Schoenfeld residuals and deemed adequate for the exposure variable. In the final models, all covariates were included as confounding factors for adjustment. The authors also stratified by age, sex, and smoking status (as smoking is a major risk factor for the symptom and disease outcomes) as a sensitivity analysis.

Within the exposed cohort, patients who received a relevant prescription in the first 6 months after the index date (and before the date of relevant diagnosis, if any) were ascertained. All models were repeated to assess the risk of long-term diagnosis for those without any initial relevant prescription or diagnosis in the first 6 months compared with those in the unexposed cohort.

The risks of early all-cause mortality between the exposed and unexposed cohorts were compared using Cox regression models, with diagnosis (the earliest diagnosis of COPD, asthma, or IHD) treated as a time-varying covariate. The risks of future disease-specific (COPD or IHD) mortality were assessed using competing risk models with death from other causes as competing events.

All analyses were performed using Stata (version 14.2).

Patient and public involvement

Members from the North Staffordshire Breathe Easy support group were invited to join a patient advisory group. At the first meeting, the research questions and study design were discussed; at the second and third meetings, views on the meaning of the results were sought, particularly how the results related to their own experiences, and to obtain advice on dissemination of the findings.

Table 1. Study population demographic and clinical characteristics at baseline

	Exposed[a] cohort	Unexposed[b] cohort	*P*-value[c]
Patients, *n*[d]	75 698	75 698	—
Year of index date, median (IQR)[d]	2005 (2001–2007)	2005 (2001–2007)	—
Age, years, *n* (%)[d]			—
18–44	16 668 (22.0)	16 668 (22.0)	
45–59	20 356 (26.9)	20 356 (26.9)	
60–74	23 813 (31.5)	23 813 (31.5)	
≥75	14 861 (19.6)	14 861 (19.6)	
Male, *n* (%)[d]	32 195 (42.5)	32 195 (42.5)	—
Geographical region, *n* (%)[d]			—
London	6154 (8.1)	6154 (8.1)	
South of England	19 592 (25.9)	19 592 (25.9)	
Midlands and East of England	24 219 (32.0)	24 219 (32.0)	
North of England	25 733 (34.0)	25 733 (34.0)	
Smoking status, *n* (%)			<0.001
Non-smoker	40 436 (53.4)	42 632 (56.3)	
Smoker, ever	24 740 (32.7)	19 143 (25.3)	
Unknown	10 522 (13.9)	13 923 (18.4)	
Alcohol consumption, *n* (%)			<0.001
Non-drinker	8623 (11.4)	7425 (9.8)	
Drinker, ever	54 991 (72.7)	52 197 (69.0)	
Unknown	12 084 (16.0)	16 076 (21.2)	
BMI, *n* (%)			<0.001
<25 kg/m^2	23 901 (31.6)	27 054 (35.7)	
≥25 kg/m^2	39 854 (52.6)	32 194 (42.5)	
Unknown	11 943 (15.8)	16 450 (21.7)	
Deprivation-level quintile, *n* (%)			<0.001
1 (least)	17 008 (22.5)	18 231 (24.1)	
2	18 123 (23.9)	19 043 (25.2)	
3	15 810 (20.9)	15 644 (20.7)	
4	13 508 (17.8)	12 772 (16.9)	
5 (most)	11 163 (14.7)	9929 (13.1)	
Unknown	86 (0.1)	79 (0.1)	
Number of comorbidities, median (IQR)	6 (3–11)	3 (1–7)	<0.001

*[a]Patients with recorded breathlessness. [b]Patients without recorded breathlessness. [c]*P*-value obtained from χ^2 or from Mann–Whitney U test as appropriate, and, where applicable, analysis excluded unknown category (missing data). [d]Unexposed cohort matched. BMI = body mass index. IQR = interquartile range.*

RESULTS

Baseline characteristics

There were 75 698 patients included in each of the exposed and unexposed cohorts (43% male; median age 60 years, interquartile range [IQR] 46–72 years). The median follow-up times were 6.1 years (IQR 3.5–9.4 years) and 6.5 years (IQR 3.9–9.7 years) in the exposed and unexposed cohorts, respectively. Characteristics of the two cohorts are given in Table 1. Data for individual comorbidities are outlined in Supplementary Table S1.

Risk of COPD, asthma, and IHD diagnosis

During the whole follow-up period, 35.4% of patients in the exposed cohort were diagnosed with at least one of COPD, asthma, or IHD; this figure was 10.4% in the unexposed cohort (Supplementary Table S2). Kaplan–Meier curves in Figure 1 show the higher rates of COPD, asthma, and IHD diagnoses during the follow-up period in the exposed cohort compared with those in the unexposed cohort.

