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MAJOR ARTICLE

Antibiotic Prescribing Before and After the Diagnosis of Comorbidity: A Cohort Study Using Primary Care Electronic Health Records

Patrick Rockenschaub,[1] Andrew Hayward,[2] and Laura Shallcross[1]

[1]Institute of Health Informatics, University College London, London, UK, and [2]Institute of Epidemiology & Healthcare, University College London, London, UK

Background. Comorbidities such as diabetes and chronic obstructive pulmonary disease (COPD) increase patients' susceptibility to infections, but it is unclear how the onset of comorbidity impacts antibiotic use. We estimated rates of antibiotic use before and after diagnosis of comorbidity in primary care to identify opportunities for antibiotic stewardship.

Methods. We analyzed UK primary care records from the Clinical Practice Research Datalink. Adults registered between 2008–2015 without prior comorbidity diagnoses were eligible for inclusion. Monthly adjusted rates of antibiotic prescribing were estimated for patients with new-onset stroke, coronary heart disease, heart failure, peripheral arterial disease, asthma, chronic kidney disease, diabetes, or COPD in the 12 months before and after diagnosis and for controls without comorbidity.

Results. 106 540/1 071 943 (9.9%) eligible patients were diagnosed with comorbidity. Antibiotic prescribing rates increased 1.9- to 2.3-fold in the 4–9 months preceding diagnosis of asthma, heart failure, and COPD before declining to stable levels within 2 months after diagnosis. A less marked trend was seen for diabetes (rate ratio, 1.55; 95% confidence interval, 1.48–1.61). Prescribing rates for patients with vascular conditions increased immediately before diagnosis and remained 30%–39% higher than baseline afterwards. Rates of prescribing to controls increased by 17%–28% in the months just before and after consultation.

Conclusions. Antibiotic prescribing increased rapidly before diagnosis of conditions that present with respiratory symptoms (COPD, heart failure, asthma) and declined afterward. Onset of respiratory symptoms may be misdiagnosed as infection. Earlier diagnosis of these comorbidities could reduce avoidable antibiotic prescribing.

Keywords. primary care; antibiotic; comorbidity; antimicrobial stewardship.

Reducing inappropriate antibiotic prescribing is a public health priority to halt the emergence of antibiotic resistance [1]. Across England and Europe, 80%–90% of antibiotics are prescribed in community settings [2, 3]. However, more than half of antibiotic prescriptions in primary care are prescribed to less than 10% of patients who have high rates of comorbidity [4], suggesting the need for stewardship interventions that focus on comorbid patients with high-frequency antibiotic use.

Patients with comorbidity and multimorbidity are at greater risk of acquiring and developing antibiotic resistance compared with healthy patients in the community due to their increased vulnerability to infection, frequent antibiotic exposure, and contact with secondary care where drug-resistant infections are prevalent [5–7]. Diabetes and chronic lung, kidney, and vascular disease are all considered to increase patients' susceptibility to bacterial infection or to increase their risk of infection-related adverse outcomes [8–12]. However, the extent of this effect varies by comorbidity, its severity, and how the condition is managed. Uncertainty around the impact of comorbidity is evident in national guidelines on the management of infections, which either specifically exclude patients with comorbidity [13–15] or provide little guidance on how or when treatment should be adapted for comorbid patients [16–18].

Although the need to reduce antibiotic prescribing for patients with conditions such as chronic obstructive pulmonary disease (COPD) is widely acknowledged [19], few studies have evaluated prescribing patterns or stewardship interventions in comorbid patients [4, 20, 21]. To identify opportunities to reduce antibiotic prescribing in patients with comorbidity, we investigated the association between the onset of comorbidity and antibiotic prescribing in primary care for 8 types of comorbidity that can increase patients' susceptibility to or risk of adverse outcomes from bacterial infection. We compared monthly rates of antibiotic prescribing in the period before and after diagnosis for each comorbid group and for a control group of patients without comorbidity.

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Correspondence: L. Shallcross, 222 Euston Road, London NW1 2DA, United Kingdom (l.shallcross@ucl.ac.uk).

