Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis

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ABSTRACT

Objective To assess the sex difference in the prevalence of COVID-19 confirmed cases.

Design Systematic review and meta-analysis.

Setting PubMed, Cochrane Library and Google Scholar were searched for related information. The authors developed a data extraction form on an Excel sheet and the following data from eligible studies were extracted: author, country, sample size, number of female patients and number of male patients. Using STATA V.14 for analysis, the authors pooled the overall prevalence of men and/or women using a random-effect meta-analysis model. The authors examined the heterogeneity in effect size using Q statistics and I² statistics. Subgroup and sensitivity analyses were performed. Publication bias was also checked.

Participants Studies on COVID-19 confirmed cases were included.

Intervention Sex (male/female) of COVID-19 confirmed cases was considered.

Primary and secondary outcome measures The primary outcome was prevalence of COVID-19 among men and women.

Results A total of 57 studies with 221,195 participants were used in the analysis. The pooled prevalence of COVID-19 among men was found to be 55.00 (51.43–56.58, I²=99.5%, p<0.001). Sensitivity analysis showed the findings were not dependent on a single study. Moreover, a funnel plot showed symmetrical distribution. Egger’s regression test p value was not significant, which indicates absence of publication bias in both outcomes.

Conclusions The prevalence of symptomatic COVID-19 was found to be higher in men than in women. The high prevalence of smoking and alcohol consumption contributed to the high prevalence of COVID-19 among men. Additional studies on the discrepancies in severity and mortality rate due to COVID-19 among men and women and the associated factors are recommended.

BACKGROUND

COVID-19, first identified in Wuhan, China in late 2019, has rapidly evolved and has resulted in a pandemic by the first quarter of 2020, as indicated by the substantial rise in the number of cases and the fast geographical spread of the disease.1–4 The WHO announced that the official name of the 2019 novel coronavirus is coronavirus disease (COVID-19).5–7 The virus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses.7 COVID-19 was declared by the WHO a public health emergency of international concern on 30 January 2020.8 COVID-19 affects people differently, in terms of infection with SARS-CoV-2 and in mortality rate.9,10

Susceptibility to symptomatic COVID-19 seems to be associated with age, biological sex and comorbidities.11 Although COVID-19 causes mild illness in a majority of cases, severe illness requiring hospital admission is not uncommon.12 Moreover, it has the potential to trigger a life-threatening critical illness, characterised by respiratory failure, circulatory shock, sepsis or other organ failure, requiring intensive care.13,14 According to Global Health 5050 data, the number of COVID-19 confirmed cases and the death rate due to the disease are high among men in different countries.15–17

A report in The Lancet and Global Health 5050 summary show that sex-disaggregated data are essential to understanding the distribution of risk, infection and disease in the population, and the extent to which sex and gender affect clinical outcomes.18 Moreover, knowing the degree to which outbreaks affect...
women and men in different ways is an important step in generating effective, equitable policies and interventions. Since the emergence of COVID-19 in Wuhan, China in December 2019, it has quickly spread across China and numerous other countries. To date, COVID-19 has affected more than 193 countries, with 2,733,591 confirmed cases, including 191,185 deaths and 751,404 recoveries. While some previously published papers have shown sex variations, the findings are not conclusive due to inconsistencies in the prevalence of COVID-19 among men and women. Moreover, there is a lack of systematic review and meta-analysis that provides a worldwide clear picture of sex variations in the risk for COVID-19. Hence, this systematic review and meta-analysis was conducted to assess the pooled prevalence of COVID-19 among men and women.

Review question
The review question for this systematic review and meta-analysis is whether men are more susceptible to acquiring symptomatic COVID-19.

