

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of English primary care
AUTHORS	Smith, David; Dolk, Christiaan; Smieszek, Timo; Robotham, Julie; Pouwels, Koen

VERSION 1 – REVIEW

REVIEWER	Daniele Piovani IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Italy
REVIEW RETURNED	07-Nov-2017

GENERAL COMMENTS	<p>The study is well designed, and it provides interesting data about the health-seeking-behaviour associated to gender differences in UK by using antibiotic prescriptions. The authors employed a very large sample size, and separated patients with comorbidities from those without comorbidities. I have just some minor comments.</p> <p>In the abstract the authors should cite that they included more than 4,5 millions of individuals in their study (Participants), otherwise it would not be clear why the authors are - appropriately - not including confidence intervals in the results section. The authors should include in the methods section of the manuscript a phrase that clearly state that the primary outcome of the study (the proportion of female/male antibiotic prescription) will not be reported by using a 95% CI because the sample size is very large.</p>
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REVIEWER	B Joseph Guglielmo University of California San Francisco, USA
REVIEW RETURNED	14-Dec-2017

GENERAL COMMENTS	<p>General: The authors' stated goal is "To explore the degree to which the gender gap in antibiotic prescribing is driven by prescribing behaviour, consultation behaviour, comorbidity and urinary tract infection." The background regarding this goal centers upon the observation that the largest % of antibiotic prescribing is in females. Less clear is whether females are more likely to receive an antibiotic than a male on a case-by-case basis, i.e. that associated with an individual consultation or visit. The authors' results suggest, with the exception of acne and impetigo, that no clinically significant gender differences exist in the case-by-case consideration for antibiotic prescribing.</p>
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	<p>They conclude the previously stated differences in antibiotic prescribing between men and women can be explained by the finding that women are more likely to be seen (consultation) than men. While the study offers new findings in this area, the background, goal, and presentation of the findings could use some reworking and clarification.</p> <p>Specific:</p> <ul style="list-style-type: none"> • Lines 17-19: The stated goal is awkwardly written (“To explore the degree to which the gender gap in antibiotic prescribing is driven by prescribing behaviour, consultation behaviour, comorbidity and urinary tract infection.”) Perhaps the more precise goal should be something like “To determine whether women are more likely than men to receive antibiotics in the treatment of community-acquired infection.” • Lines 75-85: While a number of references are provided as background, it seems as though reference 30 should be provided here. Reference 30 is very similar to the current manuscript in their conclusions that the gender gap in antibiotic prescribing was explained by increased consultations by women. Since the current study is so similar in its results, it seems the authors should provide an argument why they are performing their study. Would the results be expected to be different in English patients? Does the current study evaluate additional primary care-oriented infectious diseases over and above that in reference 30? • Results (body of manuscript, table, figures): There is considerable overlap in the presentation of the results between manuscript, table, figures, and the authors should consider using one, not all, to present the results. • Discussion: lines 274-277: The authors state “mixed results”. However, in my review of reference 6 and 30, the former simply provides gross antibiotic use concluding that more antibiotics are used in women. The latter, as mentioned previously, specifically assesses receipt of antibiotics on a case-by-case basis. Thus, they are very different study designs and not necessarily associated with mixed results.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment: "The study is well designed, and it provides interesting data about the health-seeking-behaviour associated to gender differences in UK by using antibiotic prescriptions. The authors employed a very large sample size, and separated patients with comorbidities from those without comorbidities. I have just some minor comments."

Response: We thank Dr. Piovani for his praise, insight and for taking the time to review this work.

"In the abstract the authors should cite that they included more than 4,5 millions of individuals in their study (Participants), otherwise it would not be clear why the authors are - appropriately - not including confidence intervals in the results section. The authors should include in the methods section of the manuscript a phrase that clearly state that the primary outcome of the study (the proportion of female/male antibiotic prescription) will not be reported by using a 95% CI because the sample size is very large."

