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

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1 **Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of**

2 **English primary care**

3 David RM Smith^{1*†}, F Christiaan K Dolk^{1,2*}, Timo Smieszek^{1,3}, Julie V Robotham¹, Koen B

4 Pouwels^{1,2,3}

5 1. Modelling and Economics Unit, National Infection Service, Public Health England, London,
6 United Kingdom.

7 2. PharmacoTherapy, -Epidemiology & -Economics, Department of Pharmacy, University of
8 Groningen, Groningen, The Netherlands.

9 3. MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease
10 Epidemiology, Imperial College School of Public Health, London, United Kingdom.

11 * shared first author

12 † corresponding author: david.r.m.smith@phe.gov.uk ; +44 20 8327 6651 ; 61 Colindale Ave,
13 London UK, NW9 5EQ

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1
2
3 16 Abstract
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5 17 **Objectives:** To explore the degree to which the gender gap in antibiotic prescribing is driven
6
7 18 by prescribing behaviour, consultation behaviour, comorbidity and urinary tract infection
8
9 19 (UTI).

10
11
12 20 **Design:** Cross-sectional analysis of patient consultation and antibiotic prescribing.
13

14 21 **Setting:** English primary care.
15

16 22 **Participants:** Patients who consulted general practices registered with The Health
17
18
19 23 Improvement Network between 2013 and 2015.
20

21 24 **Primary and secondary outcome measures:** Total antibiotic prescribing was measured in
22
23 25 children (<19 years), adults (19 – 64) and the elderly (65+). For twelve common conditions,
24
25 26 the number of adult consultations was measured, and the relative risk (RR) of being
26
27 27 prescribed antibiotics when consulting as female or with comorbidity was estimated.
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29

30 28 **Results:** Female patients received 67% more antibiotic prescriptions than males, and 43%
31
32 29 more when excluding antibiotics used to treat UTI (trimethoprim and nitrofurantoin). These
33
34 30 gaps were more pronounced in adult women (99% more prescriptions than males; 69%
35
36 31 more when excluding UTI) than in children (9%; 0%) or the elderly (67%; 38%). Among
37
38 32 adults, women accounted for 64% of consultations (61% among patients with comorbidity),
39
40 33 but were not substantially more likely than men to receive an antibiotic prescription when
41
42 34 consulting with common conditions such as cough (RR 1.01; CI 1.00 – 1.02), sore throat (RR
43
44 35 1.01, CI 1.00 – 1.01) and lower respiratory tract infection (RR 1.00, CI 1.00 – 1.01).
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48 36 Exceptions were skin conditions: women were less likely to be prescribed antibiotics when
49
50 37 consulting with acne (RR 0.67, CI 0.66 – 0.69) or impetigo (RR 0.85, CI 0.81 – 0.88).
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53 38 **Conclusions:** The gender gap in antibiotic prescribing can largely be explained by
54
55 39 consultation behaviour. Although in most cases adult men and women are equally likely to
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3 40 be prescribed an antibiotic when consulting primary care, it is unclear whether or not they
4
5 41 are equally indicated for antibiotic therapy.
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9
10 43 Strengths and limitations of this study:

- 11
12 44 • This study is one of the first to explore the underlying causes of the large gap in the
13
14 45 number of antibiotics prescribed to men and women in primary care.
15
16 46 • Findings are derived from a large, representative sample of primary care patients in
17
18 47 England.
19
20
21 48 • Extensive mapping of Read (diagnostic) codes to clinical conditions made it possible
22
23 49 to analyse prescribing across a range of conditions and to account for comorbidity.
24
25
26 50 • Identification of antibiotics that are used to treat UTI but rarely other conditions
27
28 51 (trimethoprim and nitrofurantoin) allowed for approximation of UTI prescribing
29
30 52 despite incomplete diagnostic coding.
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32
33 53 • The data do not include indicators of antibiotic appropriateness, such as severity of
34
35 54 illness, and so the clinical appropriateness of gender differences in prescribing could
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37 55 not be evaluated.
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57 **Introduction**

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

65
66 Gender is a key determinant of antibiotic prescribing. A recent meta-analysis across primary
67 care in nine high-income countries found that females received more antibiotics than males
68 in all age groups except those >75, with women aged 16 to 54 receiving 36% to 40% more
69 antibiotics than men of the same age.[6] Similarly, across English and Welsh primary care,
70 the rate of antibiotic prescribing has been found to be 40% higher in female than in male
71 patients.[7] Although the latter figure dates from 1996, gender disparities in England have
72 more recently been observed in out-of-hours and paediatric care, with women and girls
73 receiving more antibiotic prescriptions than men and boys.[8,9]

74
75 There are several proposed explanations for this gender gap in antibiotic prescribing. First,
76 some infectious diseases affect men and women differently. In particular, urinary tract
77 infection (UTI) is more common in adult women than in men and accounts for over 20% of
78 antibiotic prescriptions in English primary care.[10,11] However, respiratory tract infections
79 (RTIs) account for more than twice as many prescriptions as UTI,[11] and women are not
80 more susceptible to these conditions than men,[12,13] although gender differences in

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3 81 comorbidity may underlie some variation in prescribing. Second, as in many
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5 82 countries,[14,15] women in the UK consult their general practitioner (GP) more often than
6
7 83 men.[16-18] Although consultation rate is linked to antibiotic prescribing,[5] it is not clear to
8
9 84 what extent gender differences in antibiotic prescribing can be explained by gender
10
11 85 differences in health-seeking behaviour. Finally, social and behavioural factors may play a
12
13 86 role. For example, men and women communicate differently with health professionals, and
14
15 87 prescribers may have biases that cause them to be more willing to prescribe antibiotics
16
17 88 during consultations with women than with men.[19,20]
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23 90 Here, the gender gap in antibiotic prescribing was analysed using a large, representative
24
25 91 sample of primary care patients in England. Antibiotic prescribing in male and female
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27 92 children, adults and the elderly was compared at the population level. The influence of
28
29 93 gender on prescribing was assessed by controlling for consultation and comorbidity, and
30
31 94 calculating the proportions of men and women that received antibiotic prescriptions when
32
33 95 presenting to primary care with a suite of common conditions. These prescribing
34
35 96 proportions facilitate a deeper understanding of the causes of the gender gap in antibiotic
36
37 97 prescribing, and may inform prescribing intervention design.
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44 99 **Methods**

45
46 100 This study used data from English general practices registered with The Health Improvement
47
48 101 Network (THIN), a UK-based primary care electronic medical record database. Practices
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50 102 were included that provided data for at least one full calendar year between January 1,
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52 103 2013 and December 31, 2015; there were 349 such practices in 2013, 285 in 2014 and 191 in
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54 104 2015. Anonymised patient data were extracted from these practices that met acceptable
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3 105 standards for research data collection. All systemic antibiotic prescriptions (antibiotics from
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5 106 British National Formulary chapter 5.1,[21] excluding antituberculosis and antileprosy drugs)
6
7 107 recorded in THIN were analysed by patient gender and age. Patient age at the time of
8
9 108 consultation was used to classify patients as children (aged 0-18 years), adults (19-64 years)
10
11
12 109 and the elderly (65+ years).

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16 111 Read codes (the diagnostic codes used in THIN) were analysed to quantify the number of
17
18 112 male and female consultations for acute presentations of 12 common conditions that are
19
20 113 treated with antibiotics to varying degrees: acne, bronchitis, chronic obstructive pulmonary
21
22 114 disease (COPD), cough, gastroenteritis, impetigo, influenza-like illness (ILI), lower respiratory
23
24 115 tract infection (LRTI), otitis media, sinusitis, sore throat and upper respiratory tract infection
25
26 116 (URTI). A vast number of Read codes are used in THIN, and the methods used to assign
27
28 117 specific Read codes to different conditions and to link Read codes to acute antibiotic
29
30 118 prescriptions are described elsewhere.[11] The ratio of female to male consultations (F:M)
31
32 119 was then calculated to quantify gender differences in consultation for each of these
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34 120 conditions.

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40 122 In THIN, a large proportion of UTI consultations are poorly coded, particularly in patients
41
42 123 consulting for UTI prophylaxis or chronic/recurrent UTI. However, in English primary care
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44 124 the antibiotics used to prevent and treat the vast majority of UTIs – trimethoprim and
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46 125 nitrofurantoin – are rarely used for other conditions.[11] Prescriptions of trimethoprim and
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48 126 nitrofurantoin were thus used as a proxy measure for prescribing for UTI.