In total, of the exposed cohort, 3.9% received a diagnosis of COPD, 5.9% asthma, and 5.9% IHD in the initial 6 months (diagnostic window). Between 0.1% and 0.4% of the unexposed cohort received one of these diagnoses in this 6-month period (Table 2). In the long term (>6 months), incidence of COPD in the exposed cohort was 139.0 per 10 000 person-years; 168.4 per 10 000 person-years (asthma); and 203.0 per 10 000 person-years (IHD). In the unexposed cohort, incidence was 37.4 per 10 000 person-years (COPD), 26.8 per 10 000 person-years (asthma), and 107.0 per 10 000 person-years (IHD) (Table 2).

Long-term excess risk of all three diagnoses for those in the exposed cohort was evident; this reduced over time but remained statistically significant. For COPD, the adjusted HR ranged from 8.6 (95% confidence interval [CI] = 6.8 to 11.0) for >6–12 months after the index date to 2.8 (95% CI = 2.6 to 3.0) for >36 months after the index date (Table 2). The adjusted HR for asthma ranged from 11.7 (95% CI = 9.4 to 14.6) for >6–12 months to 4.3 (95% CI = 3.9 to 4.6) for >36 months; for IHD, adjusted HR ranged from 3.0 (95% CI = 2.7 to 3.4) for >6–12 months to 1.6 (95% CI = 1.5 to 1.7) for >36 months (Table 2).

Figure 1. Kaplan–Meier curves for time to first diagnosis of COPD, asthma, and IHD for the exposed[a] and unexposed[b] cohorts. Kaplan–Meier curves truncated at 12 years.[c] [a]Patients with recorded breathlessness. [b]Patients without recorded breathlessness. [c]At least 6 months' follow-up was available for 93% of patients and 12% of patients had the full 12 years of follow-up (maximum follow-up time, 18 years). COPD = chronic obstructive pulmonary disease. IHD = ischaemic heart disease.

