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Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of English primary care

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Abstract

Objectives: To explore the degree to which the gender gap in antibiotic prescribing is driven by prescribing behaviour, consultation behaviour, comorbidity and urinary tract infection (UTI).

Design: Cross-sectional analysis of patient consultation and antibiotic prescribing.

Setting: English primary care.

Participants: Patients who consulted general practices registered with The Health Improvement Network between 2013 and 2015.

Primary and secondary outcome measures: Total antibiotic prescribing was measured in children (<19 years), adults (19 – 64) and the elderly (65+). For twelve common conditions, the number of adult consultations was measured, and the relative risk (RR) of being prescribed antibiotics when consulting as female or with comorbidity was estimated.

Results: Female patients received 67% more antibiotic prescriptions than males, and 43% more when excluding antibiotics used to treat UTI (trimethoprim and nitrofurantoin). These gaps were more pronounced in adult women (99% more prescriptions than males; 69% more when excluding UTI) than in children (9%; 0%) or the elderly (67%; 38%). Among adults, women accounted for 64% of consultations (61% among patients with comorbidity), but were not substantially more likely than men to receive an antibiotic prescription when consulting with common conditions such as cough (RR 1.01; CI 1.00 – 1.02), sore throat (RR 1.01, CI 1.00 – 1.01) and lower respiratory tract infection (RR 1.00, CI 1.00 – 1.01). Exceptions were skin conditions: women were less likely to be prescribed antibiotics when consulting with acne (RR 0.67, CI 0.66 – 0.69) or impetigo (RR 0.85, CI 0.81 – 0.88).

Conclusions: The gender gap in antibiotic prescribing can largely be explained by consultation behaviour. Although in most cases adult men and women are equally likely to

be prescribed an antibiotic when consulting primary care, it is unclear whether or not they are equally indicated for antibiotic therapy.

Strengths and limitations of this study:

- This study is one of the first to explore the underlying causes of the large gap in the number of antibiotics prescribed to men and women in primary care.
- Findings are derived from a large, representative sample of primary care patients in England.
- Extensive mapping of Read (diagnostic) codes to clinical conditions made it possible to analyse prescribing across a range of conditions and to account for comorbidity.
- Identification of antibiotics that are used to treat UTI but rarely other conditions (trimethoprim and nitrofurantoin) allowed for approximation of UTI prescribing despite incomplete diagnostic coding.
- The data do not include indicators of antibiotic appropriateness, such as severity of illness, and so the clinical appropriateness of gender differences in prescribing could not be evaluated.

Introduction

Reducing the unnecessary use of antibiotics is as an essential means of mitigating the emergence of antimicrobial resistance (AMR) and its associated costs.[1,2] However, prescribing reductions are not without risk. The causes and magnitudes of prescribing vary substantially between practices and prescribers,[3-5] and sweeping, uncalibrated interventions could jeopardise some patients while failing to prevent unnecessary prescribing in others. In order to safely and effectively reduce antibiotic use, it is imperative to understand how and to whom antibiotics are prescribed.

Gender is a key determinant of antibiotic prescribing. A recent meta-analysis across primary care in nine high-income countries found that females received more antibiotics than males in all age groups except those >75, with women aged 16 to 54 receiving 36% to 40% more antibiotics than men of the same age.[6] Similarly, across English and Welsh primary care, the rate of antibiotic prescribing has been found to be 40% higher in female than in male patients.[7] Although the latter figure dates from 1996, gender disparities in England have more recently been observed in out-of-hours and paediatric care, with women and girls receiving more antibiotic prescriptions than men and boys.[8,9]

There are several proposed explanations for this gender gap in antibiotic prescribing. First, some infectious diseases affect men and women differently. In particular, urinary tract infection (UTI) is more common in adult women than in men and accounts for over 20% of antibiotic prescriptions in English primary care.[10,11] However, respiratory tract infections (RTIs) account for more than twice as many prescriptions as UTI,[11] and women are not more susceptible to these conditions than men,[12,13] although gender differences in comorbidity may underlie some variation in prescribing. Second, as in many countries,[14,15] women in the UK consult their general practitioner (GP) more often than men.[16-18] Although consultation rate is linked to antibiotic prescribing,[5] it is not clear to what extent gender differences in antibiotic prescribing can be explained by gender differences in health-seeking behaviour. Finally, social and behavioural factors may play a role. For example, men and women communicate differently with health professionals, and prescribers may have biases that cause them to be more willing to prescribe antibiotics during consultations with women than with men.[19,20]

Here, the gender gap in antibiotic prescribing was analysed using a large, representative sample of primary care patients in England. Antibiotic prescribing in male and female children, adults and the elderly was compared at the population level. The influence of gender on prescribing was assessed by controlling for consultation and comorbidity, and calculating the proportions of men and women that received antibiotic prescriptions when presenting to primary care with a suite of common conditions. These prescribing proportions facilitate a deeper understanding of the causes of the gender gap in antibiotic prescribing, and may inform prescribing intervention design.

Methods

This study used data from English general practices registered with The Health Improvement Network (THIN), a UK-based primary care electronic medical record database. Practices were included that provided data for at least one full calendar year between January 1, 2013 and December 31, 2015; there were 349 such practices in 2013, 285 in 2014 and 191 in 2015. Anonymised patient data were extracted from these practices that met acceptable standards for research data collection. All systemic antibiotic prescriptions (antibiotics from British National Formulary chapter 5.1,[21] excluding antituberculosis and antileprosy drugs) recorded in THIN were analysed by patient gender and age. Patient age at the time of consultation was used to classify patients as children (aged 0-18 years), adults (19-64 years) and the elderly (65+ years).

Read codes (the diagnostic codes used in THIN) were analysed to quantify the number of male and female consultations for acute presentations of 12 common conditions that are treated with antibiotics to varying degrees: acne, bronchitis, chronic obstructive pulmonary disease (COPD), cough, gastroenteritis, impetigo, influenza-like illness (ILI), lower respiratory tract infection (LRTI), otitis media, sinusitis, sore throat and upper respiratory tract infection (URTI). A vast number of Read codes are used in THIN, and the methods used to assign specific Read codes to different conditions and to link Read codes to acute antibiotic prescriptions are described elsewhere.[11] The ratio of female to male consultations (F:M) was then calculated to quantify gender differences in consultation for each of these conditions.

In THIN, a large proportion of UTI consultations are poorly coded, particularly in patients consulting for UTI prophylaxis or chronic/recurrent UTI. However, in English primary care the antibiotics used to prevent and treat the vast majority of UTIs – trimethoprim and nitrofurantoin – are rarely used for other conditions.[11] Prescriptions of trimethoprim and nitrofurantoin were thus used as a proxy measure for prescribing for UTI.

Prescribing proportions were then calculated by dividing the total number of prescriptions for a given condition by the number of consultations for that condition. To account for patients that consulted more than once, robust standard errors were used when calculating prescribing proportions. These data were also used to calculate the relative risk (RR) of being prescribed an antibiotic when consulting as female as opposed to male. In the main analysis, consultations were included if they occurred at a patient's primary registered practice, but in a sensitivity analysis all patient consultations recorded in THIN were included. Patients with comorbidity were analysed separately from otherwise 'healthy' patients (i.e., those without comorbidity) to minimise potential biases in consultation and prescribing due to gender differences in background health status. Further, the RR of being prescribed an antibiotic when consulting with comorbidity was also calculated for each condition and gender. Comorbidities were identified by the Read codes that indicate qualification for the free seasonal influenza vaccination programme: asthma, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease and immunosuppressive disease.[22] Patients who received at least two prescriptions of systemic or inhaled corticosteroids or immunosuppressive drugs in the 365 days prior to their consultation were also included in this group, since these drugs indicate an increased risk of serious complications after (respiratory tract) infections.[22]

All data were analysed using STATA 13.1 and R version 3.1.

Results

Of all antibiotic prescriptions observed in THIN between 2013 and 2015 (n=4,574,363), the majority (62.6%) were in female patients (Figure 1). Adult women received approximately twice (99.0%) as many antibiotic prescriptions as adult men, whereas elderly women and girls received 67.4% and 9.2% more prescriptions, respectively, than elderly men and boys. Nitrofurantoin and trimethoprim accounted for 17.1% of all prescriptions, 81.3% of which were prescribed to female patients. The prescribing gender gap narrowed in all age groups when these antibiotics were removed, and became negligible in children (0.3%), but adult and elderly women still received, respectively, 69.2% and 37.7% more antibiotic prescriptions than adult and elderly men.

Healthy adult women consulted primary care more than men for the 12 conditions included in this study, accounting for 64.3% of all consultations (61.9% among patients with comorbidity). The biggest gender gaps in consultation were in acne (F:M 2.90) and sinusitis (F:M 2.78). However, there was little gender difference in the proportions of healthy adult patients that received antibiotic prescriptions when consulting (Table 1). The greatest gaps were in acne, where 60% of consulting men received systemic antibiotics compared to 41% of women (RR 0.67; CI 0.66 – 0.69), and in impetigo, where, respectively, 62% and 52% of men and women received prescriptions (RR 0.85, CI 0.81 – 0.88). In all other conditions, the difference between the proportions of men and women that received antibiotic prescriptions when consulting was ≤2%, although these gaps were statistically significant in cough (F>M, p=0.02), LRTI (F>M, p=0.02), sinusitis (F>M, p<0.001) and URTI (M>F, p<0.001). These results held in a sensitivity analysis when consultations and prescriptions outside of patients' primary registered practice were included (see online supplementary appendix). Further, with the exception of acne and impetigo, the proportions of all antibiotics prescribed to men and women for different conditions are proportionate to the proportions of all consultations made by men and women for those conditions (Figure 2). Accordingly, the proportions of all antibiotics prescribed to women for each condition correlate strongly with the proportions of consultations made by women (Spearman's $\rho=0.92$; $p<0.001$), but not with the proportions of women that received prescriptions when consulting with those conditions (Spearman's $\rho=0.28$, $p=0.38$).

Table 1. Primary care consultations and antibiotic prescribing proportions per consultation in adult men and women (aged 19 – 64 years) with and without comorbidity for 12 different conditions. Only consultations from patients' primary registered practices are included.

