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Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies

Bart G Pijls ,[1] Shahab Jolani,[2] Anique Atherley,[3] Raissa T Derckx,[4] Janna I R Dijkstra,[5] Gregor H L Franssen,[6] Stevie Hendriks,[7] Anke Richters ,[8] Annemarie Venemans-Jellema,[9] Saurabh Zalpuri,[10] Maurice P Zeegers[11]

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For numbered affiliations see end of article.

Correspondence to
Dr Bart G Pijls;
b.g.c.w.pijls@lumc.nl

ABSTRACT

Objective We aimed to describe the associations of age and sex with the risk of COVID-19 in different severity stages ranging from infection to death.

Design Systematic review and meta-analysis.

Data sources PubMed and Embase through 4 May 2020.

Study selection We considered cohort and case–control studies that evaluated differences in age and sex on the risk of COVID-19 infection, disease severity, intensive care unit (ICU) admission and death.

Data extraction and synthesis We screened and included studies using standardised electronic data extraction forms and we pooled data from published studies and data acquired by contacting authors using random effects meta-analysis. We assessed the risk of bias using the Newcastle-Ottawa Scale.

Results We screened 11.550 titles and included 59 studies comprising 36.470 patients in the analyses. The methodological quality of the included papers was high (8.2 out of 9). Men had a higher risk for infection with COVID-19 than women (relative risk (RR) 1.08, 95% CI 1.03 to 1.12). When infected, they also had a higher risk for severe COVID-19 disease (RR 1.18, 95% CI 1.10 to 1.27), a higher need for intensive care (RR 1.38, 95% CI 1.09 to 1.74) and a higher risk of death (RR 1.50, 95% CI 1.18 to 1.91). The analyses also showed that patients aged 70 years and above have a higher infection risk (RR 1.65, 95% CI 1.50 to 1.81), a higher risk for severe COVID-19 disease (RR 2.05, 95% CI 1.27 to 3.32), a higher need for intensive care (RR 2.70, 95% CI 1.59 to 4.60) and a higher risk of death once infected (RR 3.61, 95% CI 2.70 to 4.84) compared with patients younger than 70 years.

Conclusions Meta-analyses on 59 studies comprising 36.470 patients showed that men and patients aged 70 and above have a higher risk for COVID-19 infection, severe disease, ICU admission and death.

PROSPERO registration number CRD42020180085.

Strengths and limitations of this study

- ► Our search strategy revealed 11.550 individual records and we included 59 studies.
- ► Our study focuses on the early phase of the pandemic.
- ► A thorough sensitivity analysis could not refute the conclusions.
- ► Our review has added a quality assessment of the individual studies.
- ► Most included studies, n=50, were from China involving Chinese patients with COVID-19 compared with n=9 studies from outside China.

BACKGROUND

COVID-19 or the disease caused by the SARS-CoV-2 coronavirus has caused a pandemic that has affected patients in more than 188 countries and territories around the world. The number of patients diagnosed with COVID-19 has exceeded 27 million on 8 September 2020, and to date more than 890 000 patients have died.[1]

Regarding demographics, respiratory tract infections are, in general, more severe in men and they tend to lead to higher mortality in men.[2] Higher mortality for men was also observed during the severe acute respiratory syndrome (SARS) epidemic.[3] In a mixed group of patients with COVID-19 and SARS, Jin *et al*[4] found that increased age and sex were associated with more severe disease and mortality. However, a systematic review on the association between demographic factors and different severity stages of COVID-19 is lacking.

Knowledge on the association between demographic factors and different severity stages of COVID-19 such as infection, severe disease, intensive care unit (ICU) admission and death may provide insight into the underlying pathophysiological mechanisms (immunity, coagulopathy and comorbidities). This knowledge may also guide clinical decision-making, especially when there is an impending shortage in healthcare resources such as ICU beds. Additionally, exploring demographic factors influencing COVID-19 outcomes may guide policymakers in, for instance, the prioritisation of non-pharmaceutical interventions

and screening.[5] These demographic factors may also be important for the design and interpretation of clinical trials on the efficacy of treatments as they could potentially be strong confounders. Therefore, the aim of this living systematic review is to describe the association between demographic factors and COVID-19 in different stages of the disease.