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METHODS

Database

The Clinical Practice Research Datalink (CPRD) is a primary care database that contains records from 4.4 million active patients across 674 general practices in the United Kingdom [22]. The dataset is representative of the UK general population and includes information on demographics, medical diagnoses, test results, and drug prescriptions. Diagnoses are stored as Read codes, a hierarchical coding system [23]. Consenting practices (75% of English practices, 58% of all practices) are further linked to hospital activity data from Hospital Episodes Statistics (HES) and census data from the Office for National Statistics (ONS) [22]. We included patients in the CPRD-HES-ONS linkage set in order to be able to adjust for socioeconomic status. All data were accessed via the cardiovascular disease (CVD) research using linked bespoke studies and electronic health records (CALIBER) research platform (https://www.caliberresearch.org/portal).

Study Population and Variables

Patients aged ≥18 years who were registered with a general practice between 1 January 2008 and 31 December 2015 were eligible for inclusion, provided their data met specified quality standards [22]. For each patient, information on birth date, gender, socioeconomic status (quantile of index of multiple deprivation [IMD] 2015) and comorbidity diagnoses were extracted. The earliest record of comorbidity was considered as the patient's index date. Patients were included in the final cohort if they had an index date between 1 January 2009 and 31 December 2014 and had been registered with their general practice for at least 1 year before and after their index date (to prevent misclassification of pre-existing comorbidity as new-onset comorbidity and to ensure patients had at least 1 year of follow-up after their index date).

A range of comorbidities have been previously listed in national guidance as being relevant to the primary care physicians' decisions to prescribe an antibiotic, including asthma, coronary heart disease (CHD), chronic kidney disease (CKD), COPD, diabetes, heart failure, peripheral arterial disease (PAD), and stroke [16]. We identified patients with each of these conditions using code lists adapted from the Quality and Outcomes Framework, a financial incentive scheme introduced in 2004 to improve management of chronic disease in primary care (Supplementary Table 1). Patients were added to the comorbidity group corresponding to their index diagnosis. For example, if a patient was diagnosed with diabetes on 1 January 2009 and diagnosed with COPD on 2 February 2010, the patient was added to the diabetes group with an index date of 1 January 2009. Patients were allowed to have other comorbid conditions not explicitly listed in national guidelines (such as dementia) before their index date.

A primary care consultation was randomly selected as the index date for noncomorbid controls. One control was matched to each comorbid patient based on month of index diagnosis, age at index, sex, and IMD using a nearest-neighbor approach. We did not exclude consultations for infection to ensure that cases and controls were selected in the same way, since cases could potentially be diagnosed simultaneously with an infection and comorbidity at index.

All prescriptions of systemic antibiotics within ±1 year of index were extracted from CPRD and classified by calendar season (winter, January–March; spring, April–June; summer, July–September; autumn, October–December). Systemic antibiotics were all drugs included in chapter 5.1 of the British National Formulary, excluding antituberculosis and antileprotic drugs.

Statistical Analyses

We investigated the average monthly rate of antibiotic prescribing in the 12 months before and after diagnosis of comorbidity for each comorbid group by fitting a mean and standard error for each month adjusting for age at index date (18–39, 40–59, 60–79, ≥80 years), gender, IMD, and season. Monthly averages were estimated with respect to the quarterly average and plotted. Months and quarters were defined relative to each patient's index date, ranging from -12 to 12 and from -4 to 4, respectively. Since we were interested in antibiotic prescribing in the period before and after diagnosis of comorbidity, we excluded antibiotic prescriptions that were given on the index date in our main analysis for both cases and controls.

Analyzing the data by month meant that each patient provided 24 data points–1 for each month–which tends to introduce correlation between observations. General estimating equations with an autoregressive correlation structure of order 1 and Huber–White sandwich estimators were used to account for dependence between observations and to obtain valid standard errors. All estimates were calculated relative to the first quarter of the observation period (ie, 12–10 months prior to index), which we designated as the patient's "baseline" period. Models were fitted separately for each comorbidity group.

To estimate the proportion of comorbid patients in whom higher rates of prescribing were seen, we calculated the percentage of patients in each month who received 1, 2, or 3 or more antibiotic prescriptions. We also undertook 2 sensitivity analyses, first to explore whether the prescribing trends changed if only patients with pre-existing comorbidities were included in the analysis, for example, a patient with diabetes at study entry who goes on to develop COPD. Second, we explored the impact of including prescriptions that were issued on the index date.