	Number of consultations (% of total)		F:M consultation ratio	Proportion of patients receiving prescription when consulting (95% CI)		Relative risk of receiving antibiotic prescription when consulting as female (95% CI)
	Women	Men		Women	Men	
Acne	25,676 (74%)	8,864 (26%)	2.90	41% (40% – 41%)	60% (59% – 61%)	0.67 (0.66 – 0.69) (p<0.001)
Acne with comorbidity	2,344 (66%)	1,185 (34%)	1.98	40% (38% – 42%)	55% (52% – 58%)	0.73 (0.68 – 0.78) (p<0.001)
Bronchitis	7,085 (61%)	4,584 (39)%	1.55	83% (83% – 84%)	84% (83% – 86%)	0.99 (0.97 – 1.00) (p=0.14)
Bronchitis with comorbidity	3,101 (60%)	2,065 (40%)	1.50	87% (86% – 89%)	89% (88% – 91%)	0.98 (0.96 – 1.00) (p=0.03)
COPD	3,274 (59%)	2,271 (41%)	1.44	76% (74% – 78%)	75% (73% – 77%)	1.02 (0.99 – 1.05) (p=0.25)
COPD with non-respiratory comorbidity	1,287 (56%)	1,029 (44%)	1.25	73% (70% – 76%)	70% (69% – 72%)	1.06 (1.01 – 1.11) (p=0.02)
Cough	158,614 (61%)	103,058 (39%)	1.54	48% (48% – 49%)	48% (48% – 48%)	1.01 (1.00 – 1.02) (p=0.02)
Cough with comorbidity	68,353 (60%)	46,210 (40%)	1.48	58% (57% – 58%)	56% (56% – 57%)	1.03 (1.02 – 1.04) (p<0.001)
Gastroenteritis	41,870 (58%)	30,810 (42%)	1.36	6% (6% – 6%)	6% (6% – 6%)	1.01 (0.96 – 1.08) (p=0.65)
Gastroenteritis with comorbidity	12,184 (57%)	9,216 (43%)	1.32	8% (7% – 8%)	7% (7% – 8%)	1.03 (0.94 – 1.14) (p=0.49)
ILI	10,569 (57%)	7,946 (43%)	1.33	20% (19% – 20%)	19% (18% – 20%)	1.02 (0.96 – 1.09) (p=0.47)
ILI with comorbidity	1,951 (57%)	1,468 (43%)	1.33	25% (23% – 27%)	29% (27% – 31%)	0.87 (0.78 – 0.97) (p=0.02)
Impetigo	5,272 (64%)	2,907 (36%)	1.81	52% (51% – 54%)	62% (60% – 63%)	0.85 (0.81 – 0.88) (p<0.001)
Impetigo with comorbidity	1,139 (66%)	598 (34%)	1.90	54% (51% – 57%)	63% (58% – 66%)	0.86 (0.80 – 0.94) (p<0.001)
LRTI	52,996 (60%)	35,777 (40%)	1.48	91% (91% – 92%)	91% (91% – 91%)	1.00 (1.00 – 1.01) (p=0.02)
LRTI with comorbidity	36,693 (60%)	24,519 (40%)	1.50	91% (90% – 91%)	90% (89% – 90%)	1.01 (1.01 – 1.02) (p<0.001)
Otitis	11,773	6,545	1.80	84% (84% –	84% (83% –	1.00 (0.99 – 1.02) (p=0.58)

media	(64%)	(36%)		85%)	85%)	
Otitis media with comorbidity	2,556 (65%)	1,400 (35%)	1.83	85% (84% – 87%)	84% (82% – 86%)	1.01 (0.98 – 1.04) (p=0.41)
Sinusitis	46,221 (74%)	16,625 (26%)	2.78	88% (88% – 89%)	86% (86% – 87%)	1.02 (1.02 – 1.03) (p<0.001)
Sinusitis with comorbidity	12,013 (73%)	4,394 (27%)	2.73	90% (90% – 91%)	89% (88% – 90%)	1.02 (1.00 – 1.03) (p=0.006)
Sore throat	136,117 (68%)	65,531 (32%)	2.08	57% (56% – 57%)	57% (56% – 57%)	1.00 (0.99 – 1.01) (p=0.67)
Sore throat with comorbidity	24,376 (67%)	11,968 (33%)	2.04	53% (52% – 54%)	50% (49% – 51%)	1.06 (1.04 – 1.08) (p<0.001)
URTI	90,295 (68%)	42,998 (32%)	2.10	34% (34% – 34%)	36% (35% – 36%)	0.96 (0.94 – 0.97) (p<0.001)
URTI with comorbidity	22,995 (65%)	12,515 (35%)	1.84	45% (45% – 46%)	45% (44% – 46%)	1.00 (0.98 – 1.02) (p=0.96)

These gender differences in prescribing were broadly similar among adults with comorbidity. Women with comorbidity were substantially less likely than men with comorbidity to receive antibiotic prescriptions when consulting with acne (RR 0.73, CI 0.68 – 0.78) or impetigo (RR 0.86, CI 0.80 – 0.94) (Table 1), and also ILI (RR 0.87, CI 0.78 – 0.97), but for all other conditions the difference between the proportions of men and women that received prescriptions when consulting was ≤3%. Again, among patients with comorbidity, the proportions of antibiotics prescribed to women for each condition correlate strongly with the proportions of consultations made by women (Spearman's ρ=0.78; p=0.005), but not with the proportion of women that received prescriptions when consulting with those conditions (Spearman's ρ=0.41, p=0.19).

Patients with comorbidity were generally more likely than those without comorbidity to receive antibiotic prescriptions when consulting (see online supplementary appendix). In both men and women the greatest of these differences were in URTI, cough and ILI, where the proportion of patients that received antibiotics when consulting was approximately 6-

12% higher among patients with comorbidity. Patients with comorbidity were also more likely to receive a prescription when consulting with bronchitis, gastroenteritis and sinusitis. However, among women consulting with sore throat and LRTI, and among men consulting with sore throat, LRTI and acne, the proportions of patients that received antibiotics when consulting was significantly lower among patients with comorbidity than among otherwise healthy patients.

Discussion

This study affirms that there is still a substantial gender gap in antibiotic prescribing in English primary care, and shows that this gap is in large part unexplained by biased prescribing behaviour and gender differences in UTI and comorbidity. The prescribing gap is most pronounced in adults, with women receiving approximately twice as many antibiotic prescriptions as men, and 70% more when excluding antibiotics used to treat UTI. These differences in prescribing are proximate to differences in health-seeking behaviour, with healthy adult women consulting primary care approximately 80% more than healthy adult men across the 12 conditions included in this study. Accordingly, men and women are just as likely to be prescribed antibiotics when consulting with most common RTIs. These findings provide strong support for the hypothesis that higher antibiotic prescribing in adult women is primarily driven by a higher consultation rate.

This study has a number of strengths. First, THIN is a robust data source that is representative of the English primary care patient population.[23] Second, the extensive mapping of Read codes to clinical conditions made it possible to analyse prescribing across a range of conditions and to account for comorbidities, which differ between men and women and influence whether or not a practitioner prescribes. Third, since UTI in English primary care is almost always treated with trimethoprim or nitrofurantoin, and since these antibiotics are rarely used to treat other conditions in primary care,[11] it was possible to approximate total prescribing for UTI despite incomplete diagnostic coding. There were also limitations to this work, the largest being that the clinical appropriateness of prescribing could not be determined, and so it was not possible to evaluate whether consulting men and women are differently indicated for antibiotics, and hence whether equal prescribing proportions in RTIs are clinically justified. Further, other patient characteristics that may co-vary with gender and consultation behaviour, such as socioeconomic status, could not be considered. Finally, the quality of diagnostic coding varies within and between practices, which may bias estimates of consultation and prescribing.

It is well observed that rates of primary care consultation and antibiotic prescribing are substantially higher in adult women than in adult men,[6-9,16-18] but previous studies have been unable to show that the gender gap in antibiotic prescribing can primarily be attributed to consultation, as opposed to other relevant factors such as UTI, comorbidity and other patient and prescriber behaviours. These findings builds on a previous study of prescribing in UK primary care between 1997 and 2006, which found similar male and female prescribing proportions in a selection of RTIs, but was conducted in a limited subset of patients, did not consider prescribing for UTI, and did not account for comorbidities, non-respiratory conditions, or patients consulting outside of their registered practice.[24]

Antibiotic prescribing was proportionate to consultation for most conditions, but skin conditions were notable exceptions: men consulted much less with acne and impetigo but were substantially more likely than women to receive an antibiotic prescription when consulting (although acne is unique in that women but not men can be treated with combination oral contraceptives, confounding gender comparisons in antibiotic prescribing). Although women consult more frequently, they are not known to suffer from greater incidence or severity of disease in the conditions included here.[12,13] Studies have also shown that men tend to consult later in the course of their illness and may have a higher threshold to seeking care.[17,25,26] When prescribing is truly reflective of patient need (e.g., as in skin conditions, due to low diagnostic uncertainty), a higher prescribing proportion in men may be expected if, on average, less frequent and/or delayed consultation is coupled with more severe clinical presentation. Yet, for the remaining conditions in this study – predominantly RTIs – prescribing proportions in male and female patients were strikingly similar despite vast differences in consultation. This may be indicative of imprudent prescribing. In non-skin conditions there is often (i) considerable diagnostic uncertainty (e.g., difficulty in differentiating acute bronchitis and pneumonia in primary care) and (ii) uncertainty around subjective, insensitive or unspecific clinical severity markers (e.g., reliance on patient symptom reporting and other clinical features that poorly predict benefit from antibiotic treatment).[27,28] Faced by these uncertainties, GPs may prescribe antibiotics precautiously – and imprudently – to a large proportion of patients with RTI, regardless of disease severity, resulting in high prescribing proportions in all patients.

Although imprudent prescribing has been the target of numerous antimicrobial stewardship interventions, it remains obstinate in English primary care,[29] and the combination of high consultation rates among female patients and overly precautious antibiotic prescribing behaviour among GPs could result in a disproportionate share of inappropriate (i.e., unnecessary) antibiotic prescriptions in women. However, previous studies of gender differences in inappropriate prescribing have found mixed results,[6,30] and it remains to be shown whether men and women in UK primary care differ in their objective clinical need for antibiotics when consulting with RTIs and other common conditions. Yet, regardless of whether or not women are more likely to receive an inappropriate prescription per consultation, it is likely that a higher level of antibiotic prescribing in women is accompanied by a greater total number of inappropriate prescriptions.

Conclusions

This study reaffirms known gender gaps in health-seeking behaviour and antibiotic prescribing, and shows that, with exceptions, adult men and women in English general practice are equally likely to receive an antibiotic prescription when seeking care for common conditions, and that gender differences in the number of antibiotics prescribed are largely driven by differences in consultation behaviour. Equal prescribing proportions may seem to indicate relative parity in how men and women are treated when they consult, but women consult vastly more than men yet have not been shown to suffer from more frequent or severe infection in the conditions included in this study. It is thus plausible that a higher rate of consultation in women is coupled with a milder average clinical presentation, but that overly precautious GPs prescribe even when antibiotics are not clinically necessary, resulting in high rates of prescribing in all patients. Given the urgent need to reduce unnecessary antibiotic prescribing, it is crucial to more deeply understand how and to whom antibiotics are overprescribed. To this end, future work should further investigate the clinical (in)appropriateness of gender differences in antibiotic prescribing in primary care.

Figure captions

Figure 1. All systemic antibiotic prescriptions recorded in THIN between 2013 and 2015, stratified by gender and age group. Antibiotics used to treat UTI (trimethoprim and nitrofurantoin) are identified separately from all other antibiotics.

Figure 2. For common conditions in general practice, the proportions all consultations (circles) and antibiotic prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity consulting at their primary registered practice. Conditions are ordered by consultation proportion.

Additional information

Contributors: KP and DS conceived and designed the study. KP extracted the data from The Health Improvement Network database. CD and KP conducted the analyses. DS, JR, KP and TS carried out interpretation of the data. DS drafted the manuscript. CD, JR, KP and TS critically revised the manuscript for important intellectual content. All authors approved the final version prior to submission.

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Competing interests: None.

Ethics approval: This study received approval from THIN's Scientific Review Committee (reference number 16THIN-071-A2).

Data sharing statement: This analysis is based on a large sample from The Health Improvement Network, provided by IMS Health. The authors' license for using these data precludes the sharing of raw data with third parties.