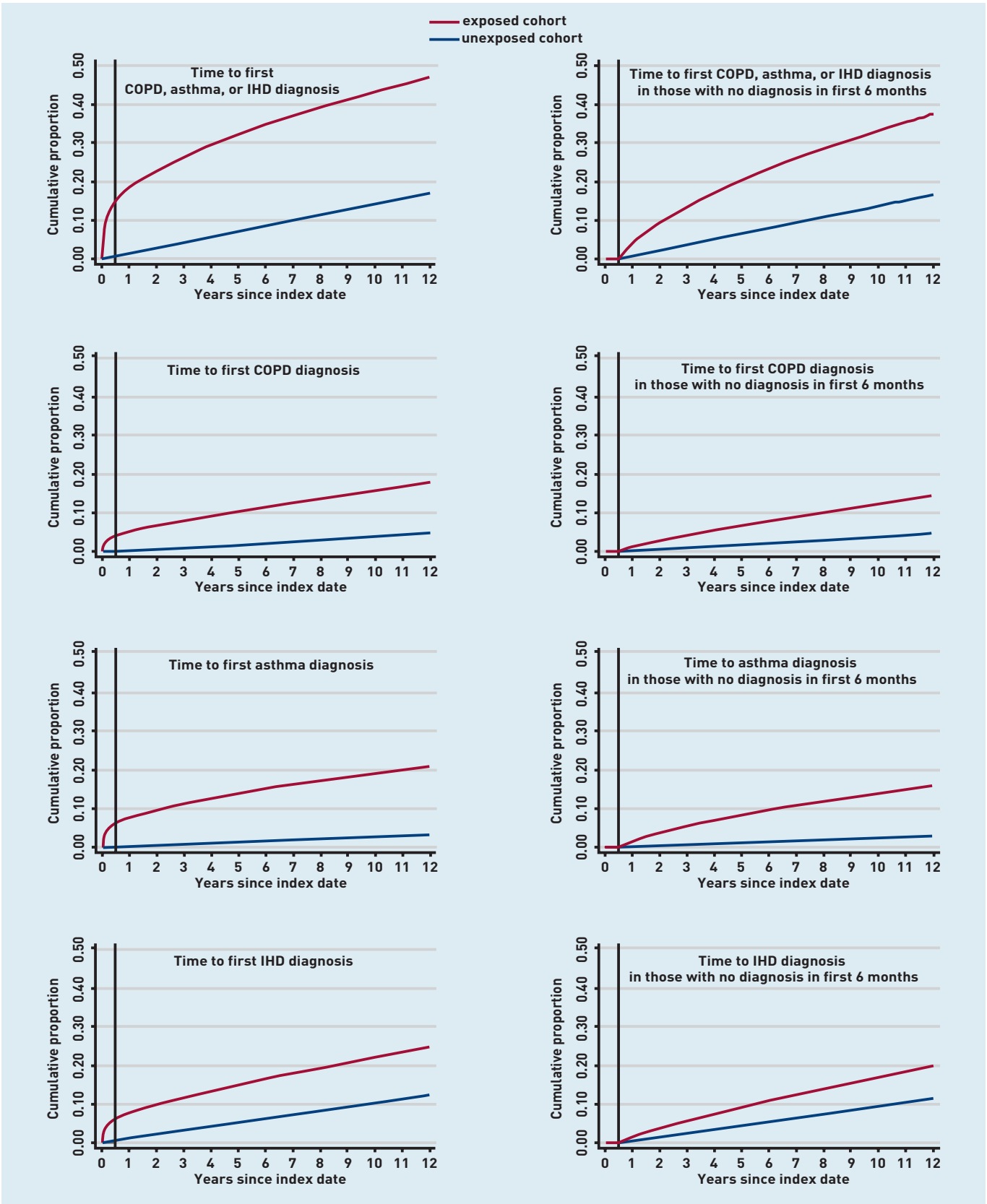

Table 2. Incidence of future diagnosis of COPD, asthma, or IHD in exposed[a] and unexposed[b] matched cohorts

	Exposed cohort, *n* = 75 698			Unexposed matched cohort, *n* = 75 698			
Time period	Patients with diagnosis, *n* (%)[c]	Time at risk, person-years	Incidence per 10 000 person-years	Patients with diagnosis, *n* (%)[c]	Time at risk, person-years	Incidence per 10 000 person-years	Exposed versus adjusted[d] unexposed, HR (95% CI)
COPD							
Diagnostic window (0–6 months)	2970 (3.9)	35 349.8	840.2	72 (0.1)	37 188.2	19.4	—
Long-term follow-up (>6 months)	6141 (8.1)	441 810.8	139.0	1883 (2.5)	503 290.6	37.4	—
>6–12 months	685 (0.9)	33 467.6	204.7	80 (0.1)	36 235.7	22.1	8.6 (6.8 to 11.0)
>12–36 months	1835 (2.4)	120 124.0	152.8	364 (0.5)	133 356.3	27.3	5.3 (4.7 to 6.0)
>36 months	3621 (4.8)	288 219.2	125.6	1439 (1.9)	333 698.6	43.1	2.8 (2.6 to 3.0)
Asthma							
Diagnostic window (0–6 months)	4430 (5.9)	34 759.7	1274.5	80 (0.1)	37 184.6	21.5	—
Long-term follow-up (>6 months)	6925 (9.1)	411 223.4	168.4	1347 (1.8)	502 628.2	26.8	—
>6–12 months	1032 (1.4)	32 539.8	317.2	89 (0.1)	36 226.2	24.6	11.7 (9.4 to 14.6)
>12–36 months	2335 (3.1)	115 176.6	202.7	347 (0.5)	133 251.3	26.0	6.8 (6.0 to 7.6)
>36 months	3558 (4.7)	263 507.0	135.0	911 (1.2)	333 150.7	27.3	4.3 (3.9 to 4.6)
IHD							
Diagnostic window (0–6 months)	4430 (5.9)	34 964.4	1267.0	338 (0.4)	37 131.6	91.0	—
Long-term follow-up (>6 months)	8680 (11.5)	427 498.9	203.0	5240 (6.9)	489 700.3	107.0	—
>6–12 months	1115 (1.5)	32 864.5	339.3	386 (0.5)	36 068.3	107.0	3.0 (2.7 to 3.4)
>12–36 months	2562 (3.4)	117 374.1	218.3	1390 (1.8)	131 714.2	105.5	1.9 (1.8 to 2.1)
>36 months	5003 (6.6)	277 260.3	180.4	3464 (4.6)	321 917.8	107.6	1.6 (1.5 to 1.7)

[a] Patients with recorded breathlessness. [b] Patients without recorded breathlessness. [c] Percentage of total number of patients in exposed/unexposed matched cohort. [d] Adjusted HR, adjusted for index year; age; sex; region; smoker, ever; alcohol drinker, ever; BMI; deprivation level; comorbidity; cough and sputum; inflammatory conditions; depression and anxiety; diabetes; non-specific chest pain; musculoskeletal pain. BMI = body mass index. COPD = chronic obstructive pulmonary disease. HR = hazard ratio. IHD = ischaemic heart disease.