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3 128 Prescribing proportions were then calculated by dividing the total number of prescriptions
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5 129 for a given condition by the number of consultations for that condition. To account for
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7 130 patients that consulted more than once, robust standard errors were used when calculating
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9 131 prescribing proportions. These data were also used to calculate the relative risk (RR) of
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11 132 being prescribed an antibiotic when consulting as female as opposed to male. In the main
12
13 133 analysis, consultations were included if they occurred at a patient's primary registered
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15 134 practice, but in a sensitivity analysis all patient consultations recorded in THIN were
16
17 135 included. Patients with comorbidity were analysed separately from otherwise 'healthy'
18
19 136 patients (i.e., those without comorbidity) to minimise potential biases in consultation and
20
21 137 prescribing due to gender differences in background health status. Further, the RR of being
22
23 138 prescribed an antibiotic when consulting with comorbidity was also calculated for each
24
25 139 condition and gender. Comorbidities were identified by the Read codes that indicate
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27 140 qualification for the free seasonal influenza vaccination programme: asthma, chronic heart
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29 141 disease, chronic kidney disease, chronic liver disease, chronic neurological disease and
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31 142 immunosuppressive disease.[22] Patients who received at least two prescriptions of
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33 143 systemic or inhaled corticosteroids or immunosuppressive drugs in the 365 days prior to
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35 144 their consultation were also included in this group, since these drugs indicate an increased
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37 145 risk of serious complications after (respiratory tract) infections.[22]
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46 147 All data were analysed using STATA 13.1 and R version 3.1.
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50 51 149 **Results**

52
53 150 Of all antibiotic prescriptions observed in THIN between 2013 and 2015 (n=4,574,363), the
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55 151 majority (62.6%) were in female patients (Figure 1). Adult women received approximately
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3 152 twice (99.0%) as many antibiotic prescriptions as adult men, whereas elderly women and
4
5 153 girls received 67.4% and 9.2% more prescriptions, respectively, than elderly men and boys.
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7 154 Nitrofurantoin and trimethoprim accounted for 17.1% of all prescriptions, 81.3% of which
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9 155 were prescribed to female patients. The prescribing gender gap narrowed in all age groups
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11 156 when these antibiotics were removed, and became negligible in children (0.3%), but adult
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13 157 and elderly women still received, respectively, 69.2% and 37.7% more antibiotic
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15 158 prescriptions than adult and elderly men.
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21 160 Healthy adult women consulted primary care more than men for the 12 conditions included
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23 161 in this study, accounting for 64.3% of all consultations (61.9% among patients with
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25 162 comorbidity). The biggest gender gaps in consultation were in acne (F:M 2.90) and sinusitis
26
27 163 (F:M 2.78). However, there was little gender difference in the proportions of healthy adult
28
29 164 patients that received antibiotic prescriptions when consulting (Table 1). The greatest gaps
30
31 165 were in acne, where 60% of consulting men received systemic antibiotics compared to 41%
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33 166 of women (RR 0.67; CI 0.66 – 0.69), and in impetigo, where, respectively, 62% and 52% of
34
35 167 men and women received prescriptions (RR 0.85, CI 0.81 – 0.88). In all other conditions, the
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37 168 difference between the proportions of men and women that received antibiotic
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39 169 prescriptions when consulting was $\leq 2\%$, although these gaps were statistically significant in
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41 170 cough (F>M, $p=0.02$), LRTI (F>M, $p=0.02$), sinusitis (F>M, $p<0.001$) and URTI (M>F, $p<0.001$).
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43 171 These results held in a sensitivity analysis when consultations and prescriptions outside of
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45 172 patients' primary registered practice were included (see online supplementary appendix).
46
47 173 Further, with the exception of acne and impetigo, the proportions of all antibiotics
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49 174 prescribed to men and women for different conditions are proportionate to the proportions
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51 175 of all consultations made by men and women for those conditions (Figure 2). Accordingly,
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176 the proportions of all antibiotics prescribed to women for each condition correlate strongly
 177 with the proportions of consultations made by women (Spearman's $\rho=0.92$; $p<0.001$), but
 178 not with the proportions of women that received prescriptions when consulting with those
 179 conditions (Spearman's $\rho=0.28$, $p=0.38$).

180

181 **Table 1.** Primary care consultations and antibiotic prescribing proportions per consultation
 182 in adult men and women (aged 19 – 64 years) with and without comorbidity for 12 different
 183 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)

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186 These gender differences in prescribing were broadly similar among adults with

187 comorbidity. Women with comorbidity were substantially less likely than men with

188 comorbidity to receive antibiotic prescriptions when consulting with acne (RR 0.73, CI 0.68 –

189 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

190 for all other conditions the difference between the proportions of men and women that

191 received prescriptions when consulting was $\leq 3\%$. Again, among patients with comorbidity,

192 the proportions of antibiotics prescribed to women for each condition correlate strongly

193 with the proportions of consultations made by women (Spearman's $\rho=0.78$; $p=0.005$), but

194 not with the proportion of women that received prescriptions when consulting with those

195 conditions (Spearman's $\rho=0.41$, $p=0.19$).

196

197 Patients with comorbidity were generally more likely than those without comorbidity to

198 receive antibiotic prescriptions when consulting (see online supplementary appendix). In

199 both men and women the greatest of these differences were in URTI, cough and ILI, where

200 the proportion of patients that received antibiotics when consulting was approximately 6-

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3 201 12% higher among patients with comorbidity. Patients with comorbidity were also more
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5 202 likely to receive a prescription when consulting with bronchitis, gastroenteritis and sinusitis.
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7 203 However, among women consulting with sore throat and LRTI, and among men consulting
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9 204 with sore throat, LRTI and acne, the proportions of patients that received antibiotics when
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11 205 consulting was significantly lower among patients with comorbidity than among otherwise
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14 206 healthy patients.
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18 208 **Discussion**

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21 209 This study affirms that there is still a substantial gender gap in antibiotic prescribing in
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23 210 English primary care, and shows that this gap is in large part unexplained by biased
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25 211 prescribing behaviour and gender differences in UTI and comorbidity. The prescribing gap is
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27 212 most pronounced in adults, with women receiving approximately twice as many antibiotic
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29 213 prescriptions as men, and 70% more when excluding antibiotics used to treat UTI. These
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31 214 differences in prescribing are proximate to differences in health-seeking behaviour, with
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33 215 healthy adult women consulting primary care approximately 80% more than healthy adult
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35 216 men across the 12 conditions included in this study. Accordingly, men and women are just
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37 217 as likely to be prescribed antibiotics when consulting with most common RTIs. These
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39 218 findings provide strong support for the hypothesis that higher antibiotic prescribing in adult
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41 219 women is primarily driven by a higher consultation rate.
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48 221 This study has a number of strengths. First, THIN is a robust data source that is
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50 222 representative of the English primary care patient population.[23] Second, the extensive
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52 223 mapping of Read codes to clinical conditions made it possible to analyse prescribing across a
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54 224 range of conditions and to account for comorbidities, which differ between men and
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3 225 women and influence whether or not a practitioner prescribes. Third, since UTI in English
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5 226 primary care is almost always treated with trimethoprim or nitrofurantoin, and since these
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7 227 antibiotics are rarely used to treat other conditions in primary care,[11] it was possible to
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9 228 approximate total prescribing for UTI despite incomplete diagnostic coding. There were also
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11 229 limitations to this work, the largest being that the clinical appropriateness of prescribing
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13 230 could not be determined, and so it was not possible to evaluate whether consulting men
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15 231 and women are differently indicated for antibiotics, and hence whether equal prescribing
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17 232 proportions in RTIs are clinically justified. Further, other patient characteristics that may co-
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19 233 vary with gender and consultation behaviour, such as socioeconomic status, could not be
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21 234 considered. Finally, the quality of diagnostic coding varies within and between practices,
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23 235 which may bias estimates of consultation and prescribing.
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30 237 It is well observed that rates of primary care consultation and antibiotic prescribing are
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32 238 substantially higher in adult women than in adult men,[6-9,16-18] but previous studies have
33
34 239 been unable to show that the gender gap in antibiotic prescribing can primarily be
35
36 240 attributed to consultation, as opposed to other relevant factors such as UTI, comorbidity
37
38 241 and other patient and prescriber behaviours. These findings builds on a previous study of
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40 242 prescribing in UK primary care between 1997 and 2006, which found similar male and
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42 243 female prescribing proportions in a selection of RTIs, but was conducted in a limited subset
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44 244 of patients, did not consider prescribing for UTI, and did not account for comorbidities, non-
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46 245 respiratory conditions, or patients consulting outside of their registered practice.[24]
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53 247 Antibiotic prescribing was proportionate to consultation for most conditions, but skin
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55 248 conditions were notable exceptions: men consulted much less with acne and impetigo but
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3 249 were substantially more likely than women to receive an antibiotic prescription when
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5 250 consulting (although acne is unique in that women but not men can be treated with
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7 251 combination oral contraceptives, confounding gender comparisons in antibiotic prescribing).
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10 252 Although women consult more frequently, they are not known to suffer from greater
11
12 253 incidence or severity of disease in the conditions included here.[12,13] Studies have also
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14 254 shown that men tend to consult later in the course of their illness and may have a higher
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16 255 threshold to seeking care.[17,25,26] When prescribing is truly reflective of patient need
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18 256 (e.g., as in skin conditions, due to low diagnostic uncertainty), a higher prescribing
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21 257 proportion in men may be expected if, on average, less frequent and/or delayed
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23 258 consultation is coupled with more severe clinical presentation. Yet, for the remaining
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26 259 conditions in this study – predominantly RTIs – prescribing proportions in male and female
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28 260 patients were strikingly similar despite vast differences in consultation. This may be
29
30 261 indicative of imprudent prescribing. In non-skin conditions there is often (i) considerable
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32 262 diagnostic uncertainty (e.g., difficulty in differentiating acute bronchitis and pneumonia in
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34 263 primary care) and (ii) uncertainty around subjective, insensitive or unspecific clinical severity
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36 264 markers (e.g., reliance on patient symptom reporting and other clinical features that poorly
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38 265 predict benefit from antibiotic treatment).[27,28] Faced by these uncertainties, GPs may
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40 266 prescribe antibiotics cautiously – and imprudently – to a large proportion of patients
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43 267 with RTI, regardless of disease severity, resulting in high prescribing proportions in all
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46 268 patients.
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51 270 Although imprudent prescribing has been the target of numerous antimicrobial stewardship
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53 271 interventions, it remains obstinate in English primary care,[29] and the combination of high
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55 272 consultation rates among female patients and overly cautious antibiotic prescribing