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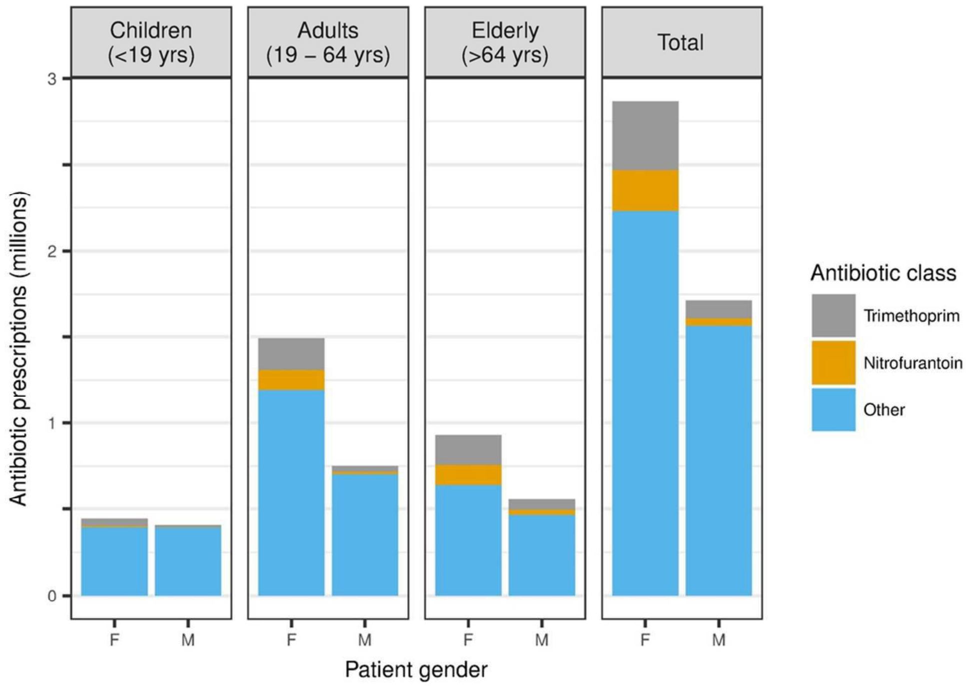

Figure 1. All systemic antibiotic prescriptions recorded in THIN between 2013 and 2015, stratified by gender and age group. Antibiotics used to treat UTI (trimethoprim and nitrofurantoin) are identified separately from all other antibiotics.

89x63mm (300 x 300 DPI)

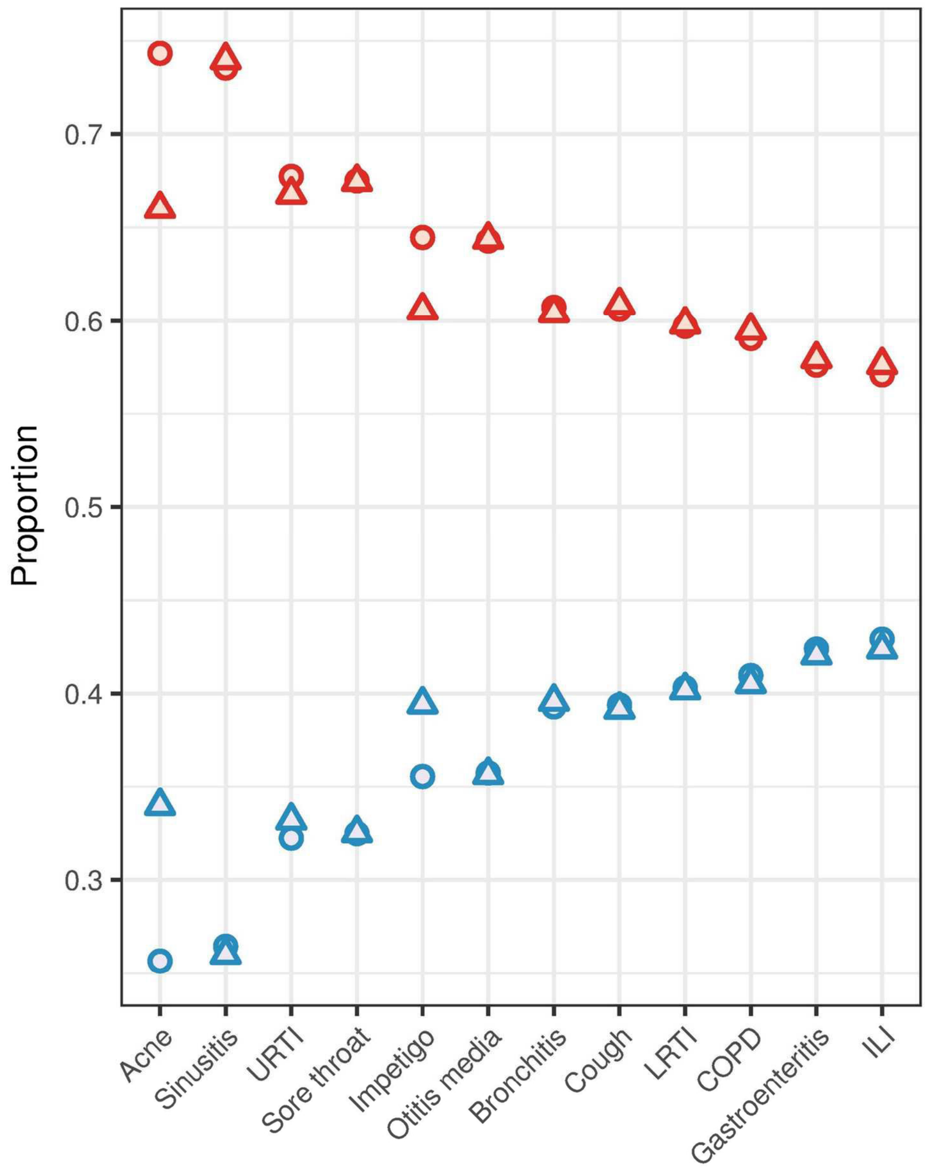

Figure 2. For common conditions in general practice, the proportions all consultations (circles) and antibiotic prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity consulting at their primary registered practice. Conditions are ordered by consultation proportion.

120x151mm (300 x 300 DPI)

Online supplementary appendix

Table S1. Primary care consultations and antibiotic prescribing proportions per consultation in adult men and women (aged 19 – 64 years) with and without comorbidities for 12 different conditions. Consultations from all practices in THIN are included, regardless of whether or not patients were registered there.

	Number of consultations (% of total)		Ratio of female:male consultation	Proportion of patients receiving prescription when consulting (95% CI)		Relative risk of receiving antibiotic prescription when consulting as female (95% CI)
	Women	Men		Women	Men	
Acne	46,041 (74%)	16,456 (26%)	2.80	41% (40% – 41%)	60% (59% – 61%)	0.67 (0.67 – 0.69) (p<0.001)
Acne with comorbidity	3,938 (66%)	1,993 (34%)	1.98	42% (40% – 44%)	55% (53% – 58%)	0.76 (0.72 – 0.80) (p<0.001)
Bronchitis	12,318 (61%)	7,977 (39%)	1.54	83% (82% – 84%)	84% (83% – 85%)	0.99 (0.98 – 1.00) (p=0.09)
Bronchitis with comorbidity	4,916 (59%)	3,375 (41%)	1.46	87% (86% – 88%)	89% (88% – 90%)	0.98 (0.96 – 1.00) (p=0.01)
COPD	5,263 (59%)	3,688 (41%)	1.43	71% (70% – 73%)	69% (67% – 71%)	1.03 (1.00 – 1.06) (p=0.04)
COPD with non-RTI comorbidity	2,050 (54%)	1,718 (46%)	1.19	70% (67% – 72%)	67% (64% – 70%)	1.04 (1.00 – 1.09) (p=0.08)
Cough	255,587 (60%)	166,899 (40%)	1.53	49% (49% – 50%)	49% (49% – 49%)	1.01 (1.00 – 1.02) (p<0.001)
Cough with comorbidity	104,317 (59%)	71,401 (41%)	1.46	58% (58% – 58%)	56% (56% – 57%)	1.03 (1.02 – 1.04) (p<0.001)
Gastroenteritis	70,835 (57%)	52,796 (43%)	1.34	6% (6% – 6%)	6% (6% – 6%)	0.98 (0.93 – 1.02) (p=0.32)
Gastroenteritis with comorbidity	19,636 (56%)	15,118 (44%)	1.30	7% (7% – 7%)	8% (7% – 8%)	0.91 (0.85 – 0.99) (p=0.02)
ILI	17,050 (58%)	12,546 (42%)	1.36	20% (19% – 20%)	20% (19% – 20%)	1.01 (0.96 – 1.05) (p=0.83)
ILI with comorbidity	3,034 (56%)	2,336 (44%)	1.30	26% (24% – 27%)	28% (26% – 30%)	0.93 (0.85 – 1.01) (p=0.09)

Impetigo	8,707 (64%)	4,803 (36%)	1.81	52% (51% – 53%)	61% (59% – 62%)	0.85 (0.83 – 0.88) (p<0.001)
Impetigo with comorbidity	1,686 (65%)	925 (35%)	1.82	51% (49% – 54%)	61% (58% – 65%)	0.84 (0.78 – 0.90) (p<0.001)
LRTI	89,644 (59%)	61,550 (41%)	1.46	88% (88% – 89%)	87% (87% – 87%)	1.01 (1.01 – 1.02) (p<0.001)
LRTI with comorbidity	57,609 (59%)	39,687 (41%)	1.45	88% (87% – 88%)	86% (85% – 86%)	1.02 (1.02 – 1.03) (p<0.001)
Otitis media	19,440 (64%)	10,985 (36%)	1.77	82% (81% – 82%)	81% (80% – 82%)	1.01 (1.00 – 1.03) (p = 0.05)
Otitis media with comorbidity	3,935 (64%)	2,246 (36%)	1.75	83% (82% – 84%)	82% (80% – 83%)	1.02 (0.99 – 1.04) (p=0.13)
Sinusitis	74,863 (73%)	27,339 (27%)	2.74	87% (87% – 88%)	86% (85% – 86%)	1.02 (1.02 – 1.03) (p<0.001)
Sinusitis with comorbidity	18,475 (73%)	6,865 (27%)	2.69	90% (89% – 90%)	88% (87% – 89%)	1.02 (1.01 – 1.03) (p<0.001)
Sore throat	224,537 (67%)	109,975 (33%)	2.04	57% (56% – 57%)	57% (57% – 57%)	0.99 (0.99 – 1.00) (p=0.03)
Sore throat with comorbidity	37,446 (66%)	18,973 (34%)	1.97	53% (53% – 54%)	50% (50% – 51%)	1.06 (1.04 – 1.08) (p<0.001)
URTI	148,959 (68%)	71,244 (32%)	2.09	35% (34% – 35%)	36% (36% – 37%)	0.96 (0.95 – 0.97) (p<0.001)
URTI with comorbidity	35,450 (64%)	19,630 (36%)	1.81	45% (45% – 46%)	46% (45% – 47%)	0.99 (0.97 – 1.01) (p=0.46)

Table S2. The relative risk of receiving an antibiotic prescription when consulting with comorbidity. All adult patients consulting at their primary registered practice are included.