In stratified analyses, the increased risk of a future diagnosis of COPD, asthma, or IHD in the exposed cohort was apparent, regardless of age, sex, or smoking status; however, it was greater in those aged <60 years (see Supplementary Tables S3–S5).

Risk of diagnosis in those with no management in initial 6 months

In the first 6 months after the index date (and before any relevant diagnosis), 34.6% of the exposed cohort received COPD/asthma medication, and 34.1% received IHD medication (Table 3). In those who received a COPD diagnosis at any time during follow-up, 52.8% received a relevant prescription in the first 6 months and prior to a diagnosis, compared with 31.9% in those without a COPD diagnosis; these rates were 71.2% versus 28.3% for asthma, and 56.1% versus 29.5% for IHD (Table 3).

Patients who received no relevant prescribing in the first 6 months after the index date still had an increased long-term

Table 3. Prescription in first 6 months after index date in exposed cohort patients

	COPD		Asthma		IHD	
Medication prescribed[b]	Patients, *n*	Who received prescription[a] in first 6 months, *n* (%)	Patients, *n*	Who received prescription[a] in first 6 months, *n* (%)	Patients, *n*	Who received prescription[a] in first 6 months, *n* (%)
In whole cohort	75 698	26 055 (34.4)	75 698	26 313 (34.8)	75 698	25 828 (34.1)
In those who received a diagnosis[c]	9111	4810 (52.8)	11 355	8080 (71.2)	13 110	7360 (56.1)
0–6 months	2970	1969 (66.3)	4430	3918 (88.4)	4430	2398 (54.1)
>6–12 months	685	390 (56.9)	1032	784 (76.0)	1115	744 (66.7)
>12–36 months	1835	878 (47.8)	2335	1511 (64.7)	2562	1591 (62.1)
>36 months	3621	1573 (43.4)	3558	1867 (52.5)	5003	2627 (52.5)
In those did not receive a diagnosis[c]	66 587	21 245 (31.9)	64 343	18 233 (28.3)	62 588	18 468 (29.5)

[a] Before the date of diagnosis if diagnosis occurred within first 6 months (pre-diagnosis prescription). [b] COPD/asthma-related medications regarding COPD and asthma; and IHD-related medications regarding IHD. [c] Diagnosis during the follow-up period. COPD = chronic obstructive pulmonary disease. IHD = ischaemic heart disease.

Table 4. Risk of future diagnosis of COPD, asthma, and IHD in patients with a coded record of breathlessness symptom, stratified by prescription management

Time period	Patient group[a]	COPD Adjusted[b] HR (95% CI)	Asthma Adjusted[b] HR (95% CI)	IHD Adjusted[b] HR (95% CI)
>6–12 months	A	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
	B	5.6 (4.3 to 7.2)	4.4 (3.5 to 5.7)	2.0 (1.8 to 2.4)
	C	16.9 (13.1 to 21.7)	29.0 (23.1 to 36.3)	4.1 (3.6 to 4.7)
>12–36 months	A	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
	B	4.0 (3.6 to 4.6)	3.7 (3.2 to 4.2)	1.5 (1.4 to 1.6)
	C	8.8 (7.7 to 10.0)	14.6 (12.9 to 16.5)	2.4 (2.2 to 2.6)
>36 months	A	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
	B	2.3 (2.1 to 2.5)	3.0 (2.7 to 3.2)	1.4 (1.3 to 1.4)
	C	4.1 (3.8 to 4.4)	7.7 (7.1 to 8.4)	2.0 (1.9 to 2.1)

[a]Patient groups: A = matched unexposed cohort; B = patients with a first coded record of breathlessness symptom, and no relevant prescribing in first 6 months after index date and before diagnosis (if any); C = patients with a first coded record of breathlessness symptom and relevant prescribing in first 6 months after index date and before diagnosis (if any). Size of patient groups: A (n = 75 698); B (COPD, n = 49 643; asthma, n = 49 385; IHD, n = 49 870); C (COPD, n= 26 055; asthma, n = 26 313; IHD, n = 25 828). [b]Adjusted for: index year; age; sex; region; smoker, ever; alcohol drinker, ever; BMI; deprivation level; comorbidity; cough and sputum; inflammatory conditions; depression and anxiety; diabetes; non-specific chest pain; musculoskeletal pain. BMI = body mass index. COPD = chronic obstructive pulmonary disease. HR = hazard ratio. IHD = ischaemic heart disease.

risk for all three diagnoses compared with the unexposed cohort, although the risk was lower than for those who had been prescribed relevant medication (Table 4). This group of patients consisted of 53.7% of all those subsequently diagnosed with COPD during the long term (>6 months) follow-up; for those subsequently diagnosed with asthma and IHD, the rates were 39.9% and 42.8%, respectively (Table 3).