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3 273 behaviour among GPs could result in a disproportionate share of inappropriate (i.e.,
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5 274 unnecessary) antibiotic prescriptions in women. However, previous studies of gender
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7 275 differences in inappropriate prescribing have found mixed results,[6,30] and it remains to be
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9 276 shown whether men and women in UK primary care differ in their objective clinical need for
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11 277 antibiotics when consulting with RTIs and other common conditions. Yet, regardless of
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13 278 whether or not women are more likely to receive an inappropriate prescription per
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15 279 consultation, it is likely that a higher level of antibiotic prescribing in women is accompanied
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17 280 by a greater total number of inappropriate prescriptions.
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23 282 *Conclusions*

24
25 283 This study reaffirms known gender gaps in health-seeking behaviour and antibiotic
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27 284 prescribing, and shows that, with exceptions, adult men and women in English general
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29 285 practice are equally likely to receive an antibiotic prescription when seeking care for
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31 286 common conditions, and that gender differences in the number of antibiotics prescribed are
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33 287 largely driven by differences in consultation behaviour. Equal prescribing proportions may
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35 288 seem to indicate relative parity in how men and women are treated when they consult, but
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37 289 women consult vastly more than men yet have not been shown to suffer from more
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39 290 frequent or severe infection in the conditions included in this study. It is thus plausible that
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41 291 a higher rate of consultation in women is coupled with a milder average clinical
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43 292 presentation, but that overly precautionous GPs prescribe even when antibiotics are not
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45 293 clinically necessary, resulting in high rates of prescribing in all patients. Given the urgent
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47 294 need to reduce unnecessary antibiotic prescribing, it is crucial to more deeply understand
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49 295 how and to whom antibiotics are overprescribed. To this end, future work should further
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3 296 investigate the clinical (in)appropriateness of gender differences in antibiotic prescribing in
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5 297 primary care.

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9 299 Figure captions

10
11 300 **Figure 1.** All systemic antibiotic prescriptions recorded in THIN between 2013 and 2015,
12 301 stratified by gender and age group. Antibiotics used to treat UTI (trimethoprim and
13 302 nitrofurantoin) are identified separately from all other antibiotics.

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16 303 **Figure 2.** For common conditions in general practice, the proportions all consultations
17 304 (circles) and antibiotic prescriptions (triangles) attributed to women (red) and men (blue).
18 305 Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity
19 306 consulting at their primary registered practice. Conditions are ordered by consultation
20 307 proportion.

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22 308
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25 309 Additional information

26
27 310 **Contributors:** KP and DS conceived and designed the study. KP extracted the data from The
28 311 Health Improvement Network database. CD and KP conducted the analyses. DS, JR, KP and
29 312 TS carried out interpretation of the data. DS drafted the manuscript. CD, JR, KP and TS
30 313 critically revised the manuscript for important intellectual content. All authors approved the
31 314 final version prior to submission.

32
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34
35 316 **Competing interests:** None.

36
37 317 **Ethics approval:** This study received approval from THIN's Scientific Review Committee
38 318 (reference number 16THIN-071-A2).

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40 319 **Data sharing statement:** This analysis is based on a large sample from The Health
41 320 Improvement Network, provided by IMS Health. The authors' license for using these data
42 321 precludes the sharing of raw data with third parties.

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38 383 in patients with upper respiratory tract infections is hardly different in female versus male patients as
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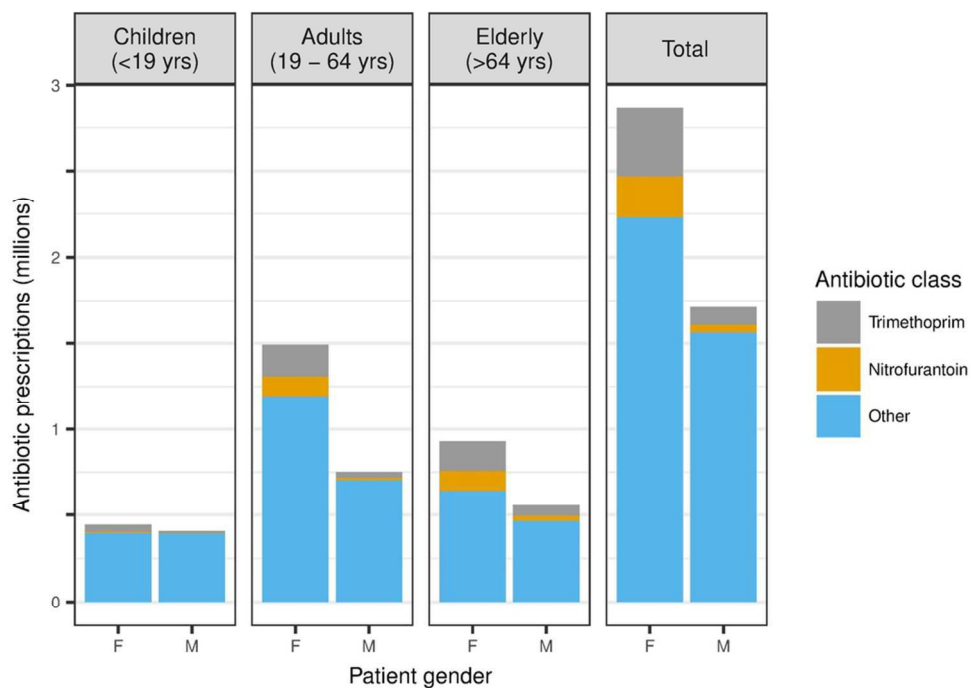


Figure 1. All systemic antibiotic prescriptions recorded in THIN between 2013 and 2015, stratified by gender and age group. Antibiotics used to treat UTI (trimethoprim and nitrofurantoin) are identified separately from all other antibiotics.

89x63mm (300 x 300 DPI)

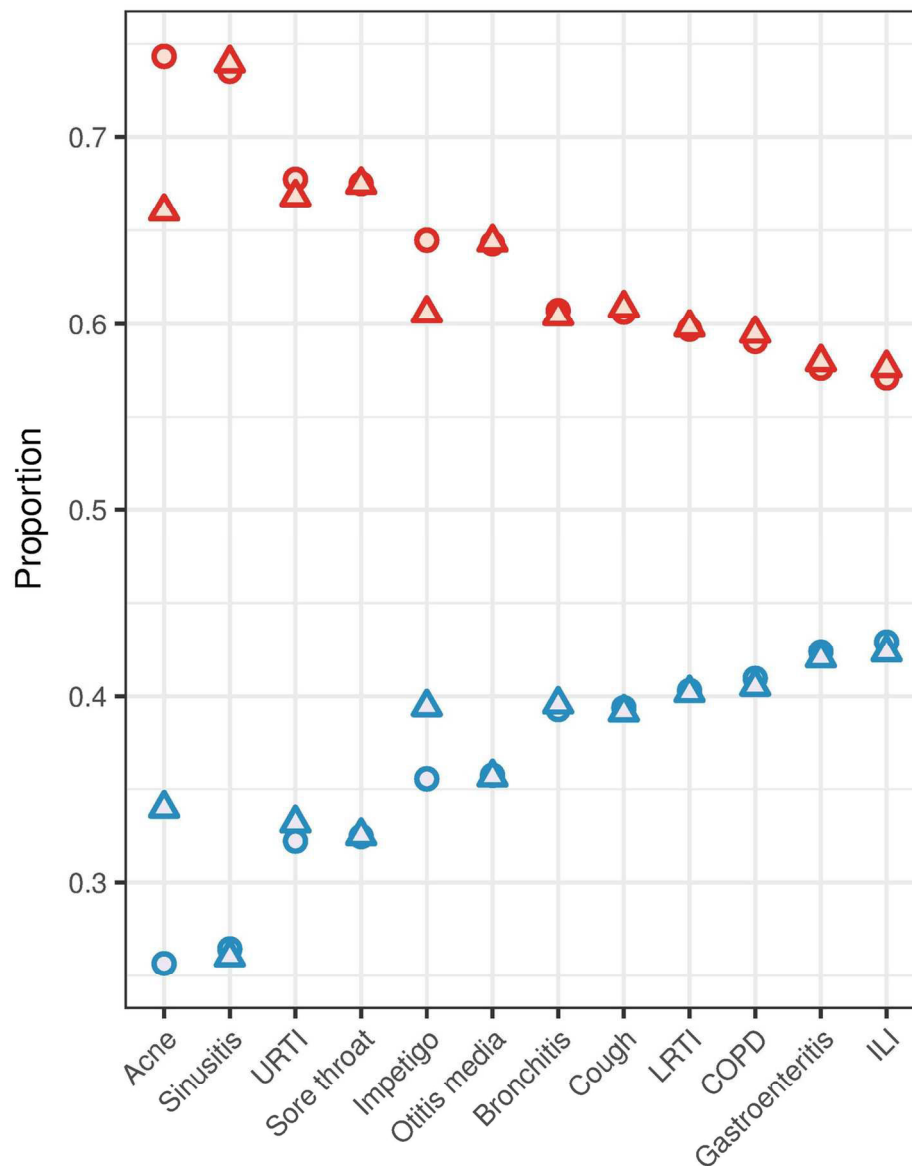


Figure 2. For common conditions in general practice, the proportions all consultations (circles) and antibiotic prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity consulting at their primary registered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