	Relative Risk (95% Confidence Interval) (p-value)	
	Women	**Men**
Acne	0.99 (0.94 – 1.05) (p=0.80)	0.91 (0.87 – 0.97) (p<0.001)

Bronchitis	1.05 (1.03 – 1.06) (p<0.001)	1.06 (1.04 – 1.08) (p<0.001)
COPD (non-respiratory comorbidity)	1.02 (0.98 – 1.05) (p=0.32)	0.98 (0.94 – 1.03) (p=0.42)
Cough	1.19 (1.18 – 1.20) (p<0.001)	1.17 (1.16 – 1.18) (p<0.001)
Gastroenteritis	1.27 (1.18 – 1.40) (p<0.001)	1.24 (1.14 – 1.35) (p<0.001)
ILI	1.29 (1.18 – 1.40) (p<0.001)	1.51 (1.38 – 1.65) (p<0.001)
Impetigo	1.04 (0.98 – 1.10) (p=0.24)	1.02 (0.95 – 1.09) (p=0.68)
LRTI	0.99 (0.99 – 1.00) (p=0.002)	0.99 (0.98 – 0.99) (p<0.001)
Otitis media	1.01 (0.99 – 1.03) (p=0.18)	1.00 (0.98 – 1.03) (p=0.76)
Sinusitis	1.02 (1.02 – 1.03) (p<0.001)	1.03 (1.02 – 1.04) (p<0.001)
Sore throat	0.94 (0.93 – 0.95) (p<0.001)	0.88 (0.87 – 0.90) (p<0.001)
URTI	1.32 (1.30 – 1.35) (p<0.001)	1.27 (1.24 – 1.30) (p<0.001)

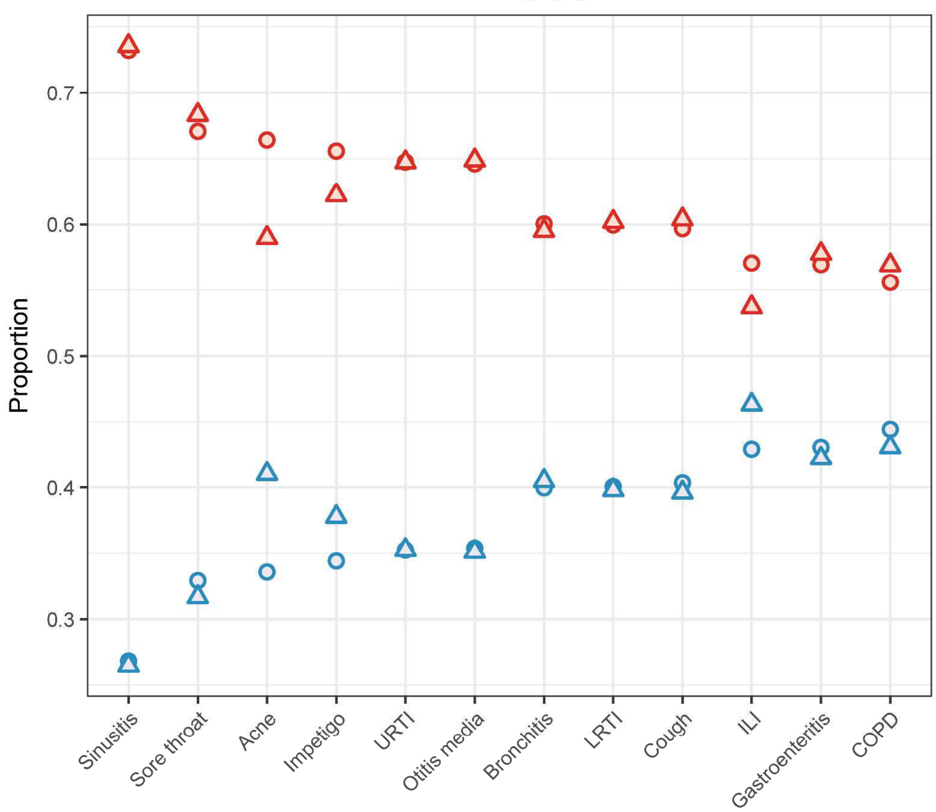

Figure S1. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) with comorbidity who consulted at their primary registered practice. Conditions are ordered by consultation proportion.

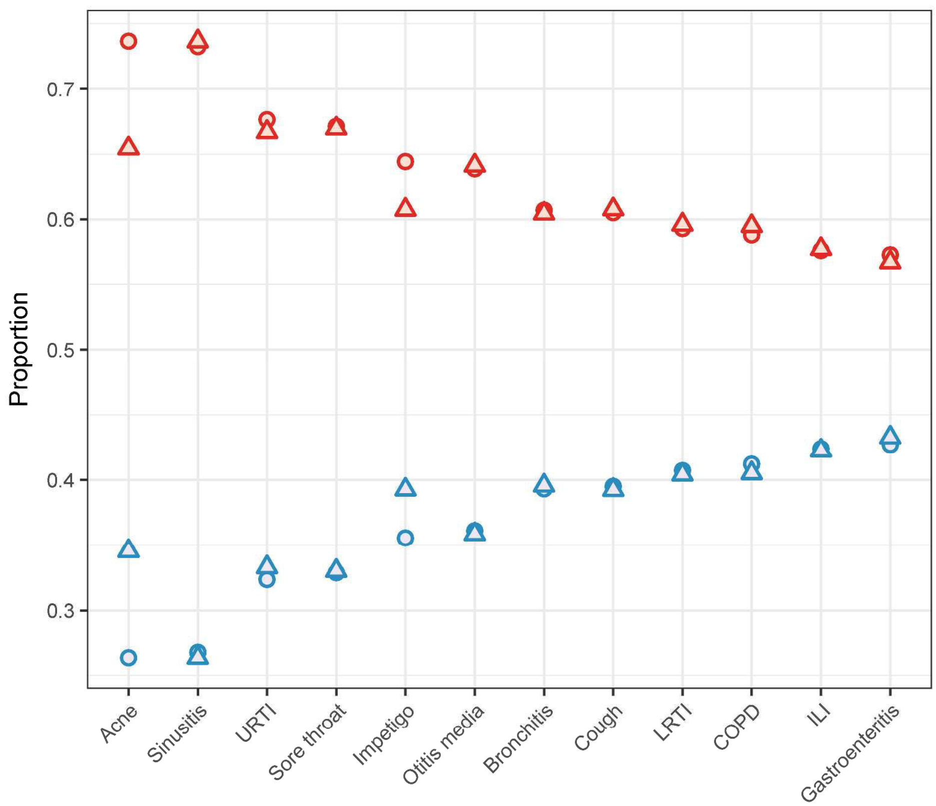

Figure S2. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity, including those who consulted outside their primary registered practice. Conditions are ordered by consultation proportion.

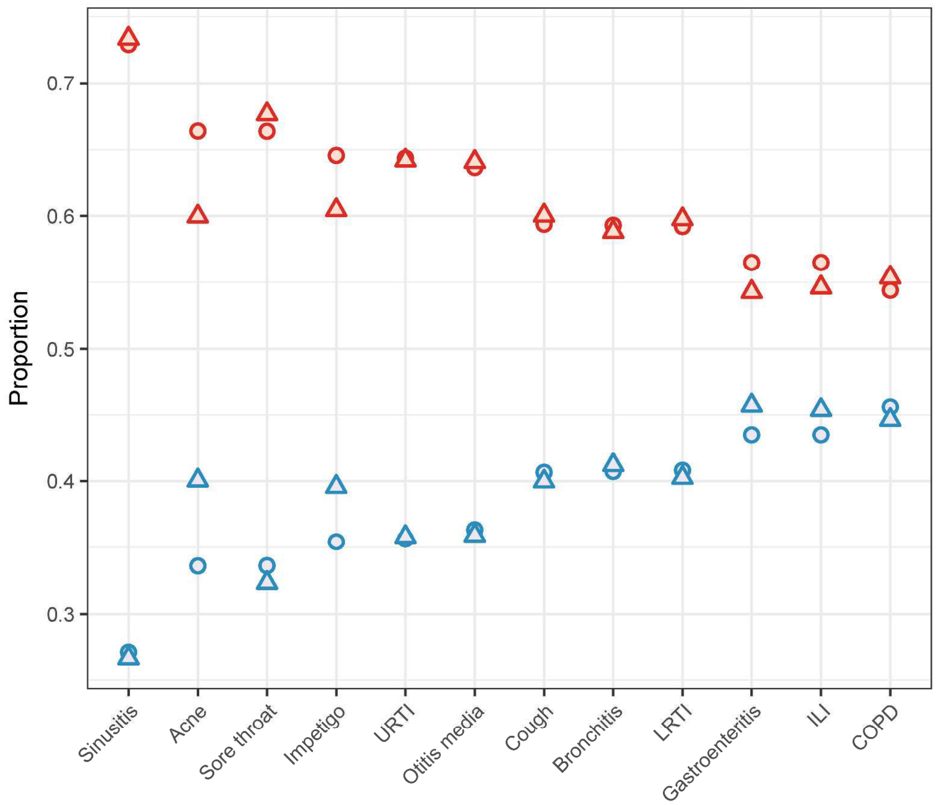

Figure S3. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) with comorbidity, including those who consulted outside their primary registered practice. Conditions are ordered by consultation proportion.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Provided in title 'cross-sectional analysis' and further detail in abstract**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Provided**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Background provided, including studies in English primary care and broader meta-analyses of gender bias in prescribing**
Objectives	3	State specific objectives, including any prespecified hypotheses **Objectives and four potential causes of the gender gap stated**
Methods		
Study design	4	Present key elements of study design early in the paper **Throughout methods**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Methods paragraph 1.**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Methods paragraph 1.**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Methods paragraphs 3-4**
Data sources/ measurement	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 **Methods paragraph 1**
Bias	9	Describe any efforts to address potential sources of bias **Throughout methods**
Study size	10	Explain how the study size was arrived at **Implicit: all eligible patients in database were included**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Methods paragraphs 2 - 4**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Methods paragraphs 2 - 4**
Results		
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 a flow diagram **Results paragraph 1**
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 **Results paragraph 1**
Outcome data	15*	Report numbers of outcome events or summary measures **Table 1**
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 **Table 1 and throughout results**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **See figures and supplementary file**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Discussion paragraph 1**
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 **Discussion paragraphs 2 and 5**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Discussion paragraphs 4 and 5**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Discussion paragraph 2**
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 **Provided; study funded internally by Public Health England**

*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 www.strobe-statement.org.

BMJ Open

Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of English primary care

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Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of English primary care

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Word count: 2720

Abstract

Objectives: To explore causes of the gender gap in antibiotic prescribing, and to determine whether women are more likely than men to receive an antibiotic prescription per consultation.

Design: Cross-sectional analysis of routinely collected electronic medical records from The Health Improvement Network (THIN).

Setting: English primary care.

Participants: Patients who consulted general practices registered with THIN between 2013 and 2015.

Primary and secondary outcome measures: Total antibiotic prescribing was measured in children (<19 years), adults (19 – 64) and the elderly (65+). For twelve common conditions, the number of adult consultations was measured, and the relative risk (RR) of being prescribed antibiotics when consulting as female or with comorbidity was estimated.