METHODS
Search strategy
This systematic review and meta-analysis identified studies that showed data on the proportion of men and women among COVID-19 confirmed cases. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to search electronic databases, presented in online supplemental file 1. We retrieved studies from Google Scholar, PubMed, Scopus, Web of Science, Cochrane Library, Research Gate and institutional repositories, as described in detail previously. The search included keywords which are combinations of population, condition/outcome and context. A snowball search for references of relevant papers was also performed. The following were the search terms and phrases included: ‘Novel coronavirus’, ‘Novel coronavirus 2019’, ‘2019 nCoV’, ‘COVID-19’, ‘Wuhan coronavirus’, ‘Wuhan pneumonia’ and ‘SARS-CoV-2’. Articles published in the English language from 1 January 2020 were considered. The search concluded on 27 March 2020, and four different researchers independently evaluated the search results. Using these key terms, the following search map was applied: (prevalence OR proportion OR magnitude) AND (Male OR Female) AND (Novel coronavirus OR Novel coronavirus 2019 OR 2019 nCoV OR COVID-19 OR Wuhan coronavirus OR Wuhan pneumonia OR SARS-CoV-2) AND COVID-19 confirmed patients, on PubMed database (online supplemental table S1). Thus, the PubMed search combines #1 AND #2 AND #3 AND #4, as shown in online supplemental table S1. The search date was from January 2000 to December 2019.

Study selection and screening
The retrieved studies were exported to EndNote V.8 reference managers to remove duplicate studies, as described in detail previously. Two investigators (BBA and AMK) independently screened the selected studies using the article’s title and abstract before retrieval of the full text. We used prespecified inclusion criteria to further screen full-text articles. Disagreements were discussed during a consensus meeting, and if necessary including the third and fourth researchers (MWA and TGA) to make the final decision on the studies to be included in the systematic review and meta-analysis.

Inclusion and exclusion criteria
Studies that reported on the proportion of men and/or women among confirmed patients with COVID-19 and published in the English language were included. Studies that did not report on the prevalence of men and/or women among confirmed patients with COVID-19 were excluded. Studies without abstract and/or full text, anonymous reports, editorials, and qualitative studies were excluded from the analysis. Prevalence was defined as the proportion of men and/or women among COVID-19 confirmed cases within a specific population, multiplied by 100.

Patient and public involvement
Patients or the public were not involved in the design, conduct, or reporting, or dissemination plans of our research.

Quality assessment
Using the Joanna Briggs Institute (JBI) Quality Appraisal Checklist, the authors appraised the quality of included studies. The papers were split among a team of four reviewers. Each paper was then assessed by two reviewers and any disagreements were discussed with the third and fourth reviewers. A study was considered as low risk or of good quality when it scored 4 and above, whereas a study that scored 3 and below was considered high risk or of poor quality, as described in detail previously (online supplemental table S2).

Data extraction
The authors developed a data extraction form on an Excel sheet and the following data from eligible studies were extracted: author, country, sample size, number of female patients and number of male patients, as described in detail previously. The data extraction sheet was piloted using four random papers, and it was adjusted after the template was piloted, as described in detail previously. Two of the authors extracted data in collaboration using the extraction form. The third and fourth authors independently checked the correctness of data. Any disagreements between the reviewers were resolved through discussions with third and fourth reviewers, as described in detail previously. Mistyping of data was resolved by crosschecking the included papers. Definitions of cases were as follows: (1) confirmed case: detection of SARS-CoV-2 nucleic acid in a clinical specimen; (2) possible case: any person with at least one of the following symptoms: cough, fever, shortness of breath,
or sudden onset of anosmia, ageusia or dysgeusia; and (3) probable case: any person with at least one of the following symptoms: cough, fever, shortness of breath, or sudden onset of anosmia, ageusia or dysgeusia, with close contact with a confirmed COVID-19 case in the 14 days prior to onset of symptom or having been a resident or a staff member in the 14 days prior to onset of symptoms in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed.