All analyses were performed using R version 3.4.3 for Windows [24]. General estimating equations were fitted using the R package geepack (version 1.2–1), and matching was performed using the package MatchIt (version 3.0.2).

RESULTS

A total of 1 071 943 adult patients were eligible for inclusion in the study (Figure 1). The average age at index was 48.8 years (standard deviation [SD], 17.0), and 559 786 (52.2%) of eligible

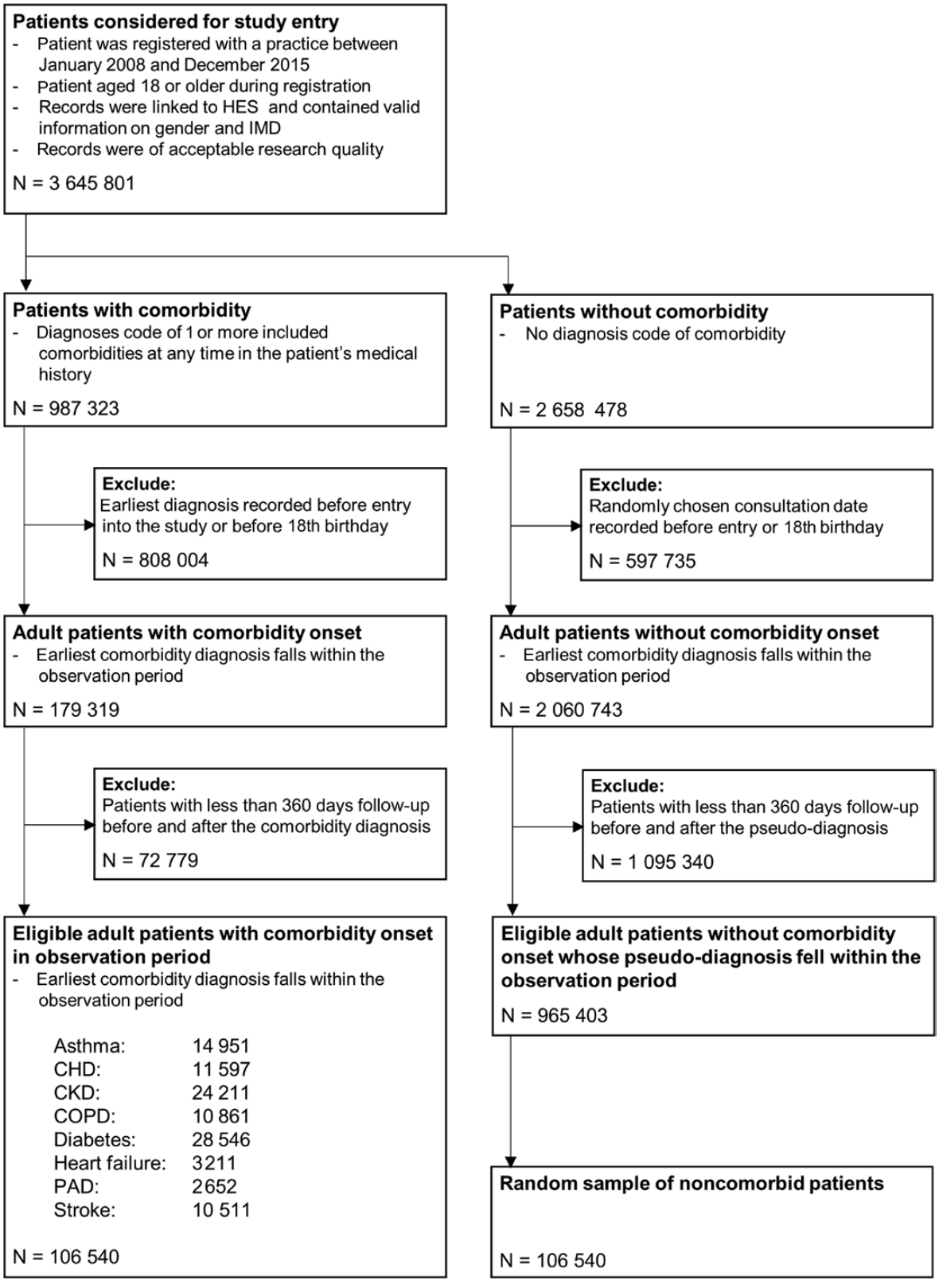

Figure 1. Flow chart of study cohort selection. Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HES, Hospital Episode Statistics; IMD, index of multiple deprivation 2015; PAD, peripheral arterial disease.