Results: Among 4.57 million antibiotic prescriptions observed in the data, female patients received 67% more prescriptions than males, and 43% more when excluding antibiotics used to treat urinary tract infection (UTI). These gaps were more pronounced in adult women (99% more prescriptions than males; 69% more when excluding UTI) than in children (9%; 0%) or the elderly (67%; 38%). Among adults, women accounted for 64% of consultations (61% among patients with comorbidity), but were not substantially more likely than men to receive an antibiotic prescription when consulting with common conditions such as cough (RR 1.01; CI 1.00 – 1.02), sore throat (RR 1.01, CI 1.00 – 1.01) and lower respiratory tract infection (RR 1.00, CI 1.00 – 1.01). Exceptions were skin conditions: women were less likely to be prescribed antibiotics when consulting with acne (RR 0.67, CI 0.66 – 0.69) or impetigo (RR 0.85, CI 0.81 – 0.88).

Conclusions: The gender gap in antibiotic prescribing can largely be explained by consultation behaviour. Although in most cases adult men and women are equally likely to be prescribed an antibiotic when consulting primary care, it is unclear whether or not they are equally indicated for antibiotic therapy.

Strengths and limitations of this study:

- This study is one of the first to explore the underlying causes of the large gap in the number of antibiotics prescribed to men and women in primary care.
- Findings are derived from a large, representative sample of primary care patients in England.
- Extensive mapping of diagnostic codes to clinical conditions made it possible to analyse prescribing across a range of conditions and to account for comorbidity.
- Identification of antibiotics that are used to treat UTI but rarely other conditions in this setting (trimethoprim and nitrofurantoin) allowed for approximation of UTI prescribing despite incomplete diagnostic coding.
- The data do not include indicators of antibiotic appropriateness, such as severity of illness, and so the clinical appropriateness of gender differences in prescribing could not be evaluated.

Introduction

Reducing the unnecessary use of antibiotics is as an essential means of mitigating the emergence of antimicrobial resistance and its associated costs,[1,2] but prescribing reductions are not without risk. The causes and magnitudes of prescribing vary substantially between practices and prescribers,[3-5] and sweeping, uncalibrated interventions could jeopardise some patients while failing to prevent unnecessary prescribing in others. In order to safely and effectively reduce antibiotic use, it is imperative to understand how and to whom antibiotics are prescribed.

Gender is a key determinant of antibiotic prescribing. A recent meta-analysis across primary care in nine high-income countries found that females received more antibiotics than males in all age groups except those >75, with women aged 16 to 54 receiving 36% to 40% more antibiotics than men of the same age.[6] Similarly, across English and Welsh primary care, the rate of antibiotic prescribing has been found to be 40% higher in female than in male patients.[7] Although the latter figure dates from 1996, gender disparities in England have more recently been observed in out-of-hours and paediatric care, with women and girls receiving more antibiotic prescriptions than men and boys.[8,9]

There are several proposed explanations for this gender gap. First, some infectious diseases affect men and women differently. In particular, urinary tract infection (UTI) is more common in adult women than in men and accounts for over 20% of antibiotic prescriptions in English primary care.[10,11] However, respiratory tract infections (RTIs) account for more than twice as many prescriptions as UTI,[11] and women are not more susceptible to these conditions than men,[12-14] although gender differences in comorbidity may underlie some variation in prescribing. Second, as in many countries,[15,16] women in the UK consult their general practitioner (GP) more often than men,[17-19] and consultation rate is linked to antibiotic prescribing.[5] Previous studies of relatively small samples of patients with RTI have found that gender differences in consultation are proportionate to differences in prescribing [20,21], but it is unclear whether or not this is true across a greater range of conditions, when taking comorbidity into account, and using a more recent, nationally representative sample of patients. Finally, other social and behavioural factors may also play a role. For example, men and women communicate differently with health professionals, and prescribers may have biases that affect their willingness to prescribe antibiotics during consultations with women versus men.[22,23] Ultimately, it remains unknown to what extent these and other factors combine to explain the gender gap in antibiotic prescribing.[6]

Here, gender differences in antibiotic prescribing were analysed using a large, representative sample of primary care patients in England. Antibiotic prescribing in male and female children, adults and the elderly was compared at the population level. The influence of gender on prescribing was assessed by controlling for consultation and comorbidity, and calculating the proportions of adult men and women that received systemic antibiotic prescriptions when presenting to primary care with a suite of common conditions. These prescribing proportions facilitate a deeper understanding of the causes of the gender gap in antibiotic prescribing, and may inform prescribing intervention design.

Methods

This study used data from English general practices registered with The Health Improvement Network (THIN), a UK-based primary care electronic medical record database. Practices were included that provided data for at least one full calendar year between January 1, 2013 and December 31, 2015; there were 349 such practices in 2013, 285 in 2014 and 191 in 2015. Anonymised patient data were extracted from these practices that met acceptable standards for research data collection. All systemic antibiotic prescriptions (antibiotics from British National Formulary chapter 5.1,[24] excluding antituberculosis and antileprosy drugs) recorded in THIN were analysed by patient gender and age. Patient age at the time of consultation was used to classify patients as children (aged 0-18 years), adults (19-64 years) and the elderly (65+ years). Due to a very large sample size, proportions of antibiotics prescribed to male versus female patients are reported without confidence intervals.

Read codes (the diagnostic codes used in THIN) were analysed to quantify the number of male and female consultations for acute presentations of 12 common conditions that are treated with antibiotics to varying degrees: acne, bronchitis, chronic obstructive pulmonary disease (COPD), cough, gastroenteritis, impetigo, influenza-like illness (ILI), lower respiratory tract infection (LRTI), otitis media, sinusitis, sore throat and upper respiratory tract infection (URTI). A vast number of Read codes are used in THIN, and the methods used to assign specific Read codes to different conditions and to link Read codes to acute antibiotic prescriptions are described elsewhere.[11] The ratio of female to male consultations (F:M) was then calculated to quantify gender differences in consultation for each of these conditions.

In THIN, a large proportion of UTI consultations are poorly coded, particularly in patients consulting for UTI prophylaxis or chronic/recurrent UTI. However, between 2013-2015 in English primary care, the antibiotics used to prevent and treat the vast majority of UTIs – trimethoprim and nitrofurantoin – were rarely used for other conditions.[11, 25] Prescriptions of trimethoprim and nitrofurantoin were thus used as a proxy measure for prescribing for UTI.

Prescribing proportions were then calculated by dividing the total number of prescriptions for a given condition by the number of consultations for that condition. To account for patients that consulted more than once, robust standard errors were used when calculating prescribing proportions. These data were also used to calculate the relative risk (RR) of being prescribed an antibiotic when consulting as female as opposed to male. In the main analysis, consultations were included if they occurred at a patient's primary registered practice, but in a sensitivity analysis all patient consultations recorded in THIN were included. Patients with comorbidity were analysed separately from otherwise 'healthy' patients (i.e., those without comorbidity) to minimise potential biases in consultation and prescribing due to gender differences in background health status. Further, the RR of being prescribed an antibiotic when consulting with comorbidity was also calculated for each condition and gender. Comorbidities were identified by the Read codes that indicate qualification for the free seasonal influenza vaccination programme: asthma, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease and immunosuppressive disease.[26] Patients who received at least two prescriptions of systemic or inhaled corticosteroids or immunosuppressive drugs in the 365 days prior to their consultation were also included in this group, since these drugs indicate an increased risk of serious complications after (respiratory tract) infections.[26]

All data were analysed using STATA 13.1 and R version 3.1.

Results

Of all antibiotic prescriptions observed in THIN between 2013 and 2015 (n=4,574,363), the majority (62.6%) were in female patients (Figure 1). Adult women received approximately twice (99.0%) as many antibiotic prescriptions as adult men, whereas elderly women and girls received 67.4% and 9.2% more prescriptions, respectively, than elderly men and boys. Nitrofurantoin and trimethoprim accounted for 17.1% of all prescriptions, 81.3% of which were prescribed to female patients. The prescribing gender gap narrowed in all age groups when these antibiotics were removed, and became negligible in children (0.3%), but adult and elderly women still received, respectively, 69.2% and 37.7% more antibiotic prescriptions than adult and elderly men.

Healthy adult women consulted primary care more than men for all 12 of the conditions included in this study, accounting for 64.3% of all consultations (61.9% among patients with comorbidity). The biggest gender gaps in consultation were in acne (F:M 2.90) and sinusitis (F:M 2.78). However, there was little gender difference in the proportions of healthy adult patients that received antibiotic prescriptions when consulting (Table 1). The greatest gaps were in acne, where 60% of consulting men received systemic antibiotics compared to 41% of women (RR 0.67; CI 0.66 – 0.69), and in impetigo, where, respectively, 62% and 52% of men and women received prescriptions (RR 0.85, CI 0.81 – 0.88). In all other conditions, the difference between the proportions of men and women that received antibiotic prescriptions when consulting was ≤2%, although these gaps were statistically significant in cough (F>M, p=0.02), LRTI (F>M, p=0.02), sinusitis (F>M, p<0.001) and URTI (M>F, p<0.001). These results held in a sensitivity analysis when consultations and prescriptions outside of patients' primary registered practice were included (see online supplementary appendix). Further, with the exception of acne and impetigo, the proportions of all antibiotics prescribed to men and women for different conditions were proportionate to the proportions of all consultations made by men and women for those conditions (Figure 2). Accordingly, the proportions of all antibiotics prescribed to women for each condition correlate strongly with the proportions of consultations made by women (Spearman's ρ=0.92; p<0.001), but not with the proportions of women that received prescriptions when consulting with those conditions (Spearman's ρ=0.28, p=0.38).

Table 1. Primary care consultations and antibiotic prescribing proportions per consultation in adult men and women (aged 19 – 64 years) with and without comorbidity for 12 different conditions. Only consultations from patients' primary registered practices are included.