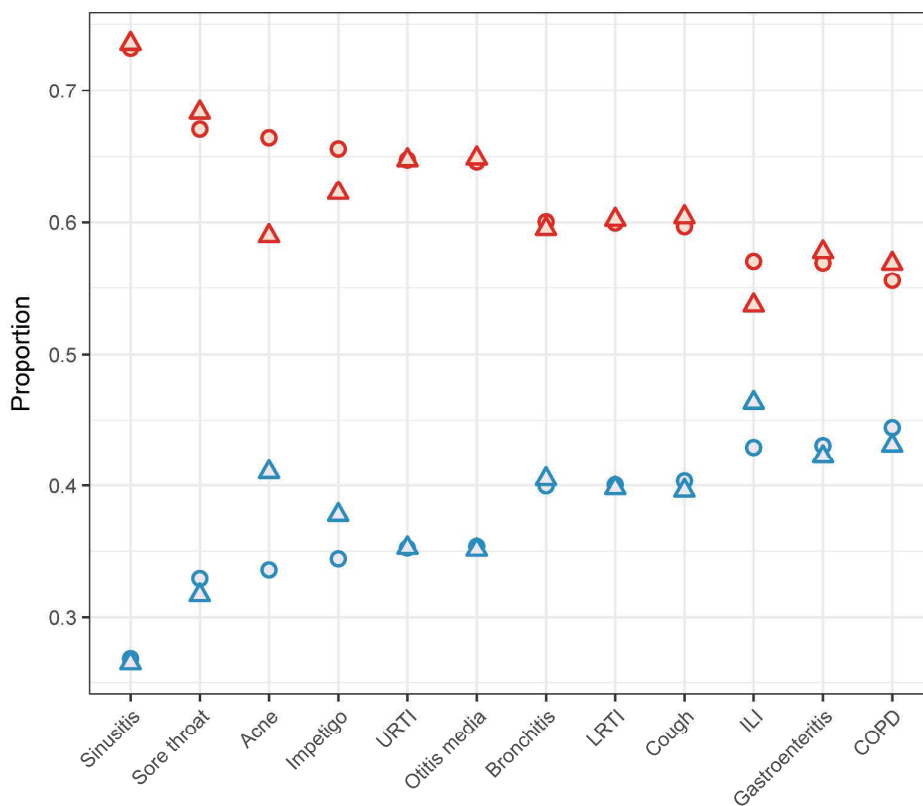


Figure S1. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) with comorbidity who consulted at their primary registered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

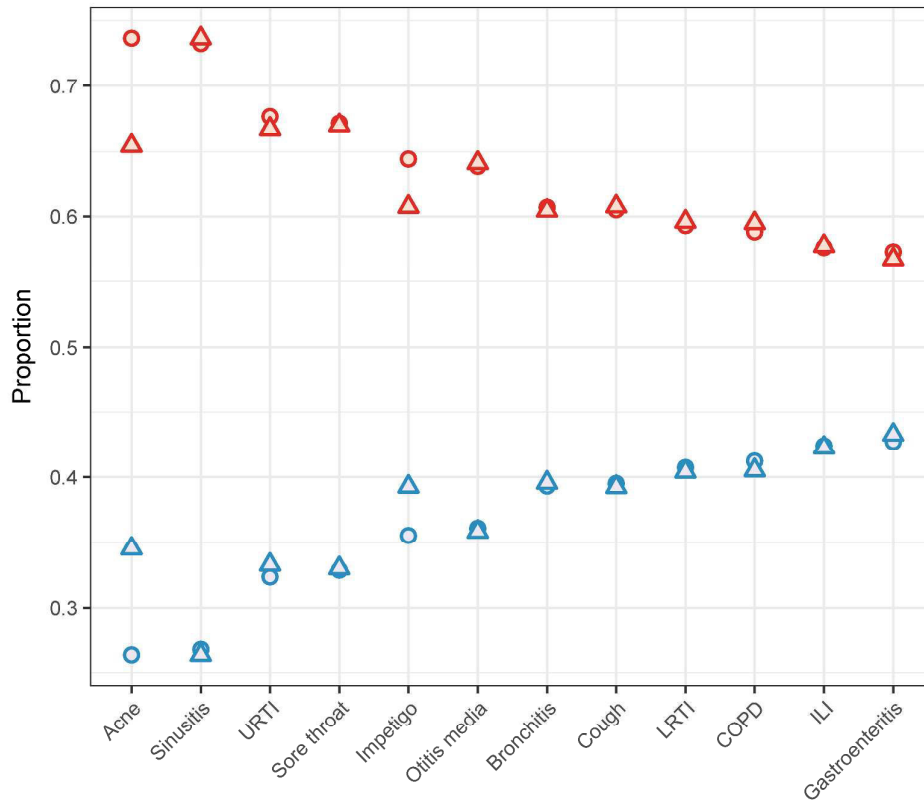


Figure S2. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity, including those who consulted outside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

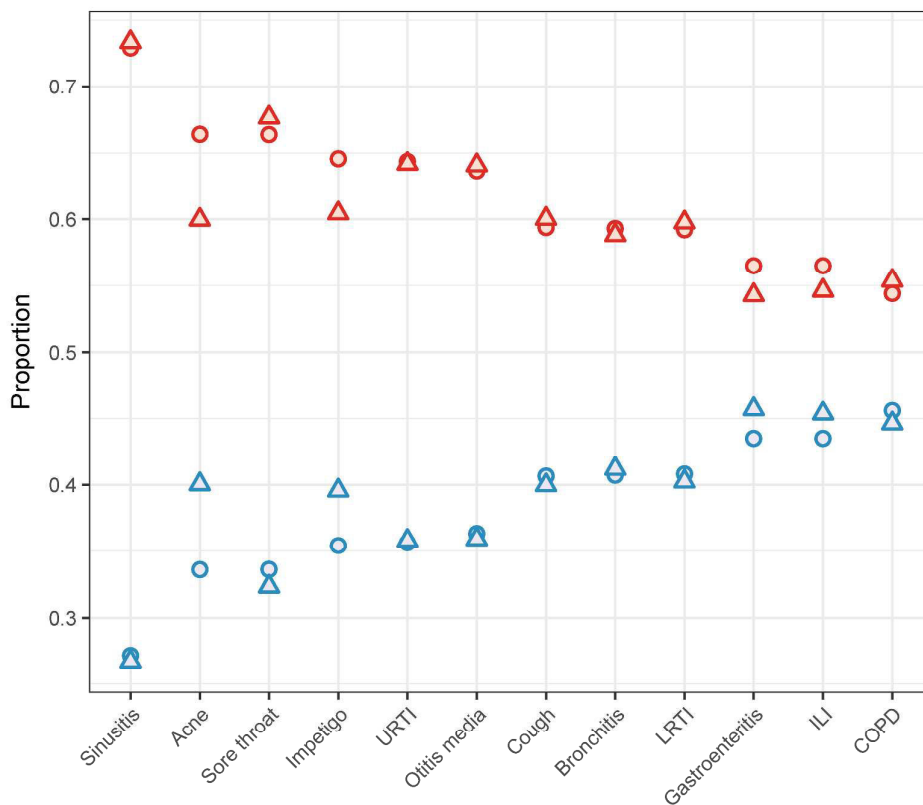


Figure S3. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) with comorbidity, including those who consulted outside 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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Keywords:	anti-bacterial agents, prescriptions, electronic health records, antibiotic prescribing, consultation, gender bias

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Manuscripts



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3 **1 Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of**

4
5 **2 English primary care**

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7 3 David RM Smith^{1*†}, F Christiaan K Dolk^{1,2*}, Timo Smieszek^{1,3}, Julie V Robotham¹, Koen B

8
9 4 Pouwels^{1,2,3}

10
11
12 5 1. Modelling and Economics Unit, National Infection Service, Public Health England, London,

13
14 6 United Kingdom.

15
16 7 2. PharmacoTherapy, -Epidemiology & -Economics, Department of Pharmacy, University of

17
18 8 Groningen, Groningen, The Netherlands.