We agree with the reviewer's comments and have modified the first sentence of the Results section of the abstract to reflect the large sample size (line 29): 'Among 4.57 million antibiotic prescriptions observed in the data, female patients received 67% more prescriptions than males, and 43% more when excluding antibiotics used to treat urinary tract infection (UTI).'

We have also added the following to the Methods section (line 114): 'Due to a very large sample size, proportions of antibiotics prescribed to male versus female patients are reported without confidence intervals.'

Reviewer 2

"General: The authors' stated goal is "To explore the degree to which the gender gap in antibiotic prescribing is driven by prescribing behaviour, consultation behaviour, comorbidity and urinary tract infection." The background regarding this goal centers upon the observation that the largest % of antibiotic prescribing is in females. Less clear is whether females are more likely to receive an antibiotic than a male on a case-by-case basis, i.e. that associated with an individual consultation or visit. The authors' results suggest, with the exception of acne and impetigo, that no clinically significant gender differences exist in the case-by-case consideration for antibiotic prescribing. They conclude the previously stated differences in antibiotic prescribing between men and women can be explained by the finding that women are more likely to be seen (consultation) than men. While the study offers new findings in this area, the background, goal, and presentation of the findings could use some reworking and clarification."

Response: We thank Dr. Guglielmo for his thoughtful, constructive comments. We believe that we have addressed his concerns about the background, goal and presentation through the comments below.

"• Lines 17-19: The stated goal is awkwardly written ("To explore the degree to which the gender gap in antibiotic prescribing is driven by prescribing behaviour, consultation behaviour, comorbidity and urinary tract infection.") Perhaps the more precise goal should be something like "To determine whether women are more likely than men to receive antibiotics in the treatment of community-acquired infection." "

Response: We agree that the wording of the objective was somewhat unwieldy. It now reads (line 17): 'Objectives: To explore causes of the gender gap in antibiotic prescribing, and to determine whether women are more likely than men to receive an antibiotic prescription per consultation.'

"• Lines 75-85: While a number of references are provided as background, it seems as though reference 30 should be provided here. Reference 30 is very similar to the current manuscript in their conclusions that the gender gap in antibiotic prescribing was explained by increased consultations by women. Since the current study is so similar in its results, it seems the authors should provide an argument why they are performing their study. Would the results be expected to be different in English patients? Does the current study evaluate additional primary care-oriented infectious diseases over and above that in reference 30?"

Response: We had identified two references that show similar prescribing proportions in men and women in a selection of RTIs – the paper cited above (Bagger et al. 2015), and another study (Gulliford et al. 2009), which was compared to our study in detail in the discussion. First, we must emphasise that neither of these papers focus on the relationship between prescribing and consultation, let alone make "conclusions that the gender gap in antibiotic prescribing can be explained by increased consultations by women." The Bagger paper's conclusions focus on gender differences in antibiotic demand and inappropriate prescribing, whereas the Gulliford paper's conclusions are related to longitudinal reductions in prescribing.

For these reasons, and also because our paper includes UTI prescribing to explore the gender gap in prescribing at a broader level, we do not believe that these studies undermine the novelty of our work.

Nevertheless, we agree that, in addition to the discussion, referencing these studies in the introduction provides worthwhile context for our paper, and we have added the following sentence (line 84): 'Previous studies of relatively small samples of patients with RTI have found that gender differences in consultation are proportionate to differences in prescribing [20,21], but it is unclear whether or not this is true across a greater range of conditions, when taking comorbidity into account, and using a more recent, nationally representative sample of patients.'

Further, our comparison to Gulliford et al. 2009 in the discussion now also includes a comparison to Bagger et al. 2015 (line 248): 'These findings build on two previous studies of antibiotic prescribing in primary care between 1997-2006 and 2007-2008, respectively.[20,21] Both studies found similar male and female prescribing proportions in a selection of RTIs, but were conducted in a limited subset of patients and did not account for comorbidities, non-respiratory conditions, patients consulting outside of their registered practice, or gender differences in gross antibiotic prescribing at the population level.'