patients were female. Eligible patients had slightly higher levels of social deprivation compared with the general population (average IMD quintile of 2.7 compared with expected 2.5; SD, 1.4; 1 means least and 5 most deprived). A total of 106 540 (9.9%) patients in this cohort were newly diagnosed with 1 of the included comorbidities during the study period. The most common new diagnosis was diabetes, with 28 546 (2.7%) newly diagnosed patients (Table 1). Patients newly diagnosed with a comorbidity tended to be older and slightly more deprived compared with the full cohort, except for patients with asthma. There were 106 540 patients who were selected as matched controls.

For all comorbid patients and controls, the rate of antibiotic prescribing increased over the 2-year study period, although this effect was smaller for controls (rate ratio [RR], 1.11 in the 10–12 months after index compared with the baseline period 10–12 months before index; 95% confidence interval [CI], 1.08–1.14; Figure 2 and Table 2). There was a clear rise in antibiotic prescribing starting 4–9 months before the diagnosis of asthma, COPD, and heart failure. Rates of antibiotic prescribing in the 7–9 months before asthma was diagnosed increased by 9% relative to baseline (RR, 1.09; 95% CI, 1.04–1.14), rising to an 88% increase in the 1–3 months before diagnosis (RR, 1.88; 95% CI, 1.79–1.96). Similarly, rates of prescribing increased by 30% relative to baseline 4–6 months before COPD diagnosis (RR, 1.30; 95% CI, 1.23–1.36), with a 2.3-fold increase in prescribing 1–3 months before diagnosis (RR, 2.28; 95% CI, 2.17–2.39). For patients with heart failure, rates of prescribing increased by 23% 4–6 months before diagnosis (RR, 1.23; 95% CI, 1.10–1.38) and doubled 1–3 months before diagnosis (RR, 2.03; 95% CI, 1.83–2.26).

Following diagnosis, there was a marked decline in rates of prescribing for all 3 of these conditions. In patients diagnosed with COPD and heart failure, rates of antibiotic prescribing declined respectively to 42% and 32% above baseline 1–3 months following diagnosis (RR, 1.42; 95% CI, 1.34–1.49 and RR, 1.32; 95% CI, 1.17–1.49). For patients with asthma, monthly averages returned to baseline levels immediately after diagnosis (RR, 1.04; 95% CI, .99–1.10). Prescribing rates in patients with new-onset diabetes showed a similar but less pronounced trend. Prescribing increased 3–4 months before diagnosis of diabetes and peaked 1–3 months before diagnosis compared with baseline (RR, 1.55; 95% CI, 1.48–1.61). There was also a 23% increase in prescribing for CKD 1–3 months before diagnosis (RR, 1.23; 95% CI, 1.18–1.29). The rate of prescribing for patients with new-onset diabetes and CKD declined following diagnosis to stabilize at a slightly higher rate than baseline for both conditions.

Antibiotic prescribing increased slightly in the 1–3 months before diagnosis of stroke and CHD and increased by 34% relative to baseline for patients with new-onset PAD (RR, 1.34; 95% CI, 1.16–1.54). Prescribing rates remained elevated or continued to increase for all 3 of these conditions, with a 30%–39% increased rate of prescribing relative to baseline 12 months after diagnosis.

In control patients without comorbidity, rates of prescribing were 17%–29% higher in the 1- to 3-month period either side of the index consultation. However, baseline rates of antibiotic prescribing were up to 43% lower in controls compared with comorbid patients, which ranged from 44.2 (95% CI, 38.5–50.7) antibiotics per 1000 patients per month in patients with new-onset stroke to 83.2 (95% CI, 77.2–89.8) in patients with new-onset COPD (rates presented for male patients aged 60–79 years). For comparison, the rate of prescribing to matched control patients was 36.5 (95% CI, 34.5–38.2) prescriptions per month (Table 2).

