

RESEARCH PAPER

Use of long-term antibiotic treatment in COPD patients in the UK: a retrospective cohort study

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Abstract

Background: Exacerbations of chronic obstructive pulmonary disease (COPD) are a burden to patients and impose a major cost on health services. Long-term antibiotic therapy may prevent exacerbations, but at present it is not recommended by management guidelines.

Aims: To identify the type and prevalence of long-term oral antibiotic treatments prescribed to patients with COPD and to assess the patient characteristics associated with long-term antibiotic use.

Methods: A retrospective cohort using all eligible practices in The Health Improvement Network (THIN) UK primary care database between 2000 and 2009 was studied. We identified patients with COPD and then those who received a course of long-term antibiotics. Long-term courses were defined as ≥ 6 months in duration with $< 50\%$ concomitant oral corticosteroid treatment.

Results: We identified 92,576 patients with COPD, but only 567 patients (0.61%) who received 998 long-term antibiotic courses. Mean follow-up time was 3 years and 10 months. The median long-term antibiotic course length was 280 days (interquartile range 224, 394) and 58 patients (0.06%) were continuously prescribed antibiotics for > 2 years. The most commonly used long-term antibiotics were oxytetracycline, doxycycline, and penicillin. Azithromycin, erythromycin, and clarithromycin were less frequently used. There was little evidence of the use of rotating courses of antibiotics. Men, people aged 50–79 years, non-smokers, and patients with poorer lung function were more likely to receive long-term antibiotic treatment.

Conclusions: Relatively few COPD patients are currently prescribed long-term antibiotics. Further clinical trials are required to determine the efficacy of this therapy. If beneficial, the use of such treatments should be incorporated into clinical guidelines.

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See linked editorial by Miravittles on pg 261

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major worldwide cause of mortality.^{1,2} There are an estimated 900,000 diagnosed sufferers in the UK alone,³ and the disease costs the UK National Health Service (NHS) over £253 million a year.⁴

Many patients experience exacerbations during the course of COPD.⁵ These are episodes of acute worsening of respiratory

systems that reduce the quality of life,⁶ hasten lung function decline,⁷ and may cause death.⁵ A third of patients with moderate to severe COPD suffer two or more exacerbations per year.⁸ The treatment of exacerbations constitutes 60% of the total cost of COPD to the NHS⁹ and generally involves a short course of antibiotics and/or oral corticosteroids, but in more severe cases may require hospitalisation.³

Current pharmacological and physiological therapies for preventing exacerbations involve daily treatment with long-acting bronchodilators and/or inhaled corticosteroids together with pulmonary rehabilitation, smoking cessation, and influenza immunisation.¹⁰ Although these therapies can reduce exacerbation

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rates, additional approaches are needed.

One possibility is long-term antibiotic treatment, but there is patchy evidence of any benefit. The clinical trials reported in the 1970s indicated only a marginal benefit in reducing exacerbation frequency and there have been no recent studies with these older antibiotics. A clinical trial of pulsed moxifloxacin did not show a significant reduction in exacerbation frequency in the intention-to-treat population.¹¹ A *post hoc* analysis did show a significant reduction in exacerbation frequency in patients with mucopurulent/purulent sputum production. The greatest successes have been achieved with macrolides. In a recent large study of 1,142 COPD patients randomly assigned to daily 250mg azithromycin or placebo, exacerbation frequency fell significantly from 1.83 per patient-year on placebo to 1.48 per patient-year with azithromycin.¹² The rate ratio (from negative binomial regression) was 0.83. In a smaller placebo-controlled randomised clinical trial of erythromycin administered in a dose of 250mg twice daily there was a significant reduction from a median of two exacerbations per year with placebo to one exacerbation per year with erythromycin. The rate ratio from generalised linear modelling was 0.65.¹³

Currently, long-term antibiotic treatment is not recommended by the National Institute for Health and Clinical Excellence (NICE)³ and Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹⁴ COPD management guidelines because of clinical uncertainty and concerns about safety relative to benefit, particularly the development of resistant bacteria. Despite the guidelines, long-term antibiotic therapy is currently prescribed as these patients are occasionally seen in clinic, but its prevalence and characteristics are unknown and such information is therefore useful.