Synthesis of results
We transported the data to STATA V.14 for analysis after extracting the data in an Excel sheet, considering the reported prevalence of men and women. We pooled the overall prevalence of men and/or women using a random-effect meta-analysis model. We examined the heterogeneity in effect size using Q statistics and I² statistics. In this study, an I² statistic value of 0 indicates true homogeneity, whereas values of 25%, 50% and 75% represented low, moderate and high heterogeneity, respectively. Subgroup analysis was performed by study country and sample size. Sensitivity analysis was employed to examine the effect of a single study on the overall estimation. Publication bias was checked by a funnel plot and more objectively through Egger’s regression test.

RESULTS
Study selection
A total of 2574 studies were identified using electronic search (databases, n=2560; other sources, n=12). After removal of duplicates, a total of 1352 articles remained (1222 duplicates). Finally, 86 studies were screened for full-text review, and 57 articles (n=221 195 patients) were selected for analysis (figure 1). The citation manager automatically identifies duplicates and creates a separate group among the imported references which can be deleted. For different citations of the same paper, we screened and de-duplicated the citations by hand and recorded them on a Microsoft Excel spreadsheet after assessment of whether they have the same author, title, publication date, volume, issue, sample size and so on. The duplicate one was then removed.

Characteristics of the included studies
A total of 57 studies were included in the systematic review and meta-analysis.1 10 13 14 24 29–75 All studies were published in 2020, with sample size ranging from 936 to 78,77146 (table 1).

Meta-analysis
Prevalence of COVID-19 among men
All studies (n=57) with a total of 221 195 patients reported on the proportion of men and women with COVID-19.1 10 13 14 24 29–75 The prevalence of COVID-19 among men ranges from 37.5 in Liu et al32 to 77.08 in Chen et al.58 Random-effects model analysis from these studies revealed that the pooled prevalence of COVID-19 confirmed cases was 55.00 (51.43–56.58, I²=99.5%, p<0.001) (figure 2).

Subgroup analysis of COVID-19 confirmed cases among men
A subgroup analysis was performed through stratification by country, province, sample size and quality score. Based on this, the prevalence of COVID-19 was found to be 55.99 (51.99–59.99), 39.21 (34.85–43.84), 59.80 (59.16–60.44), 37.77 (36.31–39.24) and 50.00 (26.90–73.10) in China, Africa, Italy, Korea and Singapore, respectively (table 2 and online supplemental figure 1).

Figure 1  PRISMA flow diagram shows the results of the search and the reasons for exclusion. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Table 1  Characteristics of included studies of men and women among COVID-19 confirmed cases

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Continued
The pooled prevalence of COVID-19 among men in Wuhan, Shanghai, Hubei, Zhonghua, outside China, Zhejiang, Shenzhen, Jiangsu and Chongqing was 72.05 (95% CI 71.71 to 72.35, I²=96.6, p=0.00), 51.01 (95% CI 50.1 to 50.80, I²=66.7, p=0.00), 50.40 (95% CI 50.1 to 50.80, I²=66.7, p=0.00), 53.17 (95% CI 52.81 to 53.53, I²=37.9, p=0.139), 63.52 (95% CI 51.64 to 75.40, I²=0.0, p=0.796), 44.84 (95% CI 35.99 to 53.68, I²=29, p=0.235) and 52.20 (95% CI 47.95 to 56.44, I²=65.1, p=0.09), respectively (table 2 and online supplemental figure 2).

With regard to quality score, the pooled prevalence of COVID-19 among men in studies which scored greater than or equal to 7 on the JBI Quality Appraisal Checklist was 53.66 (95% CI 49.23 to 58.09, I²=99.5, p=0.00), and 56.79 (95% CI 52.79 to 60.990, I²=94.7, p=0.00) among studies that scored less than 7 (table 2 and online supplemental figure 3).

With regard to sample size, the pooled prevalence of COVID-19 among men in studies with sample size greater than or equal to 384 was 53.86 (95% CI 47.09 to 60.63, I²=99.9, p=0.00) and 56.79 (95% CI 52.79 to 60.990, I²=94.7, p=0.00) among studies that scored less than 7 (table 2 and online supplemental figure 4).