	Number of consultations (% of total)		F:M consultation ratio	Proportion of patients receiving prescription when consulting (95% CI)		Relative risk of receiving antibiotic prescription when consulting as female (95% CI) (p-value)
	Women	Men		Women	Men	
Acne	25,676 (74%)	8,864 (26%)	2.90	41% (40% – 41%)	60% (59% – 61%)	0.67 (0.66 – 0.69) (p<0.001)
Acne with comorbidity	2,344 (66%)	1,185 (34%)	1.98	40% (38% – 42%)	55% (52% – 58%)	0.73 (0.68 – 0.78) (p<0.001)
Bronchitis	7,085 (61%)	4,584 (39)%	1.55	83% (83% – 84%)	84% (83% – 86%)	0.99 (0.97 – 1.00) (p=0.14)
Bronchitis with comorbidity	3,101 (60%)	2,065 (40%)	1.50	87% (86% – 89%)	89% (88% – 91%)	0.98 (0.96 – 1.00) (p=0.03)
COPD	3,274 (59%)	2,271 (41%)	1.44	76% (74% – 78%)	75% (73% – 77%)	1.02 (0.99 – 1.05) (p=0.25)
COPD with non-respiratory comorbidity	1,287 (56%)	1,029 (44%)	1.25	73% (70% – 76%)	70% (69% – 72%)	1.06 (1.01 – 1.11) (p=0.02)
Cough	158,614 (61%)	103,058 (39%)	1.54	48% (48% – 49%)	48% (48% – 48%)	1.01 (1.00 – 1.02) (p=0.02)
Cough with	68,353	46,210	1.48	58% (57% –	56% (56% –	1.03 (1.02 – 1.04) (p<0.001)

comorbidity	(60%)	(40%)		58%)	57%)	
Gastroenteritis	41,870 (58%)	30,810 (42%)	1.36	6% (6% – 6%)	6% (6% – 6%)	1.01 (0.96 – 1.08) (p=0.65)
Gastroenteritis with comorbidity	12,184 (57%)	9,216 (43%)	1.32	8% (7% – 8%)	7% (7% – 8%)	1.03 (0.94 – 1.14) (p=0.49)
ILI	10,569 (57%)	7,946 (43%)	1.33	20% (19% – 20%)	19% (18% – 20%)	1.02 (0.96 – 1.09) (p=0.47)
ILI with comorbidity	1,951 (57%)	1,468 (43%)	1.33	25% (23% – 27%)	29% (27% – 31%)	0.87 (0.78 – 0.97) (p=0.02)
Impetigo	5,272 (64%)	2,907 (36%)	1.81	52% (51% – 54%)	62% (60% – 63%)	0.85 (0.81 – 0.88) (p<0.001)
Impetigo with comorbidity	1,139 (66%)	598 (34%)	1.90	54% (51% – 57%)	63% (58% – 66%)	0.86 (0.80 – 0.94) (p<0.001)
LRTI	52,996 (60%)	35,777 (40%)	1.48	91% (91% – 92%)	91% (91% – 91%)	1.00 (1.00 – 1.01) (p=0.02)
LRTI with comorbidity	36,693 (60%)	24,519 (40%)	1.50	91% (90% – 91%)	90% (89% – 90%)	1.01 (1.01 – 1.02) (p<0.001)
Otitis media	11,773 (64%)	6,545 (36%)	1.80	84% (84% – 85%)	84% (83% – 85%)	1.00 (0.99 – 1.02) (p=0.58)
Otitis media with comorbidity	2,556 (65%)	1,400 (35%)	1.83	85% (84% – 87%)	84% (82% – 86%)	1.01 (0.98 – 1.04) (p=0.41)
Sinusitis	46,221 (74%)	16,625 (26%)	2.78	88% (88% – 89%)	86% (86% – 87%)	1.02 (1.02 – 1.03) (p<0.001)
Sinusitis with comorbidity	12,013 (73%)	4,394 (27%)	2.73	90% (90% – 91%)	89% (88% – 90%)	1.02 (1.00 – 1.03) (p=0.006)
Sore throat	136,117 (68%)	65,531 (32%)	2.08	57% (56% – 57%)	57% (56% – 57%)	1.00 (0.99 – 1.01) (p=0.67)
Sore throat with comorbidity	24,376 (67%)	11,968 (33%)	2.04	53% (52% – 54%)	50% (49% – 51%)	1.06 (1.04 – 1.08) (p<0.001)
URTI	90,295 (68%)	42,998 (32%)	2.10	34% (34% – 34%)	36% (35% – 36%)	0.96 (0.94 – 0.97) (p<0.001)
URTI with comorbidity	22,995 (65%)	12,515 (35%)	1.84	45% (45% – 46%)	45% (44% – 46%)	1.00 (0.98 – 1.02) (p=0.96)

These gender differences in prescribing were broadly similar among adults with comorbidity. Women with comorbidity were substantially less likely than men with comorbidity to receive antibiotic prescriptions when consulting with acne (RR 0.73, CI 0.68 – 0.78) or impetigo (RR 0.86, CI 0.80 – 0.94) (Table 1), and also ILI (RR 0.87, CI 0.78 – 0.97), but for all other conditions the difference between the proportions of men and women that received prescriptions when consulting was ≤3%. Again, among patients with comorbidity, the proportions of antibiotics prescribed to women for each condition correlate strongly with the proportions of consultations made by women (Spearman's ρ=0.78; p=0.005), but not with the proportion of women that received prescriptions when consulting with those conditions (Spearman's ρ=0.41, p=0.19).

Patients with comorbidity were generally more likely than those without comorbidity to receive antibiotic prescriptions when consulting (see online supplementary appendix). In both men and women the greatest of these differences were in URTI, cough and ILI, where the proportion of patients that received antibiotics when consulting was approximately 6-12% higher among patients with comorbidity. Patients with comorbidity were also more likely to receive a prescription when consulting with bronchitis, gastroenteritis and sinusitis. However, among women consulting with sore throat and LRTI, and among men consulting with sore throat, LRTI and acne, the proportions of patients that received antibiotics when consulting was significantly lower among patients with comorbidity than among otherwise healthy patients.

Discussion

This study affirms that there is still a substantial gender gap in antibiotic prescribing in English primary care, and shows that this gap is in large part unexplained by gender differences in UTI and comorbidity. The prescribing gap is most pronounced in adults, with women receiving approximately twice as many antibiotic prescriptions as men, and 70% more when excluding antibiotics used to treat UTI. These differences in prescribing are proximate to differences in health-seeking behaviour, with healthy adult women consulting primary care approximately 80% more than healthy adult men across the 12 conditions included in this study. Accordingly, men and women are just as likely to be prescribed antibiotics when consulting with most common RTIs. These findings provide strong support for the hypothesis that higher antibiotic prescribing in adult women is primarily driven by a higher consultation rate.

This study has a number of strengths. First, THIN is a robust data source that is representative of the English primary care patient population.[27] Second, the extensive mapping of Read codes to clinical conditions made it possible to analyse prescribing across a range of conditions and to account for comorbidities, which differ between men and women and influence whether or not a practitioner prescribes. Third, since UTI in English primary care was almost always treated with trimethoprim or nitrofurantoin during the years of this study, and since these antibiotics were rarely used to treat other conditions in primary care,[11, 25] it was possible to approximate total prescribing for UTI despite incomplete diagnostic coding. There were also limitations to this work, the largest being that the clinical appropriateness of prescribing could not be determined, and so it was not possible to evaluate whether consulting men and women were differently indicated for antibiotics, and hence whether equal prescribing proportions in RTIs are clinically justified. Further, other patient characteristics that may co-vary with gender and consultation behaviour, such as socioeconomic status, could not be considered. Finally, the quality of diagnostic coding varies within and between practices, which may bias estimates of consultation and prescribing.

It is well observed that rates of primary care consultation and antibiotic prescribing are substantially higher in adult women than in adult men,[6-8,17-19] but previous studies have been unable to show that the gender gap in antibiotic prescribing can primarily be attributed to consultation, as opposed to other relevant factors such as UTI, comorbidity and other patient and prescriber behaviours. These findings build on two previous studies of antibiotic prescribing in primary care between 1997-2006 and 2007-2008, respectively.[20,21] Both studies found similar male and female prescribing proportions in a selection of RTIs, but were conducted in a limited subset of patients and did not account for comorbidities, non-respiratory conditions, patients consulting outside of their registered practice, or gender differences in gross antibiotic prescribing at the population level.

Antibiotic prescribing was proportionate to consultation for most conditions, but skin conditions were notable exceptions: men consulted much less with acne and impetigo but were substantially more likely than women to receive an antibiotic prescription when consulting (although acne is unique in that women but not men can be treated with combination oral contraceptives, confounding gender comparisons in antibiotic prescribing). Although women consult more frequently, they are not known to suffer from greater incidence or severity of disease in the conditions included here.[12,13] Studies have also shown that men tend to consult later in the course of their illness and may have a higher threshold to seeking care.[18,28,29] When prescribing is truly reflective of patient need (e.g., as in skin conditions, due to low diagnostic uncertainty), a higher prescribing proportion in men may be expected if, on average, less frequent and/or delayed consultation is coupled with more severe clinical presentation. Yet, for the remaining conditions in this study – predominantly RTIs – prescribing proportions in male and female patients were strikingly similar despite vast differences in consultation. This may be indicative of imprudent prescribing. In non-skin conditions there is often (i) considerable diagnostic uncertainty (e.g., difficulty in differentiating acute bronchitis and pneumonia in primary care) and (ii) uncertainty around subjective, insensitive or unspecific clinical severity markers (e.g., reliance on patient symptom reporting and other clinical features that poorly predict benefit from antibiotic treatment).[30,31] Faced by these uncertainties, GPs may prescribe antibiotics precautiously – and imprudently – to a large proportion of patients with RTI, regardless of disease severity, resulting in high prescribing proportions in all patients.

Although imprudent prescribing has been the target of numerous antimicrobial stewardship interventions, it remains obstinate in English primary care,[32] and the combination of high consultation rates among female patients and overly precautious antibiotic prescribing behaviour among GPs could result in a disproportionate share of inappropriate (i.e., unnecessary) antibiotic prescriptions in women. However, previous studies of gender differences in inappropriate antibiotic prescribing have found mixed results,[21,33] and it remains to be shown whether men and women in UK primary care differ in their objective clinical need for antibiotics when consulting with RTIs and other common conditions. Yet, regardless of whether or not women are more likely to receive an inappropriate prescription per consultation, it is likely that a higher level of antibiotic prescribing in women is accompanied by a greater total number of inappropriate prescriptions.

Conclusions

This study reaffirms known gender gaps in health-seeking behaviour and antibiotic prescribing, and shows that, with exceptions, adult men and women in English general practice are equally likely to receive an antibiotic prescription when seeking care for common conditions, and that gender differences in the number of antibiotics prescribed are largely driven by differences in consultation behaviour. Equal prescribing proportions may seem to indicate relative parity in how men and women are treated when they consult, but women consult vastly more than men yet have not been shown to suffer from more frequent or severe infection in the conditions included in this study. It is thus plausible that a higher rate of consultation in women is coupled with a milder average clinical presentation, but that overly precautious GPs prescribe even when antibiotics are not clinically necessary, resulting in high rates of prescribing in all patients. Given the urgent need to reduce unnecessary antibiotic prescribing, it is crucial to more deeply understand how and to whom antibiotics are overprescribed. To this end, future work should further investigate gender differences in the clinical (in)appropriateness of antibiotic prescribing in primary care.

<u>Figure captions</u>

Figure 1. All systemic antibiotic prescriptions recorded in THIN between 2013 and 2015, stratified by gender and age group. Antibiotics used to treat UTI (trimethoprim and nitrofurantoin) are identified separately from all other antibiotics.

Figure 2. For common conditions in general practice, the proportions all consultations (circles) and antibiotic prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity consulting at their primary registered practice. Conditions are ordered by consultation proportion.

<u>Additional information</u>

Contributors: DS and KP conceived and designed the study. KP extracted the data from The Health Improvement Network database. CD and KP conducted the analyses. DS, JR, KP and TS carried out interpretation of the data. DS drafted the manuscript. CD, JR, KP and TS critically revised the manuscript for important intellectual content. All authors approved the final version prior to submission.

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Competing interests: None.

Ethics approval: This study received approval from THIN's Scientific Review Committee (reference number 16THIN-071-A2).

Data sharing statement: This analysis is based on a large sample from The Health Improvement Network, provided by IMS Health. The authors' license for using these data precludes the sharing of raw data with third parties.