The rise in prescribing rates was driven by higher-frequency antibiotic use in a subset of patients and by an increased prevalence of antibiotic use among patients who were diagnosed with comorbidity (Supplementary Figure 1). Sensitivity analysis that looked at multimorbidity diagnoses revealed similar but less marked temporal trends for asthma, COPD, and heart failure (Supplementary Table 2 and Supplementary Figure 2). Other comorbidities were comparable to controls but had substantially higher levels of antibiotic use at baseline. When prescriptions

Table 1. Patient Characteristics by Comorbidity

Comorbidity	Patients	Age at Onset	Gender	Index of Multiple Deprivation 2015
	N (% of Eligible)	Mean (SD)	% Male	Mean (SD)
Asthma	14 951 (1.4)	48.0 (15.9)	61.7	2.9 (1.4)
Coronary heart disease	11 597 (1.1)	64.5 (12.2)	32.1	2.8 (1.4)
Chronic kidney disease	24 211 (2.3)	71.7 (12.3)	63.9	2.7 (1.4)
Chronic obstructive pulmonary disease	10 861 (1.0)	64.7 (10.8)	47.7	3.2 (1.4)
Diabetes	28 546 (2.7)	58.7 (12.9)	42.4	2.9 (1.4)
Heart failure	3211 (0.3)	72.8 (13.5)	46.8	2.8 (1.4)
Peripheral arterial disease	2652 (0.2)	67.0 (11.6)	35.9	3.0 (1.4)
Stroke	10 511 (1.0)	69.4 (13.4)	48.2	2.7 (1.3)
Noncomorbid controls (random visit as index date)	106 540 (9.9)	63.1 (15.2)	50.0	2.8 (1.4)

Abbreviation: SD, standard deviation.