Using data from The Health Improvement Network (THIN) primary care database, this study aims to identify the number and type of antibiotics prescribed long-term to patients with COPD by general practitioners (GP) and the length of treatment, and to assess the patient characteristics associated with long-term antibiotic use.

Methods

Data source

In the UK, approximately 98% of patients are registered with a GP¹⁵ and COPD is primarily managed in general practice. Medical symptoms and diagnosis, health indicators such as weight and blood pressure, and prescribed medicines are recorded during consultations with the GP. THIN contains anonymised records of 6% of the UK population (<http://www.epic-uk.org/our-data/statistics.shtml>) and has been validated for pharmacoepidemiological research.¹⁶ THIN is broadly representative of UK general practice in terms of age, gender, and smoking status.^{17,18} Prescription data are comparable with national statistics¹⁹ and >98% of prescriptions are redeemed.²⁰ In the UK, GPs are not required to record the indication for prescriptions and do so less than 65% of the time.^{21,22} Recorded diagnoses and symptoms are classified using Read codes.²³ The dataset also includes Townsend quintile, a measure of social deprivation where 5 indicates most deprived and 1 indicates least deprived.²⁴ The prevalence, demographics, smoking habits, and

mortality of patients with COPD in THIN is similar to national data.²⁵

The THIN scheme for obtaining and providing anonymous patient data to researchers was approved by the National Health Service South-East Multicenter Research Ethics Committee (MREC) in 2002. This particular study was also reviewed by THIN Scientific Review Committee.

Study population

We identified patients aged 35–89 years between 1 January 2000 and 31 December 2009 with a diagnosis of COPD. The diagnosis was based on the Quality and Outcomes Framework (QOF) codes for COPD. These have been shown to select a subset of patients whose prevalence, geographical distribution, age, and gender distribution matches other national surveys of COPD²⁵ and has been used in other COPD studies.²⁶ People were eligible for entry to the study from the latest of either 1 January 2000, the patient joining the practice, their 35th birthday or diagnosis with COPD, or the date the practice started to contribute data to THIN. Data on eligible patients were collected until the earliest date of either death, transfer to another practice or 31 December 2009. Practices in THIN were excluded until they met acceptable recording standards – that is, records are of good quality and mortality rates are comparable to the expected UK national age- and gender-specific mortality rates²⁷ to ensure accurate data recording.

Information on gender, age, last recorded smoking status (active/non-smoker), forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), FEV₁/FVC ratio, and Townsend quintile value were extracted from the database. Predicted FEV₁ was estimated using age, sex and height. FEV₁ and FVC measurements between 0.3L and 7.0L were considered as valid measures.

Antibiotics

Patients can be treated with a very wide variety of antibiotics, so we limited our analysis to 10 oral antibiotics. Their choice was based on evidence from clinical trials that evaluated long-term use of azithromycin, erythromycin, moxifloxacin, clarithromycin, oxytetracycline, penicillin, and doxycycline (a tetracycline equivalent). Furthermore, we identified the antibiotics prescribed to COPD patients in THIN and included the three remaining most commonly used (amoxicillin, co-amoxiclav, and ciprofloxacin). Finally, we examined courses where these antibiotics have been prescribed in rotation but limited their combinations to just two different antibiotics within one long-term course.

The recent clinical trials of long-term antibiotics for prophylactic reduction of exacerbations have involved treatment for 12 months,^{11–13,28} but some of the older trials were for shorter periods.²⁹ We therefore focused on antibiotic courses lasting ≥ 6 months (long-term) to avoid misidentification of repeated antibiotic courses in patients with frequent exacerbations.

Prescription data

For each patient we extracted information on all their oral antibiotic prescriptions together with medical diagnosis records on the day of prescription. Prescription length was calculated by dividing the prescription quantity by the number of tablets to be taken per day (dosage). Hot deck imputation with adjustment for prescription quantity was used to replace missing data with an estimate based

on the typical dosage prescribed for each antibiotic.³⁰ Long-term courses of antibiotics may consist of a number of consecutive prescriptions, but there may be gaps between prescriptions if the patient misses or postpones an appointment or delays picking up the next prescription. We took 10 days as the maximum period between the end of a course and the start of another for the two courses to be considered continuous. The course length was calculated from the start of the first prescription to the end of the last.