Finally, an important conclusion of Schröder et al.'s recent meta-analysis of gender gaps in antibiotic prescribing is that there are likely many factors that contribute to this gap, [including (i) UTI, (ii) consultation behaviour, (iii) sex hormones and (iv) other patient and practitioner behaviours], but that their relative contribution is unclear. This point has now been emphasised in the introduction for additional context to this study (line 91): 'Ultimately, it remains unknown to what extent these and other factors combine to explain the gender gap in antibiotic prescribing.[6]'

"• Results (body of manuscript, table, figures): There is considerable overlap in the presentation of the results between manuscript, table, figures, and the authors should consider using one, not all, to present the results."

Response: It is true that there is overlap in Table 1 and Fig 2: both show the proportions of consultations made by men and women. However, we stand by the decision to present the data in this way.

In the table, we believe it is useful for the reader to see the number of consultations in order to put gender comparisons in context and to gauge the magnitudes of consultation and prescribing both between conditions (e.g., <10,000 patients consulting with impetigo, compared to >260,000 consulting with cough) and within conditions (e.g., comparing the proportions that consult with and without comorbidity).

As for the figure: a central finding of this paper is that gender differences in prescribing are proportional to differences in consultation across non-skin conditions. We have presented this in Fig 2 by comparing these consultation data to prescribing data (which are not shown elsewhere). An alternative to this could be to include the prescribing data in the table as well, but we believe that Table 1 is already rather large. Instead, including the consultation data in the figure allows for a clean visual comparison of the proportions of men and women consulting and receiving prescriptions, and we therefore believe the paper is stronger with the information presented as is.

"• Discussion: lines 274-277: The authors state "mixed results". However, in my review of reference 6 and 30, the former simply provides gross antibiotic use concluding that more antibiotics are used in women. The latter, as mentioned previously, specifically assesses receipt of antibiotics on a case-by-case basis. Thus, they are very different study designs and not necessarily associated with mixed results"

Response: We thank the reviewer for pointing this out. Reference 6 is indeed a meta-analysis of gross antibiotic use; we instead should have cited the study by Barlam et al. (2015) that is discussed within this meta-analysis and compared inappropriate antibiotic prescriptions for respiratory conditions in men and women, ultimately concluding that women receive more inappropriate antibiotic prescriptions than men. This contrasts with the previously mentioned ref 30 (Bagger et al. 2015), which also compared inappropriate prescribing in men and women for respiratory conditions but did not find any gender differences. We have updated the references accordingly.

Additional changes

As per Public Health England policy, this paper must be published with Crown Copyright. We have made note of this on the cover page.

Since submission, two relevant sources have been identified and added to the manuscript. First is a paper in BMJ by Sue, which provides further evidence that women are not more susceptible to respiratory infections than men. Second is a paper in Epidemiol Infect by Rosello et al., which further corroborates that the vast majority of UTIs in English primary care were treated with nitrofurantoin or trimethoprim in the years of this study (2013-15).

Our previous THIN work that is widely cited in this paper has also been accepted by J Antimicrob Chemother; these citations have been updated to include their respective DOIs and to reflect that they are now in press.

Finally, I will be leaving my post at Public Health England this spring, and so have modified my corresponding email address so that readers can still be in contact after my institutional email address expires.

On behalf of all authors, thank you for considering these revisions to our manuscript.

VERSION 2 – REVIEW

REVIEWER	B Joseph Guglielmo University California San Francisco
REVIEW RETURNED	09-Jan-2018
GENERAL COMMENTS	I believe the authors have made the appropriate changes to warrant publication. Specifically, they have more clearly articulated why they performed the study, how their investigation differs from that performed by others. Table 1 remains a bit difficult to review, however, I appreciate the authors sentiment to present the specifics in each of the respective disease states. Hopefully, there is a way for the authors to simplify the table and still achieve the authors' goals.