METHODS

The reporting of this living systematic review and meta-analysis is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and a protocol has been registered a priori at the PROSPERO registry (PROSPERO 2020).[6] For this review, we focused on the early phase of the pandemic.

Demographic factors include: age, sex, social economic status (education level), pregnancy and ethnicity. As only a few studies so far reported on the latter three factors, the current version of this review focuses on age and sex. Age was categorised into old age, defined as 70 years and older, and young age, defined as younger than 70 years. Seventy years was chosen as a cut-off point for the main analyses because this was the most commonly used cut-off in the first studies included. We also collected data on other cut-off points (60 and 65 years) where possible. We considered four stages of disease severity: (1) infection, (2) severe clinical or radiological symptoms (according to WHO guidance[7]), (3) ICU admission, and (4) death. This led to the following research questions:

What is the association between demographic factors and:

1. A confirmed COVID-19 infection among the general population?
2. Clinically/radiologically severe COVID-19 among hospitalised patients with a confirmed infection?
3. ICU admission among patients hospitalised for confirmed COVID-19 infection?
4. Death among patients hospitalised for confirmed COVID-19 infection?

Originally, we also planned to investigate 'hospitalisation' as a potential outcome. However, only one study reported on this, which did not warrant inclusion in this version of the review. Future versions of the review will re-evaluate 'hospitalisation' as an outcome. The cases and controls for each stage of the disease are defined in table 1.

Data sources and searches

The search strategy was devised with a specialised librarian (GHLF) and the following databases were searched from December 2019 up to 4 May 2020: Medline via PubMed and Embase. Additionally, EPPI Centre (COVID-19: a living systematic map of the evidence) was consulted up to 31 March 2020.[8]

We designed the search strategy to be sensitive and reproducible. The term COVID-19 was elaborated in combinations of controlled vocabulary and free text terms. See online supplemental appendix 1 for the full search strategy. No language restrictions were applied during the search strategy. Studies reported in languages spoken by the research team were included: English, Dutch, German, French and Russian. Studies published in any other language were temporarily excluded and will be reconsidered in future updates of this living review.

Study selection

Initial screening on the basis of title and abstract of eligible studies was performed by one reviewer (RTD, AVJ or BGP). A second reviewer (RTD) redid the study selection procedure on a random sample of 500 studies. The between-reviewer agreement from these 500 studies was 98.4% with a kappa of 0.74, indicating substantial agreement.[9] When the information in the abstract did not suffice or where there was any doubt, the studies remained potentially eligible. The full text of potentially eligible studies was independently evaluated in duplicate by two reviewers (from AR, SZ, AA, JIRD, SH). All records identified through the searches were collected in an electronic reference database and subjected to the following inclusion and exclusion criteria: the study had to focus on humans with COVID-19 or SARS-CoV-2 coronavirus infections providing, or potentially providing, sufficient information to calculate risk ratios for our prespecified associations (table 1). A study was excluded when no valid comparisons could be made. This was the case when less than five observations were reported in any cell of the contingency tables, when the study quality score (see next paragraph) was less than 5 out of 9 and when patients were admitted to hospital for different indications than for COVID-19 (eg, kidney transplant patients, patients with fractured bones).

Table 1 Study structure

Severity stage	Case	Control	Population
1. Infection	Test positive	Test negative	General population
2. Severe symptoms (clinically or radiologically)	Severe symptoms	Non-severe symptoms	Hospitalised COVID-19 cases
3. ICU admittance	Admitted to ICU	Not admitted to ICU	Hospitalised COVID-19 cases
4. Death	Death	Alive	Hospitalised COVID-19 cases

ICU, intensive care unit.