**Sensitivity analysis**

We employed a leave-one-out sensitivity analysis to identify the impact of individual research on the pooled prevalence of severe illness among COVID-19 confirmed cases. This sensitivity analysis showed that our findings were not dependent on a single study. Our pooled estimated prevalence of severe illness varied between 22.83 (19.12–26.53) in Li et al and 25.0 (19.87–30.13) in Yanping et al after deletion of a single study (figure 3).

**DISCUSSION**

This systematic review and meta-analysis was conducted to assess the sex difference in acquiring COVID-19. Fifty-seven studies were included in the final analysis. This systematic review and meta-analysis revealed that the pooled prevalence of COVID-19 confirmed cases among men and women was 55.00 (51.43–58.58, I²=99.5%, p<0.001) and 45.00 (41.42–48.57), respectively. This indicates COVID-19 is more prevalent in men than in women. Similar finding was reported in other studies. A study in Ontario, Canada showed that men were more likely to test positive. In Pakistan 72% of COVID-19 cases were male. According to Global Health 5050 data, the number of COVID-19 confirmed cases and the death rate due to the disease are high among men in different countries.
This might be because behavioural factors and roles which increase the risk of acquiring COVID-19 tend to be more common among men. Men are more involved in various risky behaviours, such as alcohol consumption, being involved in key activities during burial rites, and working in basic sectors and occupations that require them to continue being active, to work outside their homes and to interact with other people even during the containment phase (eg, food or pharmacy manufacturing and sales, agriculture or food production and distribution, transportation, and security). Because of this, men mostly do not stay at home, and sit together with other people and remove their mask to drink and smoke. This increased level of exposure predisposes men to a high risk of acquiring COVID-19. In China 50% of men smoke, and because it is considered not acceptable for women to smoke only 2% of them do so. Smoking is associated with adverse health outcomes, including increased risk of severe illness and mortality from COVID-19.

Figure 2  Forest plot showing the pooled prevalence of COVID-19 confirmed cases among men. ES, Estimate.
outcomes of COVID-19. For instance, the combined results of five studies showed that smokers were 1.4 times more likely than non-smokers to have severe symptoms of COVID-19. Smoking is also related to a higher expression of ACE2 (the receptor for SARS-CoV-2), which might be the reason for the higher prevalence of COVID-19 in this subgroup of patients.

Men tended to develop more symptomatic and serious disease than women, according to the clinical classification of severity. Similar incidence occurred during the previous coronavirus epidemics: men had worse outcomes of illness from severe acute respiratory syndrome and a higher risk of dying from the Middle East respiratory syndrome. Biological sex variation is said to be one of the reasons for the sex discrepancy in COVID-19 cases, severity and mortality. Women are in general able to mount a more vigorous immune response to infections and vaccinations. Some previous studies on coronaviruses in mice have suggested that oestrogen may have a protective role. Oestrogens suppress the escalation phase of the immune response that leads to increased cytokine release. Authors also showed that female mice treated with an oestrogen receptor antagonist died at close to the same rate as male mice.

The X chromosome is known to contain the largest number of immune-related genes in the whole genome. With their XX chromosome, women have a double copy of key immune genes compared with a single copy in XY in men. This boost extends both to the general reaction to infections (the innate response) and to the more specific response to microbes, including antibody formation (adaptive immunity). Thus women’s immune systems are generally more responsive to infections. This might mean women are able to tackle the novel coronavirus more effectively, but this has not yet been proven.