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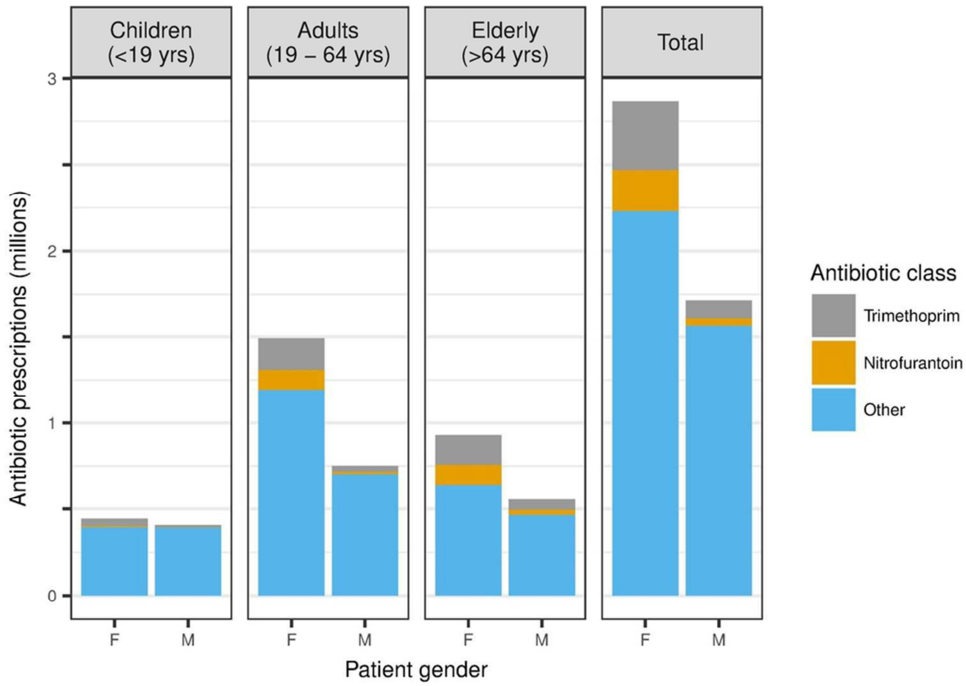

Figure 1. All systemic antibiotic prescriptions recorded in THIN between 2013 and 2015, stratified by gender and age group. Antibiotics used to treat UTI (trimethoprim and nitrofurantoin) are identified separately from all other antibiotics.

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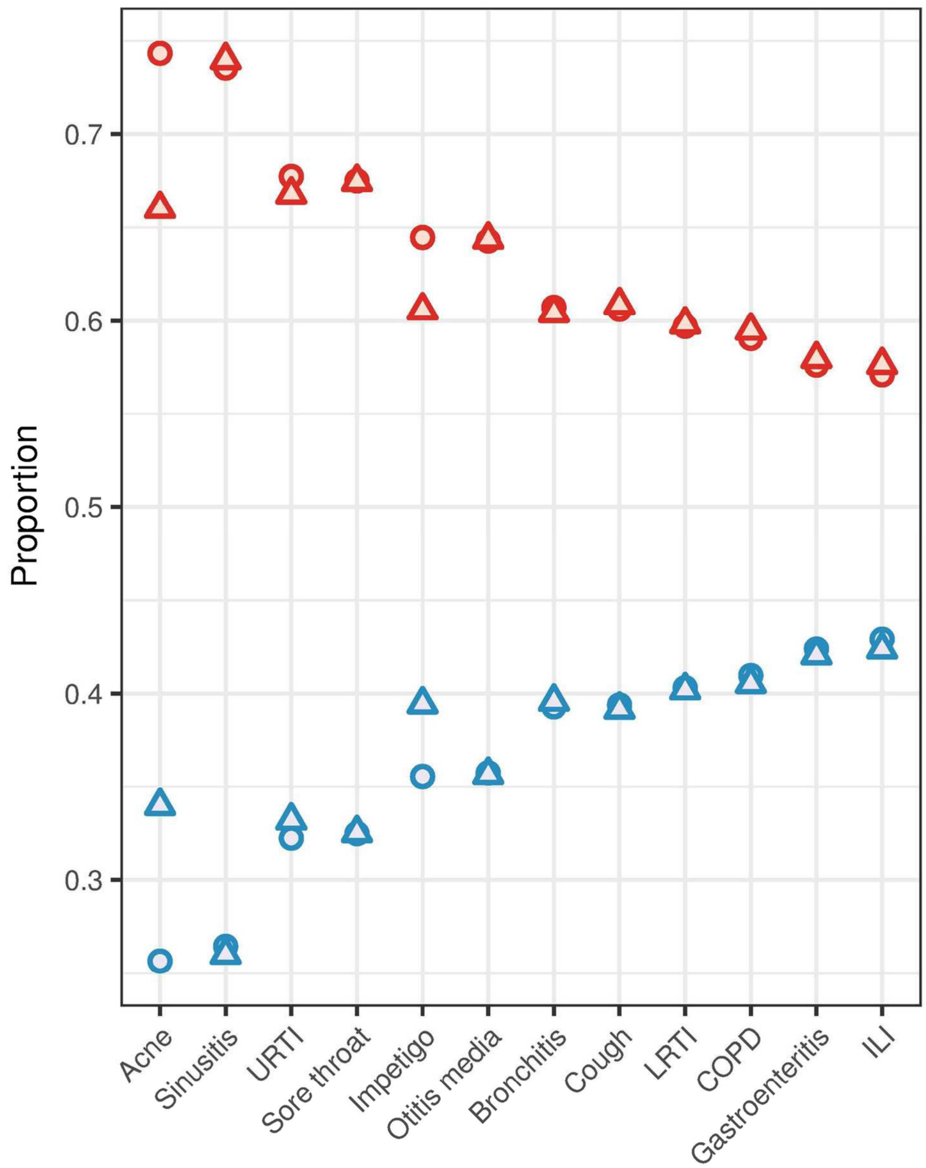

Figure 2. For common conditions in general practice, the proportions all consultations (circles) and antibiotic prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity consulting at their primary registered practice. Conditions are ordered by consultation proportion.

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Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of English primary care

Smith DRM, Dolk FCK, Smieszek T, Robotham JV, Pouwels KB

Online supplementary appendix

Table S1. Primary care consultations and antibiotic prescribing proportions per consultation in adult men and women (aged 19 – 64 years) with and without comorbidities for 12 different conditions. Consultations from all practices in THIN are included, regardless of whether or not patients were registered there.

	Number of consultations (% of total)		Ratio of female:male consultation	Proportion of patients receiving prescription when consulting (95% CI)		Relative risk of receiving antibiotic prescription when consulting as female (95% CI) (p-value)
	Women	Men		Women	Men	
Acne	46,041 (74%)	16,456 (26%)	2.80	41% (40% – 41%)	60% (59% – 61%)	0.67 (0.67 – 0.69) (p<0.001)
Acne with comorbidity	3,938 (66%)	1,993 (34%)	1.98	42% (40% – 44%)	55% (53% – 58%)	0.76 (0.72 – 0.80) (p<0.001)
Bronchitis	12,318 (61%)	7,977 (39%)	1.54	83% (82% – 84%)	84% (83% – 85%)	0.99 (0.98 – 1.00) (p=0.09)
Bronchitis with comorbidity	4,916 (59%)	3,375 (41%)	1.46	87% (86% – 88%)	89% (88% – 90%)	0.98 (0.96 – 1.00) (p=0.01)
COPD	5,263 (59%)	3,688 (41%)	1.43	71% (70% – 73%)	69% (67% – 71%)	1.03 (1.00 – 1.06) (p=0.04)
COPD with non-RTI comorbidity	2,050 (54%)	1,718 (46%)	1.19	70% (67% – 72%)	67% (64% – 70%)	1.04 (1.00 – 1.09) (p=0.08)
Cough	255,587 (60%)	166,899 (40%)	1.53	49% (49% – 50%)	49% (49% – 49%)	1.01 (1.00 – 1.02) (p<0.001)
Cough with comorbidity	104,317 (59%)	71,401 (41%)	1.46	58% (58% – 58%)	56% (56% – 57%)	1.03 (1.02 – 1.04) (p<0.001)
Gastroenteritis	70,835 (57%)	52,796 (43%)	1.34	6% (6% – 6%)	6% (6% – 6%)	0.98 (0.93 – 1.02) (p=0.32)
Gastroenteritis with	19,636 (56%)	15,118 (44%)	1.30	7% (7% – 7%)	8% (7% – 8%)	0.91 (0.85 – 0.99) (p=0.02)

comorbidity						
ILI	17,050 (58%)	12,546 (42%)	1.36	20% (19% – 20%)	20% (19% – 20%)	1.01 (0.96 – 1.05) (p=0.83)
ILI with comorbidity	3,034 (56%)	2,336 (44%)	1.30	26% (24% – 27%)	28% (26% – 30%)	0.93 (0.85 – 1.01) (p=0.09)
Impetigo	8,707 (64%)	4,803 (36%)	1.81	52% (51% – 53%)	61% (59% – 62%)	0.85 (0.83 – 0.88) (p<0.001)
Impetigo with comorbidity	1,686 (65%)	925 (35%)	1.82	51% (49% – 54%)	61% (58% – 65%)	0.84 (0.78 – 0.90) (p<0.001)
LRTI	89,644 (59%)	61,550 (41%)	1.46	88% (88% – 89%)	87% (87% – 87%)	1.01 (1.01 – 1.02) (p<0.001)
LRTI with comorbidity	57,609 (59%)	39,687 (41%)	1.45	88% (87% – 88%)	86% (85% – 86%)	1.02 (1.02 – 1.03) (p<0.001)
Otitis media	19,440 (64%)	10,985 (36%)	1.77	82% (81% – 82%)	81% (80% – 82%)	1.01 (1.00 – 1.03) (p = 0.05)
Otitis media with comorbidity	3,935 (64%)	2,246 (36%)	1.75	83% (82% – 84%)	82% (80% – 83%)	1.02 (0.99 – 1.04) (p=0.13)
Sinusitis	74,863 (73%)	27,339 (27%)	2.74	87% (87% – 88%)	86% (85% – 86%)	1.02 (1.02 – 1.03) (p<0.001)
Sinusitis with comorbidity	18,475 (73%)	6,865 (27%)	2.69	90% (89% – 90%)	88% (87% – 89%)	1.02 (1.01 – 1.03) (p<0.001)
Sore throat	224,537 (67%)	109,975 (33%)	2.04	57% (56% – 57%)	57% (57% – 57%)	0.99 (0.99 – 1.00) (p=0.03)
Sore throat with comorbidity	37,446 (66%)	18,973 (34%)	1.97	53% (53% – 54%)	50% (50% – 51%)	1.06 (1.04 – 1.08) (p<0.001)
URTI	148,959 (68%)	71,244 (32%)	2.09	35% (34% – 35%)	36% (36% – 37%)	0.96 (0.95 – 0.97) (p<0.001)
URTI with comorbidity	35,450 (64%)	19,630 (36%)	1.81	45% (45% – 46%)	46% (45% – 47%)	0.99 (0.97 – 1.01) (p=0.46)

Table S2. The relative risk of receiving an antibiotic prescription when consulting with comorbidity. All adult patients consulting at their primary registered practice are included.