Data extraction and quality assessment

Observed frequencies of outcomes and controls per level of the determinants were extracted from text, tables or figures (ie, 2×2 tables leading to unadjusted risk ratios) for each included study. One reviewer (AR or SZ) extracted data from included studies regarding the severity stages of COVID-19, patient demographics and study characteristics in a predefined electronic data sheet that was designed during a pilot data extraction phase on the first eligible studies. A second reviewer (AA, JIRD or SH) double-checked the inclusion by the data extractors. Any disagreements were resolved by consensus or by consulting a referee (BGP or MPZ). We contacted the authors of papers with data presented in a way that did not allow summarisation in contingency tables by email. We sent a reminder email after 1 week. In total, we contacted 87 authors of whom 17 supplied additional data which could be used in the analyses for 12 papers. Risk of bias of the included studies was appraised independently by one reviewer (from AA, JIRD or SH) using the Newcastle-Ottawa Scale (NOS).[10]

Data synthesis and analysis

We used the relative risk (RR) to assess the association between each severity stage (ie, diagnosis, severe disease, ICU admission and death) and demographic factors. The data from the included studies underwent random effects meta-analysis to determine the pooled effect sizes with corresponding 95% CIs and (in case of heterogeneity) 95% prediction intervals.[11] The amount of statistical heterogeneity was assessed through visual inspection of the forest plots and by calculating I^2 statistics.[12] If data allowed, we explored potential sources of statistical heterogeneity when I^2 was above 40% (1) through subgroup analyses and (2) with random effects meta-regression analyses on predefined factors. These factors include: geographical region, study quality, study size, days into the pandemic, publication date, diagnostic modality (eg, PCR test, CT signs, clinical symptoms and their combinations that led to the diagnosis of COVID-19) and clinical setting (eg, nursing home, home, hospital, general practitioner cohort). We carried out leave-one-out analyses to determine the influence of possible outlier studies on the pooled effect size. The study setting and diagnostic modality were very consistent within the different outcomes, so a sensitivity on these factors was not meaningful.

To assess publication bias we constructed funnel plots for visual inspection and statistically tested potential asymmetry using the Egger and Harbord test.[13 14] In case of asymmetry, a trim-and-fill method and cumulative meta-analyses were used to explore the magnitude and direction of publication bias.

Patient and public involvement

This systematic review and meta-analysis is part of the WHO Evidence Collaborative on COVID-19 answering their rapid review priority questions on risk factors for infection and disease severity. Patients were not involved.

RESULTS

Study selection

The literature search yielded 11 550 unique hits of which 300 studies were eligible after screening titles and abstracts. From these eligible studies, we excluded 241: 13 were reviews; 17 were written in a language not spoken by the review team; 118 did not report or evaluate demographic factors; and 93 had no valid comparisons between cases and controls. This left 59 studies in the current meta-analysis, covering a total of 36 470 patients.[15–73] Details of the study selection are given in figure 1 (PRISMA flow chart).

Study characteristics

We included studies on the effect of age (70 years or more vs less than 70 years) and sex (men vs women). There were either no studies or not enough studies on social economic status, pregnancy or ethnicity to allow any meaningful analyses. Regarding age and sex, there were not enough studies on the outcome 'hospitalization' to allow any meaningful analyses. The current meta-analysis therefore presents results on age and sex regarding risk of infection, disease severity, ICU admission and death.

From the included studies, 50 were from China, 3 from the USA, 1 from Germany, 1 from Iran, 1 from Italy, 1 from Singapore, 1 from South Korea and 1 from the UK. The included studies were published between 2 January 2020 and 15 April 2020. The mean age of the patients in the included studies ranged from 7 to 73 years. The percentage of males in the included papers ranged from 35% to 81%. The follow-up ranged from 12 to 73 days. For details of individual studies, organised by exposure and outcome, see online supplemental appendix 2.

Risk of bias

The methodological quality of the included papers was high with an average of 8.2 out of 9, as measured with the NOS. Case definition and case representativeness were acceptable in 55 out of 59 and 55 out of 59 studies, respectively. Control selection and control definition were acceptable in 59 out of 59 and 55 out of 59 studies, respectively. Exposure ascertainment and comparable ascertainment were acceptable in 57 out of 59 and 58 out of 59 studies, respectively. Non-response rate was not applicable for our study questions. Details of NOS items for individual studies, organised by exposure and outcome, are available in online supplemental appendix 2.