COPD patients can experience acute exacerbations that may occur in clusters, and receive repeated courses of antibiotics and/or oral corticosteroids.^{26,31} To minimise misclassification, we excluded long-term antibiotic courses where $\geq 50\%$ of the individual antibiotic prescriptions were accompanied by a concurrent oral corticosteroid prescription. Sensitivity analysis showed that the relative distribution of antibiotic types used for long-term courses was the same irrespective of whether courses were concurrent with 0%, $< 50\%$, or $\leq 100\%$ oral corticosteroid prescriptions (data not shown).

Statistical analysis

Patient characteristics were described using means and percentages. The long-term courses with each type of antibiotic were described by their frequency and the number of unique patients who received them, their duration, and median with interquartile range (IQR), and by their dose in mg/day.

Long-term courses were broken down by those starting in the first five and final five years of the study. The number of long-term courses per 1,000 patient-years and the percentage of time patients spent on long-term therapy were also calculated.

We used logistic regression to assess the factors associated with long-term antibiotic use after initially adjusting for age and sex, and once again after adjusting for age, sex, smoking status, and Townsend quintile. The effect of COPD severity on receiving long-term antibiotic therapy was then separately evaluated by performing logistic regression on those with a FEV₁/FVC record with adjustments made for age, sex, smoking status, and Townsend quintile. Data were 100% complete for age and sex, 95% Townsend quintile, 91% smoking status, 72% FEV₁, 52% FVC, 65% FEV₁/FVC. All statistical analyses were conducted using Stata Version 12.0 (Stata Corporation, Texas, USA).

Results

Patient characteristics

A total of 2,839,694 patients aged 35–89 years were registered in 419 eligible practices in THIN between 2000 and 2009. Of these 92,576 (3%) had a clinical record of COPD. The average time which COPD patients were registered with a general practice since diagnosis of COPD was 3 years and 10 months. The COPD patients were predominantly middle-aged or elderly, with $> 96\%$ aged > 50 years, a third still smoked, and their mean FEV₁, FEV₁/FVC ratio and FEV₁/FEV₁ predicted suggested that they had COPD (Table 1).

The COPD patients received 749,412 separate antibiotic prescriptions. The 10 most commonly prescribed antibiotics constituted 76% of the total prescriptions in the COPD patients; dosage information was unavailable for 15% of prescriptions.

A total of 998 long-term courses (≥ 6 months) were prescribed to

Table 1. Characteristics of patients with a clinical record for COPD

	Category	Frequency	%
Total number of patients	–	92,576	–
Age (years)	35–49	4,116	4
	50–79	68,447	74
	80–89	20,013	22
Gender	Male	49,839	54
	Female	42,737	46
Townsend quintile	1 (least deprived)	14,424	16
	2	15,844	17
	3	18,701	20
	4	20,861	23
	5 (most deprived)	17,774	19
	Unknown	4,972	5
Smoking	Non	12,072	13
	Active	27,336	30
	Ex	44,380	48
	Unknown	8,788	9
			Mean
FEV ₁ (litres)	–	–	1.4
FVC (litres)	–	–	2.4
FEV ₁ /FVC	–	–	0.56
FEV ₁ /FEV ₁ predicted	–	–	0.59

COPD=chronic obstructive pulmonary disease, FEV₁=forced expiratory volume in one second, FVC=forced vital capacity.

567 patients (0.61%) and were used in the analysis. They received an average of two long-term courses (Table 2). This corresponds to three courses per 1,000 patient-years for all patients with COPD. The median course length was 280 days (IQR 224, 394). In the 233 patients who had two or more consecutive antibiotic courses there was no difference in the median length of the first courses (280 days, IQR 224, 394) compared with the consecutive courses. Courses consisted of a median of eight prescriptions (IQR 5, 12). The median length of each prescription was 28 days (IQR 28, 50). For those on a long-term course, 31% of their time in the practice (1 year and 2 months) was spent on long-term antibiotic therapy. Of the 998 courses, 811 (81%) had no concurrent oral corticosteroid prescriptions. The remainder (187, 19%) received oral corticosteroids concurrently for a mean of 20% of antibiotic prescriptions within a long-term course. The 998 long-term courses consisted of 10,554 prescriptions in total, of which 1,347 (13%) had their dose value imputed because it was not available. Had we not used hot deck imputation in these circumstances, it would have resulted in a reduction in the number of estimated long-term courses by 185.