Risk of all-cause and disease-specific mortality

During the whole follow-up period, higher rates of all-cause mortality (288.5 per 10 000 person-years), COPD-related mortality (22.2 per 10 000 person-years), and IHD-related mortality (69.3 per 10 000 person-years) were observed in the exposed cohort compared with the unexposed cohort (all-cause mortality 154.8 per 10 000 person-years, COPD-related mortality 3.9 per 10 000 person-years, IHD-related mortality 32.2 per 10 000 person-years) (Table 5).

In the long-term (>6 months), patients with an initial recorded symptom of breathlessness had increased excess risk of all-cause mortality (adjusted HR 1.2, 95% CI = 1.1 to 1.3), COPD-related mortality (adjusted HR 1.8, 95% CI = 1.5 to 2.1), and IHD-related mortality (adjusted HR 1.2, 95% CI = 1.1 to 1.3), even after adjustment for a later diagnosis (Table 5).

The increased risk of mortality with breathlessness was apparent regardless of age (see Supplementary Table S6).

Sensitivity analysis

Repeating analyses excluding patients with missing data on covariates gave similar results (data not shown).

DISCUSSION

Summary

This study of over 150 000 primary care patients showed an increased long-term risk of COPD, asthma, and IHD diagnosis, and of early mortality among patients

Table 5. Risk of mortality in patients in the exposed[a] and unexposed[b] cohorts

		Exposed cohort			Unexposed matched cohort			Exposed versus unexposed
	Time period, months	Events, *n* (%)	Time at risk, person-years	Incidence per 10 000 person-years	Events, *n* (%)	Time at risk, person-years	Incidence per 10 000 person-years	Adjusted[c] HR[e] (95% CI)
All-cause	0–6	3119 (4.1)	35 962.2	867.3	423 (0.6)	36 801.9	114.9	6.0 (5.4 to 6.7)
	>6	11 251 (14.9)	462 060.6	243.5	7726 (10.2)	489 616.9	157.8	1.2 (1.1 to 1.3)
COPD-related	0–6	78 (0.1)	35 962.2	21.7	5 (0.0)	36 801.9	1.4	11.5 (4.5 to 28.9)
	>6	1030 (1.4)	462 060.6	22.3	198 (0.3)	489 616.9	4.0	1.8 (1.5 to 2.1)
IHD-related	0–6	452 (0.6)	35 962.2	125.7	70 (0.1)	36 801.9	19.0	4.7 (3.6 to 6.2)
	>6	2999 (4.0)	462 060.6	64.9	1625 (2.1)	489 616.9	33.2	1.2 (1.1 to 1.3)

[a]Patients with recorded breathlessness. [b]Patients without recorded breathlessness. [c]Adjusted for: index year; age; sex; region; smoker, ever; alcohol drinker, ever; BMI; deprivation level; comorbidity; cough and sputum; inflammatory conditions; depression and anxiety; diabetes; non-specific chest pain; musculoskeletal pain; later diagnosis. Later diagnosis as a time-varying covariate: for all-cause mortality, later diagnosis is the earliest diagnosis of asthma, COPD, or IHD. [e]Sub-distribution HR was used in completing risk models for disease-specific mortality (other death was treated as competing events) and in Cox models for all-cause mortality. BMI = body mass index. COPD = chronic obstructive pulmonary disease. HR = hazard ratio. IHD = ischaemic heart disease.

presenting with an initially undiagnosed symptom of breathlessness. Over a median of 6.1 years, more than one-third of these patients subsequently received a diagnosis of COPD, asthma, or IHD.

The high risk of diagnoses in the first 6 months is likely to reflect the fact that the diagnostic period from the initial presentation of breathlessness allowed time for tests and the monitoring of symptoms. However, the majority of patients who received a diagnosis of COPD, asthma, or IHD did so after this 6-month period, which may imply a delay in diagnosis. The higher long-term risks of a subsequent diagnosis of COPD, asthma, or IHD and of mortality suggest the important prognostic value of this symptom, with 1 in 10 patients receiving a diagnosis >3 years after their initial symptom presentation.