Synthesis of results

Meta-analyses of the primary outcomes for the risk factors sex and age revealed differences among men and women and among patients 70 years of age or older (70+) and below 70 years (70–). An overview of the pooled results

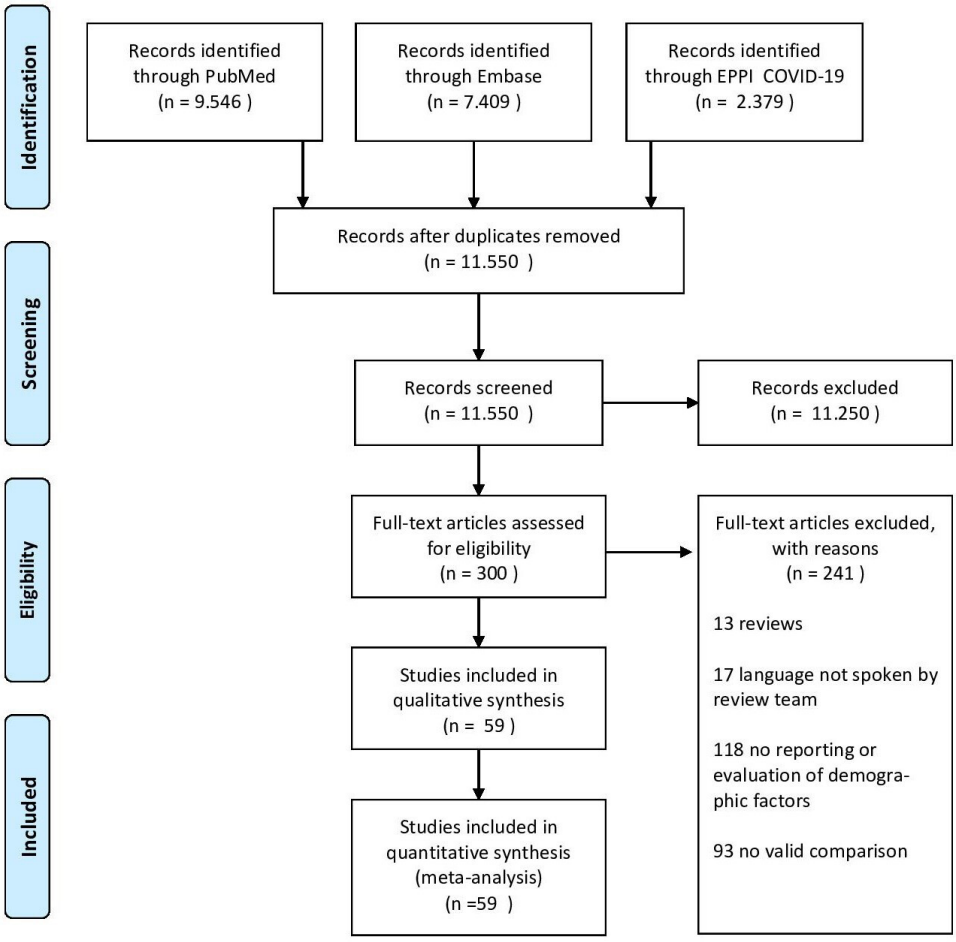

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart showing study selection.

from random effects meta-analyses for each demographic factor separately can be found in table 2.

Demographic factor: sex

There was an unambiguous association between each stage of disease severity and sex with men having a higher risk of infection, disease severity, ICU admission and death than women. Men have a statistically significant 8% higher risk of being diagnosed with COVID-19 than women (RR: 1.08, 95% CI 1.03 to 1.12; 8 studies) (see figure 2). When diagnosed, men also experienced more severe disease than women (RR 1.18, 95% CI 1.10 to 1.27; 35 studies), implying that the risk of severe COVID-19 disease for men is 18% higher than that for women (see figure 3). Moreover, the rate of admission to ICU in patients with COVID-19 was higher among men as compared with women. The aggregated random effect was 1.38 (95% CI 1.09 to 1.74; 11 studies) (see figure 4). Finally, we observed that men were at higher risk of death

Table 2 Summary of data synthesis

Exposure	Outcome	Studies (n)	Patients (n)	Pooled estimate (RR)	95% CI	95% PI	Heterogeneity (I^2)
Sex (male vs female)	Infection	8	16 286	1.08	1.03 to 1.12	NA	0%
	Severe disease	35	7832	1.18	1.10 to 1.27	NA	15%
	ICU	11	1493	1.38	1.09 to 1.74	NA	32%
	Death	14	12 792	1.50	1.18 to 1.91	0.73 to 3.10	62%
Age (70+ vs 70–)	Infection	4	12 996	1.65	1.50 to 1.81	NA	35%
	Severe disease	7	1102	2.05	1.27 to 3.32	0.42 to 9.93	87%
	ICU	5	688	2.70	1.59 to 4.60	0.47 to 15.7	69%
	Death	5	9222	3.61	2.70 to 4.84	1.51 to 8.67	60%

ICU, intensive care unit; NA, not applicable; PI, prediction interval; RR, risk ratio.