The three most commonly used long-term antibiotics were oxytetracycline, doxycycline, and penicillin (Table 3). Only two rotating courses (in one patient) and four courses of daily moxifloxacin were identified. Since 2005, patients were significantly more likely to begin a long-term course of azithromycin ($p < 0.01$,

Table 2. Long-term (≥ 6 months) antibiotic courses in COPD patients

Antibiotic	COPD population		Courses No.	Course description	
	Patients No.	%		Course length (days) Median (IQR)	Dose per day (mg) Median (IQR)
Oxytetracycline	128	0.14	252	284 (224, 416)	500 (500, 879)
Doxycycline	125	0.14	191	260 (224, 364)	100 (100, 100)
Penicillin	101	0.11	208	300 (225, 448)	631 (500, 1000)
Clarithromycin	69	0.07	109	300 (224, 392)	417 (250, 667)
Azithromycin	58	0.06	80	288 (238, 392)	250 (250, 292)
Ciprofloxacin	50	0.05	64	280 (210, 400)	500 (500, 1000)
Amoxicillin	40	0.04	57	294 (224, 362)	750 (500, 1000)
Erythromycin	9	0.01	24	242 (200, 320)	1000 (1000, 2000)
Co-amoxiclav	7	0.01	7	262 (231, 352)	1125 (1125, 1875)
Moxifloxacin	3	0.00	4	355 (315, 385)	400 (400, 400)
Rotating antibiotic	1	0.00	2	200 (198, 202)	300 (278, 322)
Total	591	0.61	998	280 (224, 394)	–
Total number of unique patients	567*	–	–	–	–

COPD=chronic obstructive pulmonary disease, IQR = interquartile range. *Number of unique patients (some patients had more than one type of antibiotic course).

Table 3. Long-term antibiotic course start dates

Antibiotic	Start before 1/1/2005		Start on or after 1/1/2005		Difference Post 2005 vs. pre 2005	p Value
	No. of courses	%	No. of courses	%		
Oxytetracycline	103	30	149	23	7 (-14, -1)	0.03
Doxycycline	59	17	132	20	3 (-3, 8)	0.33
Penicillin	90	26	118	18	-8 (-15, -2)	<0.01
Clarithromycin	23	7	86	13	6 (2, 10)	<0.01
Azithromycin	7	2	73	11	9 (6, 12)	<0.01
Ciprofloxacin	24	7	40	6	-1 (-4, 2)	0.58
Amoxicillin	20	6	37	6	0 (-3, 3)	0.89
Erythromycin	13	4	11	2	-1 (-3, 1)	0.25
Co-amoxiclav	3	1	4	1	–	–
Moxifloxacin	0	<1	4	1	–	–
Rotating antibiotic	0	<1	2	<1	–	–
Total courses	342	100	656	100	–	–

Table 3) or clarithromycin ($p < 0.01$) and significantly less likely to begin a long-term course of penicillin ($p < 0.01$) or oxytetracycline ($p = 0.03$). Patients were equally likely to begin a long-term course of erythromycin ($p = 0.25$), doxycycline ($p = 0.33$), ciprofloxacin ($p = 0.58$), or amoxicillin ($p = 0.89$). There were insufficient data to assess changes in co-amoxiclav, moxifloxacin, or rotated antibiotics.

Of the 998 antibiotic courses, 489 had no associated diagnostic code entered in their record on prescription days within the duration of the course, 142 had codes referring to COPD, and 304 referred to conditions or indications for which antibiotic treatment would not be warranted (e.g. hypertension, headaches, sciatica). The remaining 63 courses had indications such as bronchiectasis (11 courses), dressing of wound, rosacea, acne vulgaris, folliculitis, splenectomy, aspergillosis, or Mycobacterium infection for which long-term antibiotics might be prescribed. If we excluded these 63 courses, the number of patients on a long-term course would fall from 567 (0.61%) to 535 (0.58%).