19
20 9 3. MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease

21
22 10 Epidemiology, Imperial College School of Public Health, London, United Kingdom.

23
24
25 11 * contributed equally

26
27
28 12 † corresponding author: davidrobertmundysmith@gmail.com ; +44 20 8327 6651 ; 61

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30 13 Colindale Ave, London UK, NW9 5EQ

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1
2
3 16 Abstract
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5 17 **Objectives:** To explore causes of the gender gap in antibiotic prescribing, and to determine
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7 18 whether women are more likely than men to receive an antibiotic prescription per
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9 19 consultation.
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12 20 **Design:** Cross-sectional analysis of routinely collected electronic medical records from The
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14 21 Health Improvement Network (THIN).
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16
17 22 **Setting:** English primary care.
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19 23 **Participants:** Patients who consulted general practices registered with THIN between 2013
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21 24 and 2015.
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23 25 **Primary and secondary outcome measures:** Total antibiotic prescribing was measured in
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25 26 children (<19 years), adults (19 – 64) and the elderly (65+). For twelve common conditions,
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27 27 the number of adult consultations was measured, and the relative risk (RR) of being
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29 28 prescribed antibiotics when consulting as female or with comorbidity was estimated.
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31 31

32 29 **Results:** Among 4.57 million antibiotic prescriptions observed in the data, female patients
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34 30 received 67% more prescriptions than males, and 43% more when excluding antibiotics
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36 31 used to treat urinary tract infection (UTI). These gaps were more pronounced in adult
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38 32 women (99% more prescriptions than males; 69% more when excluding UTI) than in
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40 33 children (9%; 0%) or the elderly (67%; 38%). Among adults, women accounted for 64% of
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42 34 consultations (61% among patients with comorbidity), but were not substantially more likely
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44 35 than men to receive an antibiotic prescription when consulting with common conditions
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46 36 such as cough (RR 1.01; CI 1.00 – 1.02), sore throat (RR 1.01, CI 1.00 – 1.01) and lower
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48 37 respiratory tract infection (RR 1.00, CI 1.00 – 1.01). Exceptions were skin conditions: women
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50 38 were less likely to be prescribed antibiotics when consulting with acne (RR 0.67, CI 0.66 –
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52 39 0.69) or impetigo (RR 0.85, CI 0.81 – 0.88).
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3 40 **Conclusions:** The gender gap in antibiotic prescribing can largely be explained by
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5 41 consultation behaviour. Although in most cases adult men and women are equally likely to
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7 42 be prescribed an antibiotic when consulting primary care, it is unclear whether or not they
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9 43 are equally indicated for antibiotic therapy.
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13
14 45 Strengths and limitations of this study:
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- 16 46 • This study is one of the first to explore the underlying causes of the large gap in the
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18 47 number of antibiotics prescribed to men and women in primary care.
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21 48 • Findings are derived from a large, representative sample of primary care patients in
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23 49 England.
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26 50 • Extensive mapping of diagnostic codes to clinical conditions made it possible to
27
28 51 analyse prescribing across a range of conditions and to account for comorbidity.
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31 52 • Identification of antibiotics that are used to treat UTI but rarely other conditions in
32
33 53 this setting (trimethoprim and nitrofurantoin) allowed for approximation of UTI
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35 54 prescribing despite incomplete diagnostic coding.
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38 55 • The data do not include indicators of antibiotic appropriateness, such as severity of
39
40 56 illness, and so the clinical appropriateness of gender differences in prescribing could
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42 57 not be evaluated.
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58 Introduction

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

66
67 Gender is a key determinant of antibiotic prescribing. A recent meta-analysis across primary
68 care in nine high-income countries found that females received more antibiotics than males
69 in all age groups except those >75, with women aged 16 to 54 receiving 36% to 40% more
70 antibiotics than men of the same age.[6] Similarly, across English and Welsh primary care,
71 the rate of antibiotic prescribing has been found to be 40% higher in female than in male
72 patients.[7] Although the latter figure dates from 1996, gender disparities in England have
73 more recently been observed in out-of-hours and paediatric care, with women and girls
74 receiving more antibiotic prescriptions than men and boys.[8,9]

75
76 There are several proposed explanations for this gender gap. First, some infectious diseases
77 affect men and women differently. In particular, urinary tract infection (UTI) is more
78 common in adult women than in men and accounts for over 20% of antibiotic prescriptions
79 in English primary care.[10,11] However, respiratory tract infections (RTIs) account for more
80 than twice as many prescriptions as UTI,[11] and women are not more susceptible to these
81 conditions than men,[12-14] although gender differences in comorbidity may underlie some

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3 82 variation in prescribing. Second, as in many countries,[15,16] women in the UK consult their
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5 83 general practitioner (GP) more often than men,[17-19] and consultation rate is linked to
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7 84 antibiotic prescribing.[5] Previous studies of relatively small samples of patients with RTI
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9 85 have found that gender differences in consultation are proportionate to differences in
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11 86 prescribing [20,21], but it is unclear whether or not this is true across a greater range of
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14 87 conditions, when taking comorbidity into account, and using a more recent, nationally
15
16 88 representative sample of patients. Finally, other social and behavioural factors may also play
17
18 89 a role. For example, men and women communicate differently with health professionals,
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21 90 and prescribers may have biases that affect their willingness to prescribe antibiotics during
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23 91 consultations with women versus men.[22,23] Ultimately, it remains unknown to what
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25 92 extent these and other factors combine to explain the gender gap in antibiotic
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28 93 prescribing.[6]

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33 95 Here, gender differences in antibiotic prescribing were analysed using a large,
34
35 96 representative sample of primary care patients in England. Antibiotic prescribing in male
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37 97 and female children, adults and the elderly was compared at the population level. The
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39 98 influence of gender on prescribing was assessed by controlling for consultation and
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41 99 comorbidity, and calculating the proportions of adult men and women that received
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44 100 systemic antibiotic prescriptions when presenting to primary care with a suite of common
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46 101 conditions. These prescribing proportions facilitate a deeper understanding of the causes of
47
48 102 the gender gap in antibiotic prescribing, and may inform prescribing intervention design.

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53 104 **Methods**

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3 105 This study used data from English general practices registered with The Health Improvement
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5 106 Network (THIN), a UK-based primary care electronic medical record database. Practices
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7 107 were included that provided data for at least one full calendar year between January 1,
8
9 108 2013 and December 31, 2015; there were 349 such practices in 2013, 285 in 2014 and 191 in
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11 109 2015. Anonymised patient data were extracted from these practices that met acceptable
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13 110 standards for research data collection. All systemic antibiotic prescriptions (antibiotics from
14
15 111 British National Formulary chapter 5.1,[24] excluding antituberculosis and antileprosy drugs)
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17 112 recorded in THIN were analysed by patient gender and age. Patient age at the time of
18
19 113 consultation was used to classify patients as children (aged 0-18 years), adults (19-64 years)
20
21 114 and the elderly (65+ years). Due to a very large sample size, proportions of antibiotics
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23 115 prescribed to male versus female patients are reported without confidence intervals.
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29 117 Read codes (the diagnostic codes used in THIN) were analysed to quantify the number of
30
31 118 male and female consultations for acute presentations of 12 common conditions that are
32
33 119 treated with antibiotics to varying degrees: acne, bronchitis, chronic obstructive pulmonary
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35 120 disease (COPD), cough, gastroenteritis, impetigo, influenza-like illness (ILI), lower respiratory
36
37 121 tract infection (LRTI), otitis media, sinusitis, sore throat and upper respiratory tract infection
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39 122 (URTI). A vast number of Read codes are used in THIN, and the methods used to assign
40
41 123 specific Read codes to different conditions and to link Read codes to acute antibiotic
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43 124 prescriptions are described elsewhere.[11] The ratio of female to male consultations (F:M)
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45 125 was then calculated to quantify gender differences in consultation for each of these
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47 126 conditions.
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3 128 In THIN, a large proportion of UTI consultations are poorly coded, particularly in patients
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5 129 consulting for UTI prophylaxis or chronic/recurrent UTI. However, between 2013-2015 in
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7 130 English primary care, the antibiotics used to prevent and treat the vast majority of UTIs –
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9 131 trimethoprim and nitrofurantoin – were rarely used for other conditions.[11, 25]
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11 132 Prescriptions of trimethoprim and nitrofurantoin were thus used as a proxy measure for
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13 133 prescribing for UTI.
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18 135 Prescribing proportions were then calculated by dividing the total number of prescriptions
19
20 136 for a given condition by the number of consultations for that condition. To account for
21
22 137 patients that consulted more than once, robust standard errors were used when calculating
23
24 138 prescribing proportions. These data were also used to calculate the relative risk (RR) of
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26 139 being prescribed an antibiotic when consulting as female as opposed to male. In the main
27
28 140 analysis, consultations were included if they occurred at a patient's primary registered
29
30 141 practice, but in a sensitivity analysis all patient consultations recorded in THIN were
31
32 142 included. Patients with comorbidity were analysed separately from otherwise 'healthy'
33
34 143 patients (i.e., those without comorbidity) to minimise potential biases in consultation and
35
36 144 prescribing due to gender differences in background health status. Further, the RR of being
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38 145 prescribed an antibiotic when consulting with comorbidity was also calculated for each
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40 146 condition and gender. Comorbidities were identified by the Read codes that indicate
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42 147 qualification for the free seasonal influenza vaccination programme: asthma, chronic heart
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44 148 disease, chronic kidney disease, chronic liver disease, chronic neurological disease and
45
46 149 immunosuppressive disease.[26] Patients who received at least two prescriptions of
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48 150 systemic or inhaled corticosteroids or immunosuppressive drugs in the 365 days prior to
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3 151 their consultation were also included in this group, since these drugs indicate an increased
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5 152 risk of serious complications after (respiratory tract) infections.[26]
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9 154 All data were analysed using STATA 13.1 and R version 3.1.
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14 156 **Results**