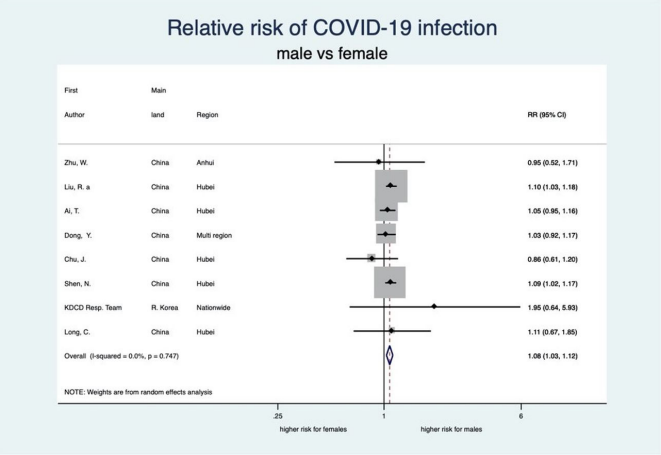

Figure 2 Forest plot showing the association between sex and risk of COVID-19 infection. Overall, men have a 1.08 times higher risk of COVID-19 infection than women. Liu *et al*.[32] RR, relative risk.

from COVID-19 as compared with women (RR 1.50, 95% CI 1.18 to 1.91; 14 studies) (see figure 5). These increased risks for men across all severity stages were statistically significant, with little heterogeneity (see table 2).

Demographic factor: age

This meta-analysis also showed a clear-cut distinction between patients aged 70 years or older (70+) and 70 years or younger (70–) with respect to each stage of disease severity for COVID-19 (see figures 6–9). Patients aged 70+ appear to have a 65% higher risk for infection of COVID-19 (RR 1.65, 95% CI 1.50 to 1.81; 4 studies).

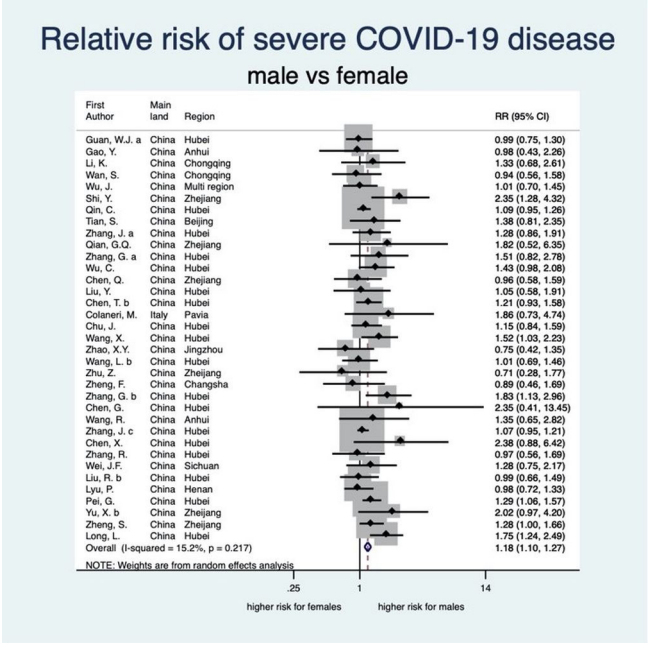

Figure 3 Forest plot showing the association between sex and risk of severe COVID-19. Overall, men have a 1.18 times higher risk of severe COVID-19 than women. Zhang *et al*;[67] Zhang *et al*;[65] Zhang *et al*;[64] Zhang *et al*;[66] Liu *et al*.[33] RR, relative risk.