### Table 2

Subgroup analysis of the pooled prevalence of COVID-19 by country, province, quality score and sample size

<table>
<thead>
<tr>
<th>Variables</th>
<th>Characteristics</th>
<th>Pooled prevalence (95% CI)</th>
<th>I² (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>By province in China</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wuhan</td>
<td></td>
<td>72.05 (71.71 to 72.35)</td>
<td>96.6 (0.00)</td>
</tr>
<tr>
<td>Shanghai</td>
<td></td>
<td>51.01 (44.05 to 57.97)</td>
<td>–</td>
</tr>
<tr>
<td>Hubei</td>
<td></td>
<td>50.40 (50.1 to 50.80)</td>
<td>66.7 (0.001)</td>
</tr>
<tr>
<td>Zhonghua</td>
<td></td>
<td>54.07 (51.63 to 56.51)</td>
<td>37.9 (0.139)</td>
</tr>
<tr>
<td>Zhejiang</td>
<td></td>
<td>46.45 (39.10 to 53.81)</td>
<td>99.4 (0.00)</td>
</tr>
<tr>
<td>Shenzhen</td>
<td></td>
<td>63.52 (51.64 to 75.40)</td>
<td>0.0 (0.796)</td>
</tr>
<tr>
<td>Jiangsu</td>
<td></td>
<td>44.84 (35.99 to 53.68)</td>
<td>29 (0.235)</td>
</tr>
<tr>
<td>Chongqing</td>
<td></td>
<td>52.20 (47.95 to 56.44)</td>
<td>65.1 (0.09)</td>
</tr>
<tr>
<td>Outside China</td>
<td></td>
<td>53.17 (52.81 to 53.53)</td>
<td>99.4 (0.00)</td>
</tr>
<tr>
<td>By country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td></td>
<td>55.99 (51.99 to 59.99)</td>
<td>99.5 (0.00)</td>
</tr>
<tr>
<td>Africa</td>
<td></td>
<td>39.21 (34.85 to 43.84)</td>
<td>–</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td>59.80 (59.16 to 60.44)</td>
<td>–</td>
</tr>
<tr>
<td>Korea</td>
<td></td>
<td>37.77 (36.31 to 39.24)</td>
<td>–</td>
</tr>
<tr>
<td>Singapore</td>
<td></td>
<td>50.00 (26.90 to 73.10)</td>
<td>–</td>
</tr>
<tr>
<td>By JBI quality score</td>
<td>≥7</td>
<td>53.66 (49.23 to 58.09)</td>
<td>99.5 (0.00)</td>
</tr>
<tr>
<td></td>
<td>&lt;7</td>
<td>56.79 (52.79 to 60.990)</td>
<td>94.7 (0.00)</td>
</tr>
<tr>
<td>By sample size</td>
<td>≥384</td>
<td>53.86 (47.09 to 60.63)</td>
<td>99.9 (0.00)</td>
</tr>
<tr>
<td></td>
<td>&lt;384</td>
<td>54.96 (52.35 to 57.57)</td>
<td>64.5 (0.00)</td>
</tr>
</tbody>
</table>

**JBI**, Joanna Briggs Institute.
Moreover, the above-listed behavioural factors, such as smoking and alcohol consumption, tend to be more common among men, and these behaviours predispose men to cardiac and respiratory diseases. This may also explain the overall higher mortality rate among men. A systematic review and meta-analysis revealed that comorbid diseases such as respiratory system disease, hypertension and cardiovascular disease are risk factors for death.

**CONCLUSIONS**

The prevalence of symptomatic COVID-19 was found to be higher in men than in women. The high prevalence of smoking and alcohol consumption contributed to the high prevalence of COVID-19 among men, along with occupational exposures which prevent men from staying at home, as well as sitting together with other people and removing their mask to drink and smoke. This increased level of exposure predisposes men to a high risk of acquiring COVID-19, making it more prevalent among men. Smoking and drinking alcohol reduce overall health and therefore make an individual more susceptible to symptomatic COVID-19 infection. Although there has been a rapid surge in research in response to the COVID-19 outbreak, additional studies with regard to discrepancies in severe illness and mortality due to COVID-19 among men and women and the factors that determine exposure, severity and mortality due to COVID-19 are recommended.

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