Being male, not smoking, or aged 50–79 years was associated with a greater chance of being prescribed long-term antibiotics (Table 4). An obstructive ratio was not available for all patients but, of those with a FEV₁/FVC record, 0.66% received a long-term course compared with 0.54% of patients without a FEV₁/FVC record. The effects of the sociodemographic variables on the probability of receiving a long-term course did not change when the logistic model was rerun only including those with a FEV₁/FVC record. However, in this sub-population, greater airways obstruction was associated with an increased likelihood of receiving a long-term course, a decrease of 1 unit in FEV₁/FVC being associated with a 1% (95% CI 1% to 2%) chance of a patient being prescribed long-term antibiotics.

Discussion

Main findings

The main findings of this study are that 0.61% of COPD patients have received a course of oral antibiotics lasting a median of 280

Table 4. Odds of COPD patients taking long-term (LT) antibiotics for different subgroups

Variable	Category	No LT	LT	Adjusted for age and sex		Adjusted for age, sex, smoking, and TQ	
				Odds ratio	p Value	Odds ratio	p Value
Total number of patients (n)	–	92,009	567	–	–	–	–
Age, years (n)	35–49	4,094	22	0.79 (0.52, 1.22)	0.29	0.96 (0.63, 1.49)	0.87
	50–79 (ref)	67,979	468	1	–	1	–
	80–89	19,936	77	0.57 (0.45, 0.72)	<0.01	0.54 (0.42, 0.69)	<0.01
Sex (n)	Male	49,477	362	1.50 (1.27, 1.78)	<0.01	1.46 (1.23, 1.74)	<0.01
	Female (ref)	42,532	205	1	–	1	–
Smoking (n)	Non	56,018	434	2.00 (1.62, 2.48)	<0.01	1.97 (1.59, 2.44)	<0.01
	Current (ref)	27,225	111	1	–	1	–
	Unknown	8,766	22	0.70 (0.44, 1.11)	0.13	0.69 (0.44, 1.10)	0.12
Townsend quintile (n)	1 (Most affluent) (ref)	14,322	102	1	–	1	–
	2	15,743	101	0.91 (0.69, 1.19)	–	0.92 (0.70, 1.22)	–
	3	18,584	117	0.89 (0.68, 1.16)	–	0.94 (0.72, 1.22)	–
	4	20,744	117	0.79 (0.61, 1.04)	–	0.86 (0.66, 1.13)	–
	5 (Most deprived)	17,683	91	0.72 (0.54, 0.96)	–	0.82 (0.61, 1.09)	–
	Unknown	4,933	39	1.15 (0.79, 1.67)	0.19*	1.23 (0.85, 1.79)	0.67*

COPD=chronic obstructive pulmonary disease, TQ=Townsend quintile. *p value relates to test of trends.

days. The most commonly prescribed antibiotics were oxytetracycline, doxycycline, and penicillin. The low proportion of COPD patients receiving long-term antibiotics could be explained by the fact that management guidelines for COPD do not recommend this therapy. The choice of older antibiotics could be cost-driven, based on clinical experience, or to reserve newer types of antibiotics for other circumstances. It may be that the latest clinical trial data have yet to be fully translated into clinical practice, as we observed that the use of azithromycin and clarithromycin for long-term therapy increased significantly in the last five years.

There are a number of reasons why macrolides have proved successful in reducing exacerbation frequency. Approximately 50% of patients with COPD have lower airways that are colonised with bacteria,³² and colonised patients have a higher exacerbation frequency.³³ COPD patients with frequent exacerbations also have higher inflammatory markers,³⁴ and macrolides appear to have an anti-inflammatory effect decreasing neutrophil activity and downregulating cytokine expression in various cell types.³⁵

Interpretation of findings in relation to previously published work

To our knowledge, no other study has examined the current prevalence of long-term antibiotic use in COPD patients in a primary care setting. There are a number of clinical trials of long-term antibiotics which suggest they may be of benefit,^{11–13} but current management guidelines do not recommend their use in COPD.

Strengths and limitations of this study

The main strength of this study is the large primary care population (6% of the UK population) so the results are therefore highly generalisable. Other positive features are the use of validated codes for identifying COPD patients²⁵ and a long observation period which permitted investigation of this relatively uncommon prescribing practice.