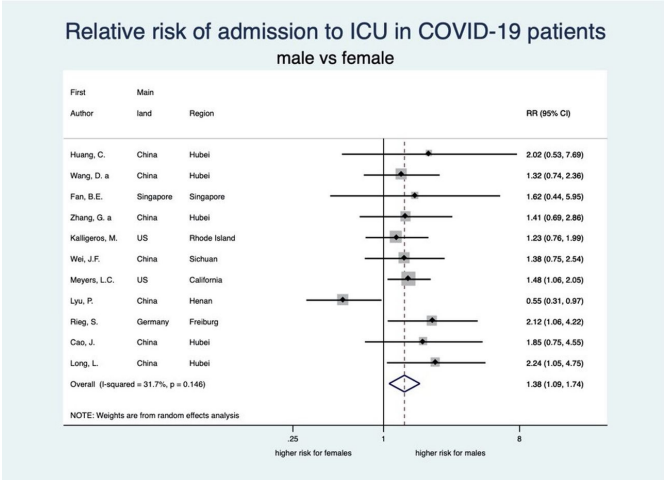

Figure 4 Forest plot showing the association between sex and risk of ICU admission due to COVID-19. Overall, men have a 1.38 times higher risk of ICU admission due to COVID-19 than women. Zhang *et al*.[65] ICU, intensive care unit; RR, relative risk.

When infected, they also appear to have a higher risk for severe COVID-19 disease, need for intensive care and death (RR 2.05, 95% CI 1.27 to 3.32; 7 studies, RR 2.70, 95% CI 1.59 to 4.60; 5 studies, and RR 3.61, 95% CI 2.70 to 4.84; 5 studies, respectively). These increased risks for older patients across all severity stages were statistically significant and very consistent, though there was some observed heterogeneity in the magnitude of this effect but not in the direction of the effect.

Sensitivity analyses

Funnel plots showed some asymmetry for the relation between sex and the outcomes of severe disease, ICU admission and death (all p values above 0.063; Harbord test). Although the subsequent trim-and-fill

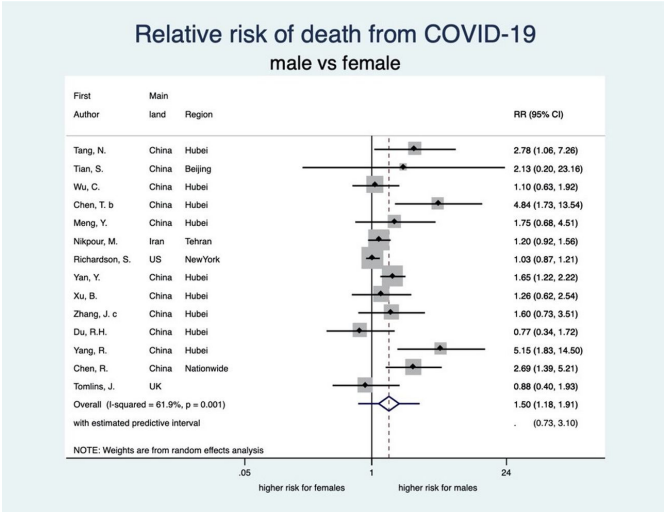

Figure 5 Forest plot showing the association between sex and risk of death due to COVID-19. Overall, men have a 1.50 times higher risk of death due to COVID-19 than women. RR, relative risk.

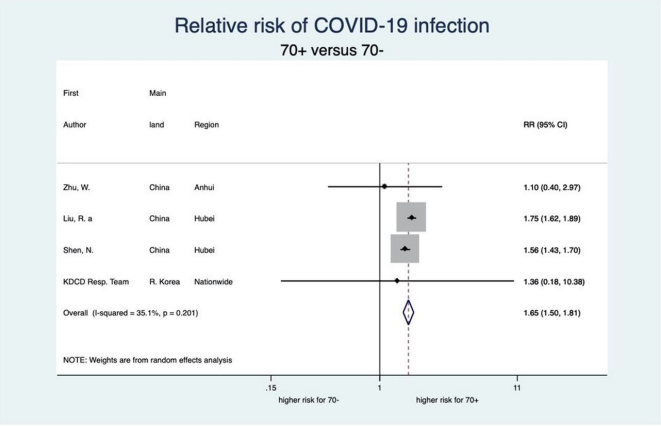

Figure 6 Forest plot showing the association between age and risk of COVID-19 infection. Overall, patients aged 70 years or older have a 1.65 times higher risk of COVID-19 infection than patients younger than 70 years. Liu *et al.*[32] RR, relative risk.