15
16 157 Of all antibiotic prescriptions observed in THIN between 2013 and 2015 (n=4,574,363), the
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18 158 majority (62.6%) were in female patients (Figure 1). Adult women received approximately
19
20 159 twice (99.0%) as many antibiotic prescriptions as adult men, whereas elderly women and
21
22 160 girls received 67.4% and 9.2% more prescriptions, respectively, than elderly men and boys.
23

24
25 161 Nitrofurantoin and trimethoprim accounted for 17.1% of all prescriptions, 81.3% of which
26
27 162 were prescribed to female patients. The prescribing gender gap narrowed in all age groups
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29 163 when these antibiotics were removed, and became negligible in children (0.3%), but adult
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31 164 and elderly women still received, respectively, 69.2% and 37.7% more antibiotic
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33 165 prescriptions than adult and elderly men.
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39 167 Healthy adult women consulted primary care more than men for all 12 of the conditions
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41 168 included in this study, accounting for 64.3% of all consultations (61.9% among patients with
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43 169 comorbidity). The biggest gender gaps in consultation were in acne (F:M 2.90) and sinusitis
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45 170 (F:M 2.78). However, there was little gender difference in the proportions of healthy adult
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47 171 patients that received antibiotic prescriptions when consulting (Table 1). The greatest gaps
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49 172 were in acne, where 60% of consulting men received systemic antibiotics compared to 41%
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51 173 of women (RR 0.67; CI 0.66 – 0.69), and in impetigo, where, respectively, 62% and 52% of
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53 174 men and women received prescriptions (RR 0.85, CI 0.81 – 0.88). In all other conditions, the
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175 difference between the proportions of men and women that received antibiotic
 176 prescriptions when consulting was $\leq 2\%$, although these gaps were statistically significant in
 177 cough (F>M, $p=0.02$), LRTI (F>M, $p=0.02$), sinusitis (F>M, $p<0.001$) and URTI (M>F, $p<0.001$).
 178 These results held in a sensitivity analysis when consultations and prescriptions outside of
 179 patients' primary registered practice were included (see online supplementary appendix).
 180 Further, with the exception of acne and impetigo, the proportions of all antibiotics
 181 prescribed to men and women for different conditions were proportionate to the
 182 proportions of all consultations made by men and women for those conditions (Figure 2).
 183 Accordingly, the proportions of all antibiotics prescribed to women for each condition
 184 correlate strongly with the proportions of consultations made by women (Spearman's
 185 $\rho=0.92$; $p<0.001$), but not with the proportions of women that received prescriptions when
 186 consulting with those conditions (Spearman's $\rho=0.28$, $p=0.38$).

187

188 **Table 1.** Primary care consultations and antibiotic prescribing proportions per consultation
 189 in adult men and women (aged 19 – 64 years) with and without comorbidity for 12 different
 190 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% – 58%)	56% (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)

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193 These gender differences in prescribing were broadly similar among adults with

194 comorbidity. Women with comorbidity were substantially less likely than men with

195 comorbidity to receive antibiotic prescriptions when consulting with acne (RR 0.73, CI 0.68 –

196 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

197 for all other conditions the difference between the proportions of men and women that

198 received prescriptions when consulting was $\leq 3\%$. Again, among patients with comorbidity,

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3 199 the proportions of antibiotics prescribed to women for each condition correlate strongly
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5 200 with the proportions of consultations made by women (Spearman's $\rho=0.78$; $p=0.005$), but
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7 201 not with the proportion of women that received prescriptions when consulting with those
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9 202 conditions (Spearman's $\rho=0.41$, $p=0.19$).
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14 204 Patients with comorbidity were generally more likely than those without comorbidity to
15
16 205 receive antibiotic prescriptions when consulting (see online supplementary appendix). In
17
18 206 both men and women the greatest of these differences were in URTI, cough and ILI, where
19
20 207 the proportion of patients that received antibiotics when consulting was approximately 6-
21
22 208 12% higher among patients with comorbidity. Patients with comorbidity were also more
23
24 209 likely to receive a prescription when consulting with bronchitis, gastroenteritis and sinusitis.
25
26 210 However, among women consulting with sore throat and LRTI, and among men consulting
27
28 211 with sore throat, LRTI and acne, the proportions of patients that received antibiotics when
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30 212 consulting was significantly lower among patients with comorbidity than among otherwise
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32 213 healthy patients.
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41 215 **Discussion**

42 216 This study affirms that there is still a substantial gender gap in antibiotic prescribing in
43
44 217 English primary care, and shows that this gap is in large part unexplained by gender
45
46 218 differences in UTI and comorbidity. The prescribing gap is most pronounced in adults, with
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48 219 women receiving approximately twice as many antibiotic prescriptions as men, and 70%
49
50 220 more when excluding antibiotics used to treat UTI. These differences in prescribing are
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52 221 proximate to differences in health-seeking behaviour, with healthy adult women consulting
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54 222 primary care approximately 80% more than healthy adult men across the 12 conditions
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3 223 included in this study. Accordingly, men and women are just as likely to be prescribed
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5 224 antibiotics when consulting with most common RTIs. These findings provide strong support
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7 225 for the hypothesis that higher antibiotic prescribing in adult women is primarily driven by a
8
9 226 higher consultation rate.
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14 228 This study has a number of strengths. First, THIN is a robust data source that is
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16 229 representative of the English primary care patient population.[27] Second, the extensive
17
18 230 mapping of Read codes to clinical conditions made it possible to analyse prescribing across a
19
20 231 range of conditions and to account for comorbidities, which differ between men and
21
22 232 women and influence whether or not a practitioner prescribes. Third, since UTI in English
23
24 233 primary care was almost always treated with trimethoprim or nitrofurantoin during the
25
26 234 years of this study, and since these antibiotics were rarely used to treat other conditions in
27
28 235 primary care,[11, 25] it was possible to approximate total prescribing for UTI despite
29
30 236 incomplete diagnostic coding. There were also limitations to this work, the largest being
31
32 237 that the clinical appropriateness of prescribing could not be determined, and so it was not
33
34 238 possible to evaluate whether consulting men and women were differently indicated for
35
36 239 antibiotics, and hence whether equal prescribing proportions in RTIs are clinically justified.
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38 240 Further, other patient characteristics that may co-vary with gender and consultation
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40 241 behaviour, such as socioeconomic status, could not be considered. Finally, the quality of
41
42 242 diagnostic coding varies within and between practices, which may bias estimates of
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44 243 consultation and prescribing.
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53 245 It is well observed that rates of primary care consultation and antibiotic prescribing are
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55 246 substantially higher in adult women than in adult men,[6-8,17-19] but previous studies have
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3 247 been unable to show that the gender gap in antibiotic prescribing can primarily be
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5 248 attributed to consultation, as opposed to other relevant factors such as UTI, comorbidity
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7 249 and other patient and prescriber behaviours. These findings build on two previous studies of
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9 250 antibiotic prescribing in primary care between 1997-2006 and 2007-2008,
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11 251 respectively.[20,21] Both studies found similar male and female prescribing proportions in a
12
13 252 selection of RTIs, but were conducted in a limited subset of patients and did not account for
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15 253 comorbidities, non-respiratory conditions, patients consulting outside of their registered
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17 254 practice, or gender differences in gross antibiotic prescribing at the population level.
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21 256 Antibiotic prescribing was proportionate to consultation for most conditions, but skin
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23 257 conditions were notable exceptions: men consulted much less with acne and impetigo but
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25 258 were substantially more likely than women to receive an antibiotic prescription when
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27 259 consulting (although acne is unique in that women but not men can be treated with
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29 260 combination oral contraceptives, confounding gender comparisons in antibiotic prescribing).
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31 261 Although women consult more frequently, they are not known to suffer from greater
32
33 262 incidence or severity of disease in the conditions included here.[12,13] Studies have also
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35 263 shown that men tend to consult later in the course of their illness and may have a higher
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37 264 threshold to seeking care.[18,28,29] When prescribing is truly reflective of patient need
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39 265 (e.g., as in skin conditions, due to low diagnostic uncertainty), a higher prescribing
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41 266 proportion in men may be expected if, on average, less frequent and/or delayed
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43 267 consultation is coupled with more severe clinical presentation. Yet, for the remaining
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45 268 conditions in this study – predominantly RTIs – prescribing proportions in male and female
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47 269 patients were strikingly similar despite vast differences in consultation. This may be
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49 270 indicative of imprudent prescribing. In non-skin conditions there is often (i) considerable