	Relative Risk (95% Confidence Interval) (p-value)	
	Women	**Men**
Acne	0.99 (0.94 – 1.05) (p=0.80)	0.91 (0.87 – 0.97) (p<0.001)
Bronchitis	1.05 (1.03 – 1.06) (p<0.001)	1.06 (1.04 – 1.08) (p<0.001)
COPD (non-respiratory comorbidity)	1.02 (0.98 – 1.05) (p=0.32)	0.98 (0.94 – 1.03) (p=0.42)
Cough	1.19 (1.18 – 1.20) (p<0.001)	1.17 (1.16 – 1.18) (p<0.001)
Gastroenteritis	1.27 (1.18 – 1.40) (p<0.001)	1.24 (1.14 – 1.35) (p<0.001)
ILI	1.29 (1.18 – 1.40) (p<0.001)	1.51 (1.38 – 1.65) (p<0.001)
Impetigo	1.04 (0.98 – 1.10) (p=0.24)	1.02 (0.95 – 1.09) (p=0.68)
LRTI	0.99 (0.99 – 1.00) (p=0.002)	0.99 (0.98 – 0.99) (p<0.001)
Otitis media	1.01 (0.99 – 1.03) (p=0.18)	1.00 (0.98 – 1.03) (p=0.76)
Sinusitis	1.02 (1.02 – 1.03) (p<0.001)	1.03 (1.02 – 1.04) (p<0.001)
Sore throat	0.94 (0.93 – 0.95) (p<0.001)	0.88 (0.87 – 0.90) (p<0.001)
URTI	1.32 (1.30 – 1.35) (p<0.001)	1.27 (1.24 – 1.30) (p<0.001)

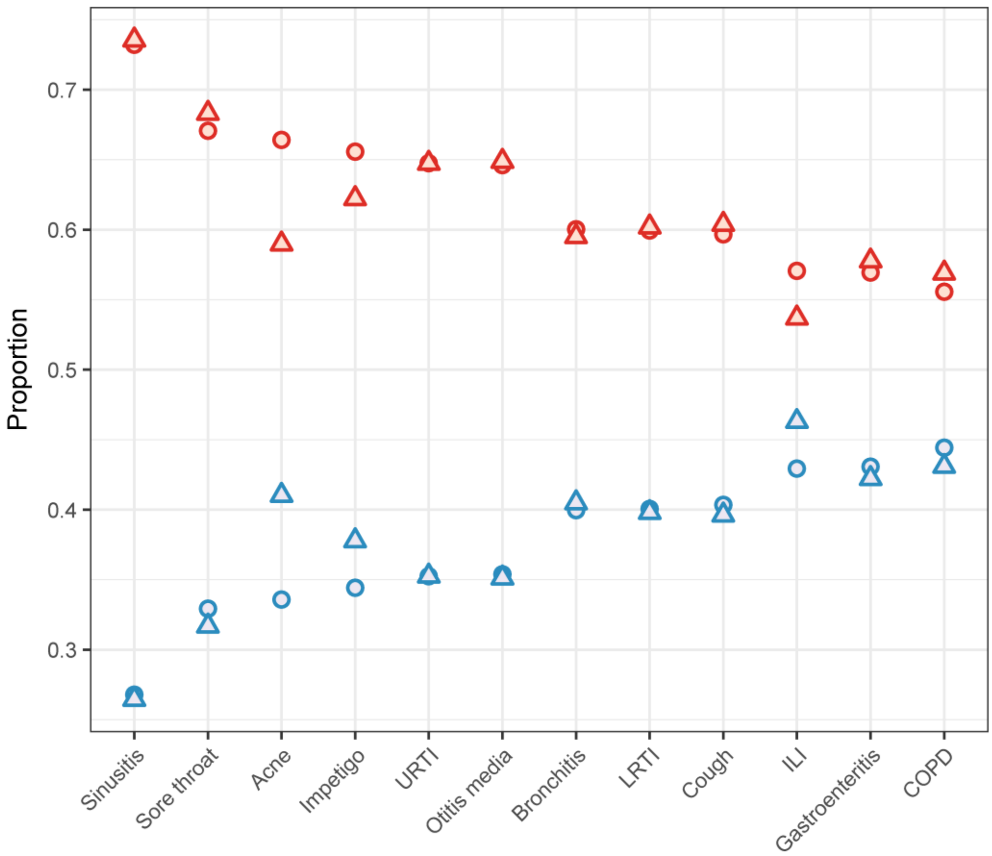

Figure S1. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) with comorbidity who consulted at their primary registered practice. Conditions are ordered by consultation proportion.

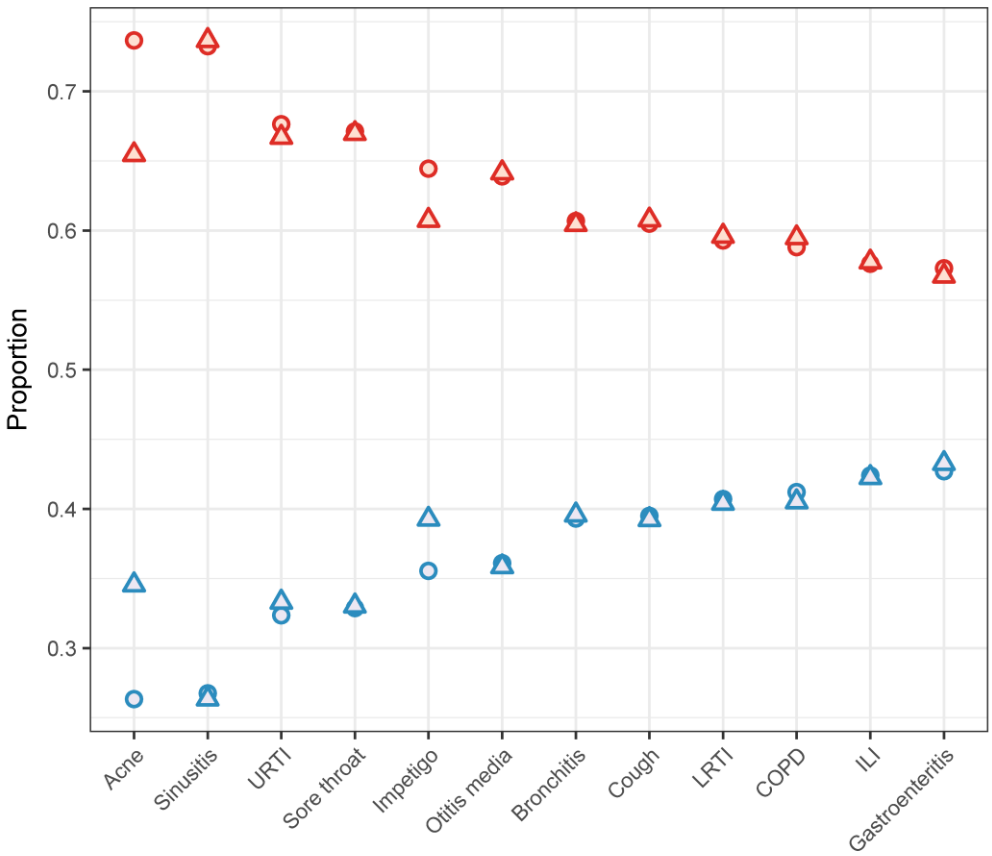

Figure S2. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity, including those who consulted outside their primary registered practice. Conditions are ordered by consultation proportion.

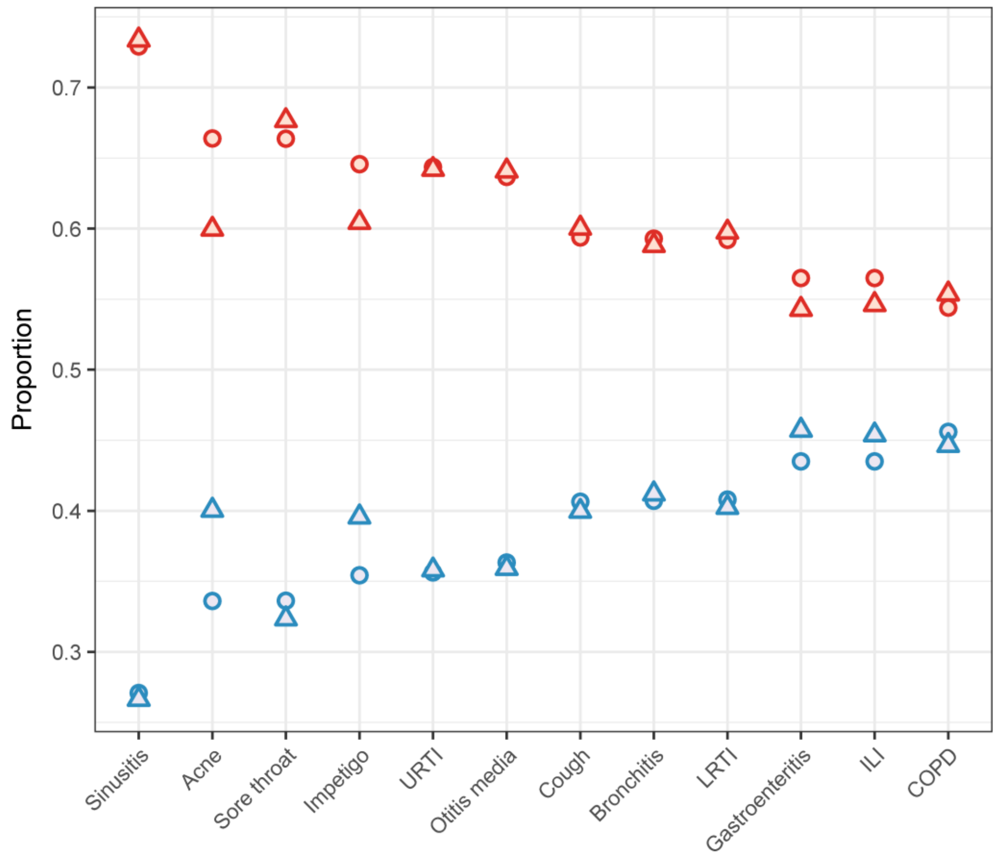

Figure S3. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) with comorbidity, including those who consulted outside their primary registered practice. Conditions are ordered by consultation proportion.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Provided, page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Provided, pages 2-3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Introduction paragraphs 1-3, pages 4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses **Introduction paragraph 4, page 5**
Methods		
Study design	4	Present key elements of study design early in the paper **Throughout methods, pages 6-8**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Methods paragraph 1, page 6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Methods paragraphs 1-2, page 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Methods paragraphs 3-4, pages 7-8**
Data sources/ measurement	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 **Methods paragraphs 1-2, page 6**
Bias	9	Describe any efforts to address potential sources of bias **Throughout methods, pages 6-8**
Study size	10	Explain how the study size was arrived at **Methods paragraph 1, page 6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Methods paragraphs 2-4, pages 6-8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Methods paragraphs 2-4, pages 6-8**
Results		
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 a flow diagram **Results paragraph 1, page 8**
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 **Results paragraph 1, page 8; Table 1, pages 9-10**
Outcome data	15*	Report numbers of outcome events or summary measures **Table 1, pages 9-10; online supplementary appendix Table S2, page 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 **Table 1 and throughout results, pages 8-11**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Results paragraphs 2-4, pages 8-11; online supplementary appendix Table S1 and Figures S1-S3, pages 1-2 and 4-6**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Discussion paragraph 1, pages 11-12**
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 **Discussion paragraphs 2 and 5, pages 12 and 14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Discussion paragraphs 4-6, pages 13-15**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Discussion paragraph 2, page 12**
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 **Funding statement provided page 16**

*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 www.strobe-statement.org.