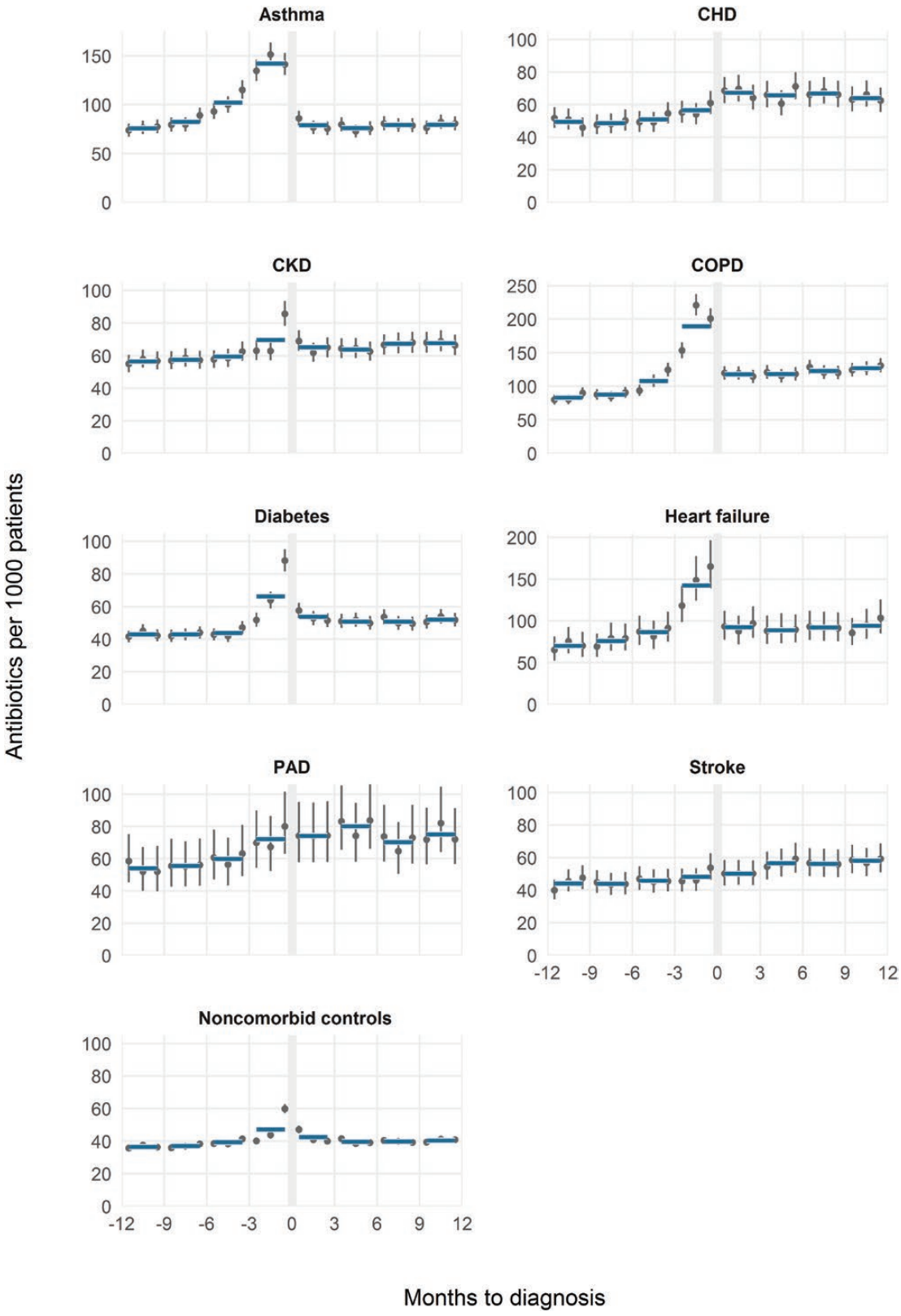

Figure 2. Quarterly trends in average rates of antibiotic prescribing before and after diagnosis of comorbidity. Rates of antibiotic prescribing are shown for all quarters (horizontal lines) and months (black dots; including 95% confidence intervals) within ±12 months of the comorbidity index date (at t = 0). Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PAD, peripheral arterial disease.

Table 2. Estimated Rate Ratios and 95% Confidence Intervals Within ±12 Months of Comorbidity Index Date

Comorbidity	Before Index				After Index			
	10–12 Months (Baseline)	7–9 Months	4–6 Months	1–3 Months	1–3 Months	4–6 Months	7–9 Months	10–12 Months
	Antibiotics per Month[a]	RR (95% CI)[b]	RR (95% CI)[b]	RR (95% CI)[b]	RR (95% CI)[b]	RR (95% CI)[b]	RR (95% CI)[b]	RR (95% CI)[b]
Asthma	75.8 (70.3–81.8)	1.09 (1.04–1.14)	1.35 (1.29–1.41)	1.88 (1.79–1.96)	1.04 (.99–1.10)	1.00 (.95–1.05)	1.05 (.99–1.10)	1.05 (1.00–1.11)
Coronary heart disease	49.4 (44.5–54.9)	0.98 (.92–1.06)	1.03 (.96–1.11)	1.15 (1.07–1.23)	1.37 (1.27–1.47)	1.33 (1.24–1.44)	1.35 (1.26–1.46)	1.30 (1.20–1.40)
Chronic kidney disease	56.5 (51.8–61.7)	1.02 (.98–1.06)	1.05 (1.01–1.10)	1.23 (1.18–1.29)	1.15 (1.10–1.20)	1.13 (1.08–1.18)	1.19 (1.14–1.25)	1.20 (1.15–1.25)
Chronic obstructive pulmonary disease	83.2 (77.2–89.8)	1.05 (1.00–1.11)	1.30 (1.23–1.36)	2.28 (2.17–2.39)	1.42 (1.34–1.49)	1.42 (1.35–1.50)	1.48 (1.40–1.56)	1.53 (1.45–1.61)
Diabetes	42.9 (39.8–46.3)	1.00 (.96–1.04)	1.02 (.98–1.07)	1.55 (1.48–1.61)	1.25 (1.20–1.31)	1.18 (1.13–1.24)	1.19 (1.13–1.24)	1.21 (1.16–1.27)
Heart failure	70.2 (58.6–84.1)	1.08 (.97–1.21)	1.23 (1.10–1.38)	2.03 (1.83–2.26)	1.32 (1.17–1.49)	1.27 (1.12–1.44)	1.31 (1.16–1.48)	1.34 (1.19–1.52)
Peripheral arterial disease	54.0 (43.1–67.7)	1.03 (.90–1.18)	1.11 (.96–1.29)	1.34 (1.16–1.54)	1.37 (1.18–1.60)	1.49 (1.28–1.72)	1.30 (1.12–1.51)	1.39 (1.21–1.60)
Stroke	44.2 (38.5–50.7)	1.00 (.93–1.06)	1.04 (.97–1.11)	1.09 (1.02–1.17)	1.14 (1.06–1.22)	1.28 (1.19–1.38)	1.27 (1.18–1.38)	1.32 (1.22–1.42)
No. comorbid controls (random visit as index date)	36.5 (34.5–38.2)	1.01 (.99–1.04)	1.08 (1.05–1.11)	1.29 (1.26–1.33)	1.17 (1.14–1.20)	1.09 (1.06–1.11)	1.09 (1.06–1.12)	1.11 (1.08–1.14)