There are some limitations to this study. We identified 63 courses

during which there was mention of a condition which might require long-term antibiotics. The most frequent (11/63) was bronchiectasis, which is a condition that can occur independently of COPD but can also be seen on high-resolution computed tomography scans in a high proportion of COPD patients.³⁶ Prophylactic antibiotics are sometimes prescribed to patients with bronchiectasis,³⁷ but it was not possible to determine whether or not bronchiectasis or the other conditions were the primary cause of the long-term antibiotic prescription; however, exclusion of these 63 courses would produce only a small reduction in the estimated percentage of patients receiving long-term antibiotics from 0.61% to 0.58%. We could not identify intermittent antibiotic therapy, such as the PULSE study's regime of five days moxifloxacin every four weeks,¹¹ as this could not be differentiated from antibiotic therapy for repeated exacerbations.

Pharmacoepidemiology databases are the only feasible way to investigate little-used treatment regimes in a specific disease, but one drawback is that the physician's intention for starting a particular treatment may not always be clear. This was a particular limitation in this study because there is no specific Read code for COPD exacerbation prophylaxis. We also noticed that, in many instances, no diagnostic codes were recorded. However, this is common practice in UK primary care.^{21,22} This might be explained by the treatment being initiated in secondary care and continued in primary care. We noticed that about 10% of patients who were on antibiotics took these for at least two years, but we could not determine why a long-term antibiotic course was ended and if any specific follow-up was performed.

We found that patients prescribed a long-term antibiotic course were more likely to have a lower FEV₁, to be aged between 50 and 79 years, and to be a non-smoker than patients not prescribed long-term antibiotics. Smoking cessation is one of a number of measures – such as optimising treatment with inhaled medication and/or oral

mucolytics – which could be undertaken before embarking on long-term antibiotic therapy.

Implications for future research, policy and practice

A greater understanding of the mechanisms by which long-term antibiotics reduce exacerbation frequency and airway inflammation is needed. We found a number of patients who had been prescribed antibiotics for over a year. Physicians should carefully follow up patients to whom they have prescribed long-term antibiotics to ensure that course durations are not excessive. We found it difficult to distinguish between treatment of stable COPD and exacerbations of COPD in the computerised recording of consultations. Clear distinction would be helpful as an accurate exacerbation history is important in determining treatment under some management guidelines.

Conclusions

This study has shown that a small proportion of COPD patients, typically those with more severe disease who are non-smokers, are prescribed long-term antibiotic courses that last a median of 280 days. To help the development of patient management guidelines, further clinical trials are needed to determine the best antibiotic, dose, and treatment schedule for long-term therapy.

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Conflicts of interest The authors declare that they have no conflicts of interest in relation to this article.

Contributorship GDJ designed the analysis in collaboration with GCD and IP. GDJ undertook data extraction, analysis and interpretation. All authors contributed to the literature review, drafting of the paper and development of core ideas. IP, IN, JAW, and GCD were principal investigators who initiated and supervised the study. GDJ is the guarantor.

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Appendix 1. STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Item No	Recommendation	Reported on page =
Title and abstract		
1	(a) Indicate the study's design within a commonly used term in the title or the abstract	1
	(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction		
2	Explain the scientific background and rationale for the investigation being reported	1-2
3	State specific objectives, including any prespecified hypotheses	2
Methods		
4	Present key elements of study design early in the paper	2-3
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2-3
6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2
	(b) For matched studies, give matching criteria and number of exposed and unexposed	.
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	2-3
8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2-3
9	Describe any efforts to address potential sources of bias	2-3
10	Explain how the study size was arrived at	2
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	2-3
Statistical methods		
12	(a) Describe all statistical methods, including those used to control for confounding	3
	(b) Describe any methods used to examine subgroups and interactions	3
	(c) Explain how missing data were addressed	3
	(d) If applicable, explain how loss to follow-up was addressed	.
	(e) Describe any sensitivity analyses	2-3
Results		

Appendix 1. STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies continued

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of flow diagram	3 3 .
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	3 3 3
Outcome data	15*	Report numbers of outcome events or summary measures over time	3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	3-4 . .
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	3-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	4
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4-5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4-5
Generalisability	21	Discuss the generalisability (external validity) of the study results	5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org>, Annals of Internal Medicine at <http://www.annals.org>, and Epidemiology at <http://www.epidem.com>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.