In the first 6 months after presenting with an undiagnosed breathlessness symptom, over one-third of patients received medications related to COPD/asthma and one-third IHD medications; this might suggest that their GP was considering a diagnosis of a more serious illness but had not coded this. However, in those who received no relevant prescription in the first 6 months, there remained an increased risk of future diagnosis of COPD, asthma, or IHD, and approximately half of all future diagnoses were made in such patients. This implies the possibility of a missed opportunity for more investigation of symptom causation and earlier initiation of treatment for COPD, asthma, and IHD.

Breathlessness symptom was associated with all-cause, COPD-related, and IHD-related mortality in the short and long term. All-cause mortality in the first 6 months after initial breathlessness symptom was particularly high and it is possible the symptom may have been related to an underlying terminal disease. However, there were also increased long-term risks (>6 months) for disease-specific mortality, which remained after adjustment for later diagnosis; this indicates that, in addition to being a marker of underlying diseases such as COPD, asthma, and IHD, breathlessness remains an independent marker of long-term mortality risk.

Strengths and limitations

A strength of this study is that it used a large primary care database (CPRD) with previous validation of the identification of recording of COPD.[21] The diagnosis recorded is that believed by the GP to be accurate at that time.

Breathlessness symptoms recorded in the consultation free text were not included, which could be seen as a limitation, although it is likely that those patients for whom a coded symptom was documented were those with more troublesome symptoms of breathlessness and those without an obvious reason for the symptom. However, it must be acknowledged that the free text of a consultation may have given further indication around symptom severity and potential diagnosis. No attempt was made to grade the severity of breathlessness.

Although the diagnoses of COPD, asthma, and IHD are likely to be based on a combination of symptoms, this study aimed to consider the prognostic value of breathlessness specifically. As such, the authors did not separately investigate the combined effect of breathlessness with other recorded respiratory symptoms (such as cough and sputum) on the risks of future diagnosis. However, it should be noted that these were adjusted for in the analyses.

Comparison with existing literature

In this study, 12.0% of those with a newly recorded symptom of breathlessness went on to develop COPD; two community cohort studies found broadly similar results (4–15%) over 5–7 years with the COPD diagnosis confirmed by spirometry.[22,23] Another study using CPRD data found that >20% of patients who were diagnosed with COPD had previously consulted with respiratory symptoms and >40% diagnosed with COPD had already been prescribed a medication in the 2 years before diagnosis.[24] In an earlier case–control study using a regional primary care database, undertaken by authors of the study presented here, 20% of those patients who received a diagnosis of IHD had a prior code for breathlessness;[25] this is consistent with the finding of 17% using data from CPRD.

In alignment with the findings of the present study, breathlessness was found to be a significant predictor of long-term IHD mortality in a large Norwegian study.[26] It has also been found to be a short-term predictor of cardiac arrest and myocardial infarction.[27,28] In a study of older people (aged ≥70 years) in the UK community, breathlessness was found to be associated with all-cause mortality after adjustment for baseline COPD and left ventricular dysfunction.[29]

Implications for research and practice

Primary care clinicians (including out-of-hours providers) who see patients consulting with breathlessness should be

aware that, although this symptom may represent an acute self-limiting illness, it is also associated with an elevated risk of more serious and potentially chronic problems in the future, including premature mortality. The findings presented here suggest the potential need for more detailed investigation, assessment, and monitoring over time in order to:

- earlier confirm or rule out COPD, asthma, and IHD; and
- obtain a broad assessment of mortality risk in this common group of patients with breathlessness but no diagnosis.

However, a 'watchful waiting' approach ('time as a diagnostic test') is a strong feature of general practice, often preventing unnecessary diagnostic procedures and treatment. Therefore, in order to directly inform clinical decision making and primary care policy, the next step is to establish for which patients the potential for early intervention in everyday practice is most feasible, beneficial, and cost-effective.

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Ethical approval

This study was approved by the Clinical Practice Research Datalink Independent Scientific and Advisory Committee (ISAC, Protocol No. 15_140). This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of its care and support. Hospital Episode Statistics data and Office for National Statistics data were re-used with the permission of the Health and Social Care Information Centre (now NHS Digital).

Provenance

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Competing interests

The authors have declared no competing interests.

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