Rates were estimated by quarter and compared to levels at baseline (12–9 months before index date).
Abbreviations: CI, confidence interval; RR, rate ratio.
[a]Rates given per 1000 male patients aged 60–79 years with index of multiple deprivation 2015 3; models fitted separately for each comorbidity.
[b]Compared to rates 9–12 months before index.

during the index consultation were included in the analysis, the estimated RRs in the quarter after diagnosis were notably higher for asthma (RR, 1.22; 95% CI, 1.16–1.28) and the control group (RR, 1.34; 95% CI, 1.31–1.37; Supplementary Table 3 and Supplementary Figure 3).

DISCUSSION

In this large primary care study, we found evidence of a rapid increase in antibiotic prescribing, which starts 6–9 months before comorbidities that present with respiratory symptoms (COPD, heart failure, asthma) are diagnosed and is followed by a rapid decline in prescribing 1–3 months after diagnosis. The RR for prescribing increased by 1.9- to 2.3-fold in the 1–3 months preceding diagnosis of asthma, COPD, and heart failure compared with baseline before declining to baseline (asthma) or an intermediate stable rate (heart failure and COPD) 1–3 months after diagnosis. A similar pattern was seen to a lesser extent for diabetes but was not seen for patients with vascular disease, with CKD, or for control patients without any of the specified comorbidities.

The reported rates of prescribing were adjusted for season, age, gender, and IMD. The potential confounding effect of preexisting comorbidity was eliminated by restricting the analysis to patients with no record of the specified comorbidities at study entry. We also compared rates of prescribing for month of diagnosis, age, gender, and IMD-matched control patients without comorbidity. We report a clear pattern of a rapid increase in antibiotic prescribing and subsequent decline after diagnosis for each of the 3 conditions (COPD, heart failure, asthma), which usually present with respiratory symptoms such as cough or breathlessness [25–27]. This pattern of prescribing is likely to be driven by difficulties in distinguishing first presentation of asthma, heart failure, and COPD from respiratory tract infections in primary care [27–29].

An alternative explanation is that repeat infections may trigger the onset of specific chronic diseases, as has been shown for viral infections and acute events such as myocardial infarction [30] and encephalitis [31]. Evidence linking bacterial infection and onset of chronic disease is less clear, with a recent study reporting the prevalence of self-reported lower respiratory tract infection in the prior 12 months to be 35.8% in patients with new-onset asthma and 7.3% for controls [32]. Since general practitioners rarely record the likelihood that infection is bacterial or viral [33], it is difficult to disentangle whether higher rates of prescribing in the period preceding diagnosis reflect a genuine increase in bacterial infection, inappropriate prescribing for viral infections, or misdiagnosis of underlying chronic disease. Nonetheless, a rapid increase in frequency of antibiotic prescribing may be a useful warning sign for onset of chronic disease.

A less marked pattern of increased antibiotic use was also seen in the 1–3 months preceding diagnosis of diabetes. This may indicate that certain infections such as urinary tract infection (UTI) may prompt primary care physicians to investigate patients for conditions such as diabetes, since UTIs are

comparatively common in diabetics relative to the general population [34]. Hyperglycemia secondary to diabetes can also cause urinary frequency, which may mimic clinical presentation of UTI [35]. By contrast, for patients with vascular conditions such as PAD and stroke, we found that rates of antibiotic prescribing continued to increase following diagnosis. This may reflect increased susceptibility to infection in these patients, for example, due to poor mobility and/or perceptions around these patients' risk of infection-related complications.