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3 271 diagnostic uncertainty (e.g., difficulty in differentiating acute bronchitis and pneumonia in
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5 272 primary care) and (ii) uncertainty around subjective, insensitive or unspecific clinical severity
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7 273 markers (e.g., reliance on patient symptom reporting and other clinical features that poorly
8
9 274 predict benefit from antibiotic treatment).[30,31] Faced by these uncertainties, GPs may
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11 275 prescribe antibiotics cautiously – and imprudently – to a large proportion of patients
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13 276 with RTI, regardless of disease severity, resulting in high prescribing proportions in all
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15 277 patients.
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21 279 Although imprudent prescribing has been the target of numerous antimicrobial stewardship
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23 280 interventions, it remains obstinate in English primary care,[32] and the combination of high
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25 281 consultation rates among female patients and overly cautious antibiotic prescribing
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27 282 behaviour among GPs could result in a disproportionate share of inappropriate (i.e.,
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29 283 unnecessary) antibiotic prescriptions in women. However, previous studies of gender
30
31 284 differences in inappropriate antibiotic prescribing have found mixed results,[21,33] and it
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33 285 remains to be shown whether men and women in UK primary care differ in their objective
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35 286 clinical need for antibiotics when consulting with RTIs and other common conditions. Yet,
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37 287 regardless of whether or not women are more likely to receive an inappropriate prescription
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39 288 per consultation, it is likely that a higher level of antibiotic prescribing in women is
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41 289 accompanied by a greater total number of inappropriate prescriptions.
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47 291 *Conclusions*

48
49 292 This study reaffirms known gender gaps in health-seeking behaviour and antibiotic
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51 293 prescribing, and shows that, with exceptions, adult men and women in English general
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53 294 practice are equally likely to receive an antibiotic prescription when seeking care for
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3 295 common conditions, and that gender differences in the number of antibiotics prescribed are
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5 296 largely driven by differences in consultation behaviour. Equal prescribing proportions may
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7 297 seem to indicate relative parity in how men and women are treated when they consult, but
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9 298 women consult vastly more than men yet have not been shown to suffer from more
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11 299 frequent or severe infection in the conditions included in this study. It is thus plausible that
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13 300 a higher rate of consultation in women is coupled with a milder average clinical
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15 301 presentation, but that overly precautionary GPs prescribe even when antibiotics are not
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17 302 clinically necessary, resulting in high rates of prescribing in all patients. Given the urgent
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19 303 need to reduce unnecessary antibiotic prescribing, it is crucial to more deeply understand
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21 304 how and to whom antibiotics are overprescribed. To this end, future work should further
22
23 305 investigate gender differences in the clinical (in)appropriateness of antibiotic prescribing in
24
25 306 primary care.
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308 Figure captions

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

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

318 Additional information

319 **Contributors:** DS and KP conceived and designed the study. KP extracted the data from The
320 Health Improvement Network database. CD and KP conducted the analyses. DS, JR, KP and
321 TS carried out interpretation of the data. DS drafted the manuscript. CD, JR, KP and TS

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3 322 critically revised the manuscript for important intellectual content. All authors approved the
4
5 323 final version prior to submission.

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10
11 326 **Ethics approval:** This study received approval from THIN's Scientific Review Committee
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14 327 (reference number 16THIN-071-A2).

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16 328 **Data sharing statement:** This analysis is based on a large sample from The Health
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19 329 Improvement Network, provided by IMS Health. The authors' license for using these data
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21 330 precludes the sharing of raw data with third parties.

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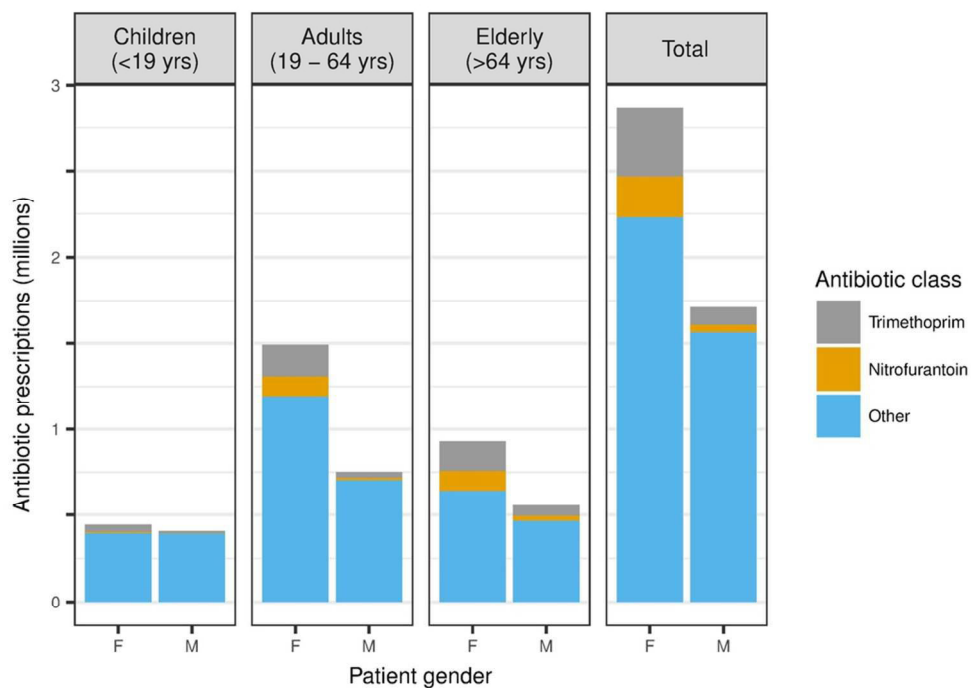


Figure 1. All systemic antibiotic prescriptions recorded in THIN between 2013 and 2015, stratified by gender and age group. Antibiotics used to treat UTI (trimethoprim and nitrofurantoin) are identified separately from all other antibiotics.

89x63mm (300 x 300 DPI)

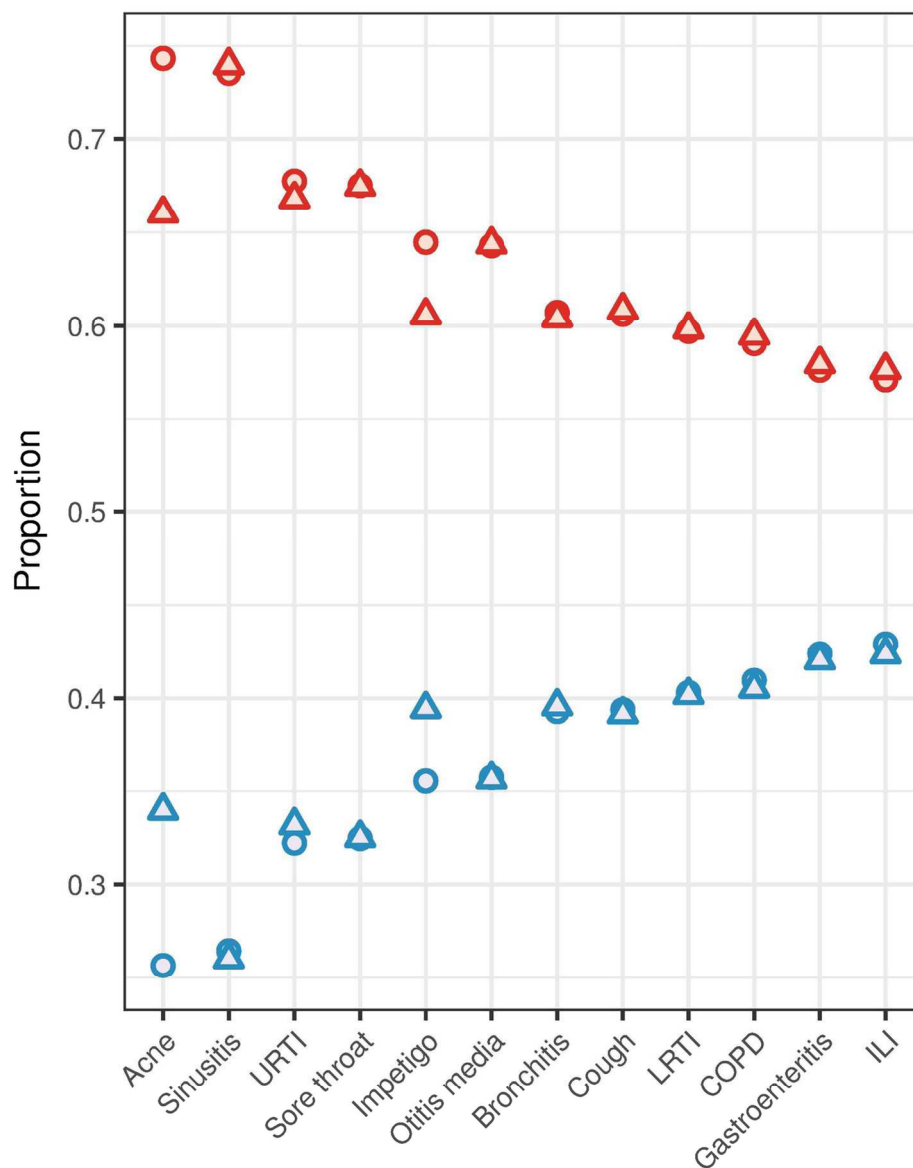


Figure 2. For common conditions in general practice, the proportions all consultations (circles) and antibiotic prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity consulting at their primary registered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

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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)

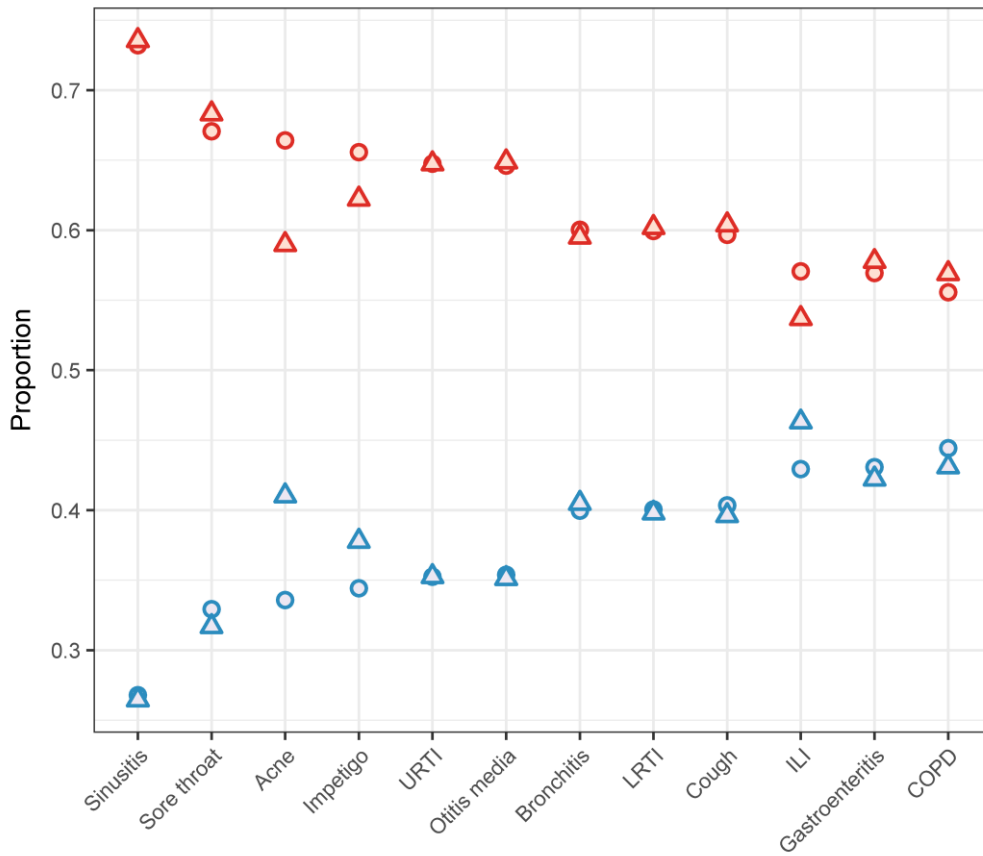


Figure S1. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) with comorbidity who consulted at their primary registered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

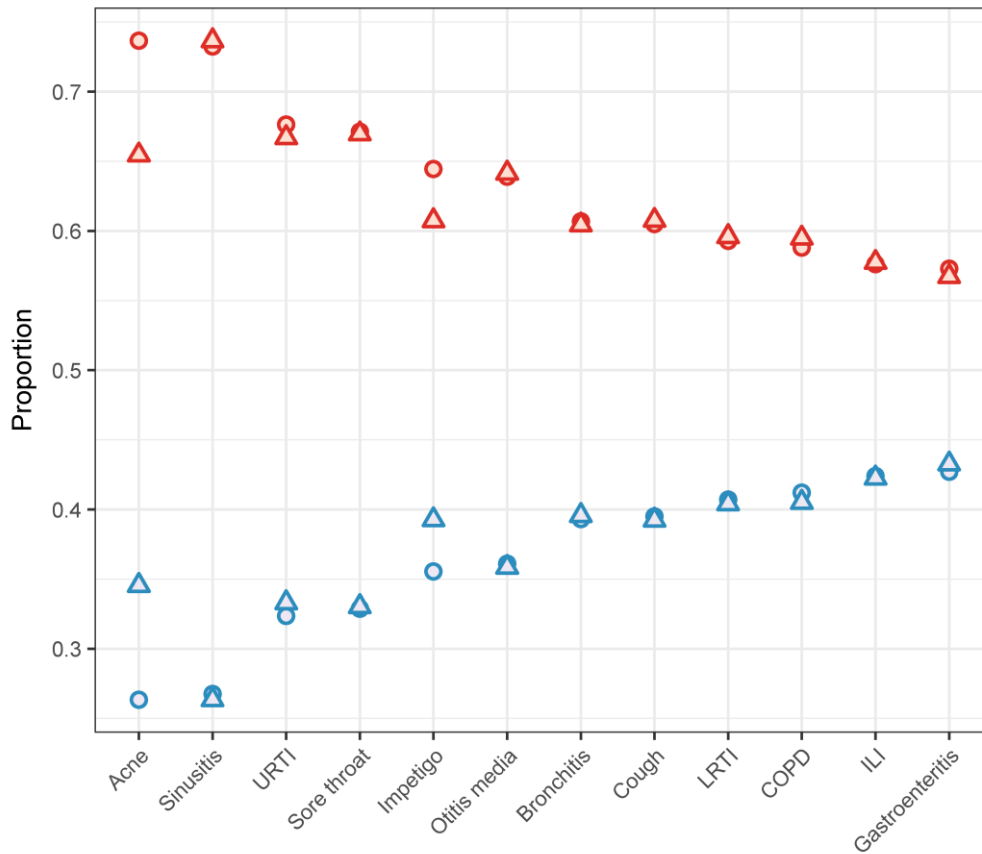


Figure S2. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) without comorbidity, including those who consulted outside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

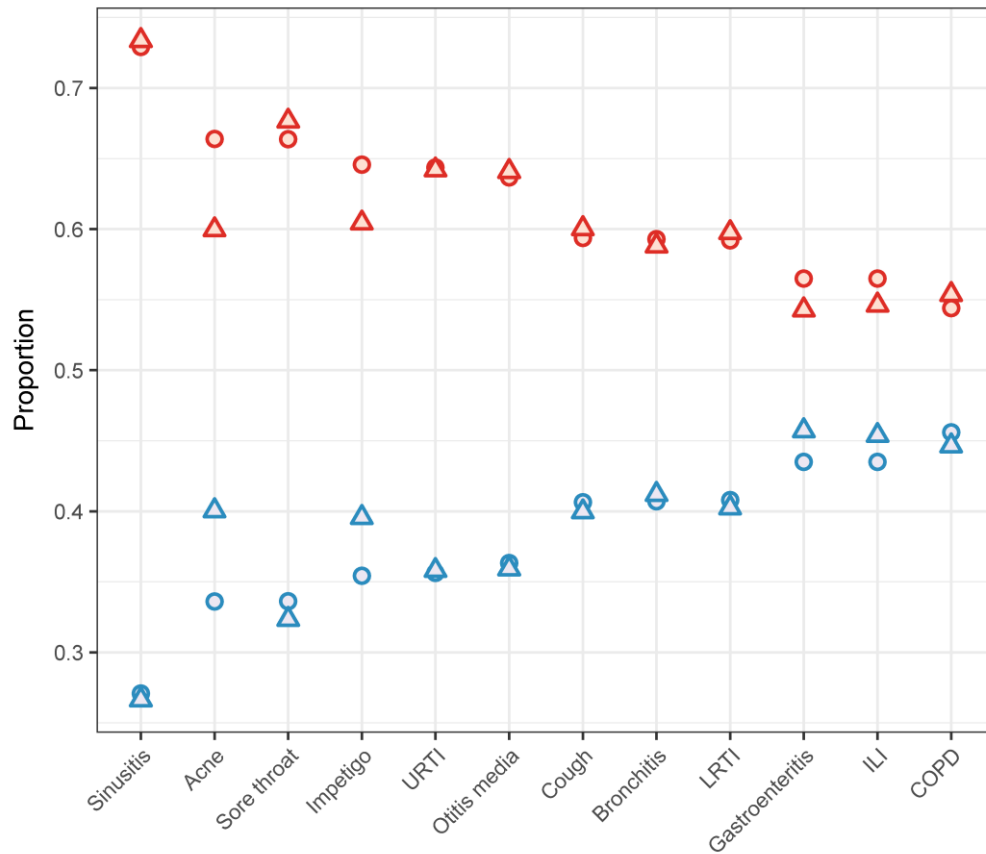


Figure S3. For common conditions in general practice, the proportions of all consultations (circles) and prescriptions (triangles) attributed to women (red) and men (blue). Consultations and prescriptions include all adult patients (aged 19-64) with comorbidity, including those who consulted outside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