In primary care, the dilemma of whether to prescribe an antibiotic is exacerbated by the lack of rapid and reliable tests that can discriminate between symptoms of chronic disease and symptoms of infection. The median time from symptom onset to diagnosis is more than 2.5 years for heart failure [36] and 6–13 years for diabetes [37]. Over-, under-, and misdiagnosis of chronic diseases in this setting is common [38–40] and is likely to drive antibiotic overuse in this vulnerable group of patients, increasing their risk of antibiotic-related side effects in the short term and antibiotic treatment failure in the longer term.

The major strengths of our analysis are that we used a large and nationally representative primary care database with individual-level patient data from more than 100 000 patients with new-onset comorbidity. Our main outcome of antibiotic prescribing is extremely well-recorded in CPRD, and our estimates can be generalized to the UK population [22]. The limitations of our analysis relate to the fact that electronic health records are designed for clinical care rather than research, so information that may be relevant to the prescribing decision such as the reason for the prescription is not well recorded in CPRD [33].

As this study is observational, we cannot rule out alternative explanations for our findings. We were unable to account for antibiotic prescribing that took place in other settings such as in the hospital, and the date of diagnosis was based solely on primary care data, so there could be a delay in recording conditions that are usually diagnosed in hospital, such as stroke. We also did not capture data on other comorbidities that might influence a patient's susceptibility to infection, such as cancer or rheumatological conditions. While onset or treatment for other comorbidities might impact on the time trends that we report, immunosuppressive disorders remain relatively rare in primary care. Our conclusions are further strengthened by the fact that we see similar patterns of prescribing across multiple comorbidities and, to some extent, in sensitivity analysis of patients with multimorbidity.

Our findings suggest that increased antibiotic prescribing for respiratory symptoms should prompt general practitioners to consider an underlying diagnosis of COPD, heart failure, or asthma. However, the estimates reported in this study denote population averages, and the effect for any given patient may be difficult to discern in clinical practice. Clinicians will need to be sensitive to what constitutes above-average prescribing by comparison with their local population and for an individual over time. For example, an average patient without comorbidity might be expected to receive 1–2 prescriptions over a 3-year period, but individuals who are subsequently diagnosed with COPD, asthma, or heart failure would be expected to receive at least twice this amount over a comparable time period. This suggests that the ability to monitor such trends over time at the individual patient level could help to reduce avoidable prescribing in primary care by raising awareness and educating practitioners about the possibility that chronic conditions are being misdiagnosed as infection. For researchers, there is a need to develop and evaluate strategies to safely reduce antibiotic prescribing in patients with comorbidity and multimorbidity.

CONCLUSIONS

Results from this study show that there is a rapid increase in rates of antibiotic prescribing in the 4–9 months before diagnosis of COPD, heart failure, and asthma, which declines following diagnosis. This suggests that onset of respiratory symptoms may be misdiagnosed as respiratory tract infection. Earlier diagnosis and treatment for these comorbidities in primary care represents an opportunity to reduce unnecessary antibiotic prescribing for these patients.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. P. R. and L. S. designed the study, interpreted the data, and wrote the manuscript. P. R. performed all statistical analyses reported in this study. A. H. contributed to the study design and substantively revised the draft manuscript. All authors read and approved the final manuscript.

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Disclaimer. This article represents independent research, and the views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute of Health Research (NIHR), or the Department of Health and Social Care. The analysis reported in this study was approved by the Medicines and Healthcare Products Regulatory Agency's independent scientific advisory committee (protocol 17 048). cardiovascular disease (CVD) research using linked bespoke studies and electronic health records (CALIBER), led from the University College London Institute of Health Informatics, is a research resource consisting of anonymised, coded variables extracted from linked electronic health records, methods and tools, specialised infrastructure, and training and support. This study is based on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the UK National Health Service (NHS) as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. More information can be found at https://www.cprd.com. The code for used for all analyses can be found at https://github.com/prockenschaub/CPRD_comorbidity_onset.

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