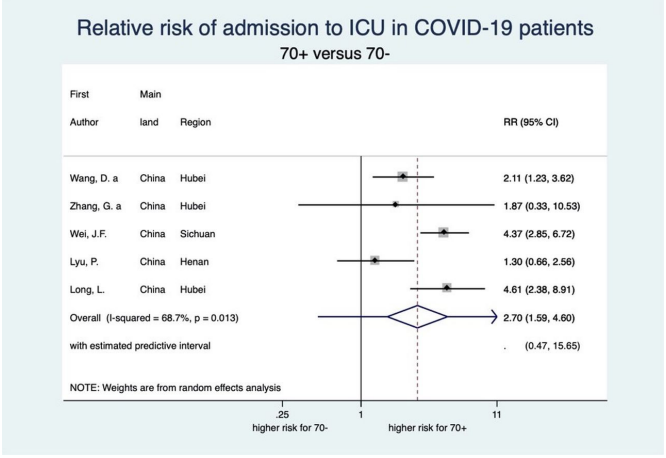

Figure 8 Forest plot showing the association between age and risk of ICU admission due to COVID-19. Overall, patients aged 70 years or older have a 2.70 times higher risk of ICU admission due to COVID-19 than patients younger than 70 years. Zhang *et al.*[65] ICU, intensive care unit; RR, relative risk.

analysis revealed some reduction in the effect sizes, all conclusions remained the same. More specifically, the RR for severity changed from 1.18 to 1.16, for ICU from 1.38 to 1.20 and for death from 1.50 to 1.20. We also redid the meta-analysis by excluding studies with possible overlap in patients, to make sure each patient was only included once. We assumed this to be the case when studies were similar in terms of region, recruitment period and hospital; in a group of studies with a possible overlap, only the largest study was included in the analysis. The results remained almost identical (see table 3). We also performed exhaustive sensitivity analyses consisting of subgroup analyses and meta-regression (see online supplemental appendix 3). The conclusions of our study did not change in subgroups, nor were any factors identified as significant sources of heterogeneity in meta-regression analyses. The main reason for this is the low level between study variance. For sex, however, little heterogeneity was observed. For age, there was some heterogeneity in the magnitude of this effect but not in the direction of the effect.

DISCUSSION

Summary of evidence

In this systematic review we described the association between demographic factors and COVID-19 infection, severity, ICU admission and death. There were not enough data to report on pregnancy, socioeconomic status or ethnicity. Our results showed that men were more often severely affected by COVID-19 than women on all stages of the disease. Men more often had a higher risk for COVID-19 infection. When hospitalised with COVID-19, men more often developed severe COVID-19 disease and more often required intensive care admission, ultimately

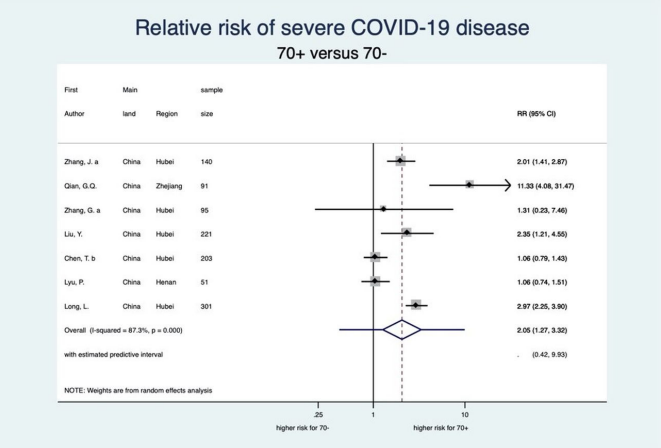

Figure 7 Forest plot showing the association between age and risk of severe COVID-19. Overall, patients aged 70 years or older have a 2.05 times higher risk of severe COVID-19 than patients younger than 70 years. Zhang *et al*;[67] Zhang *et al.*[65] RR, relative risk.

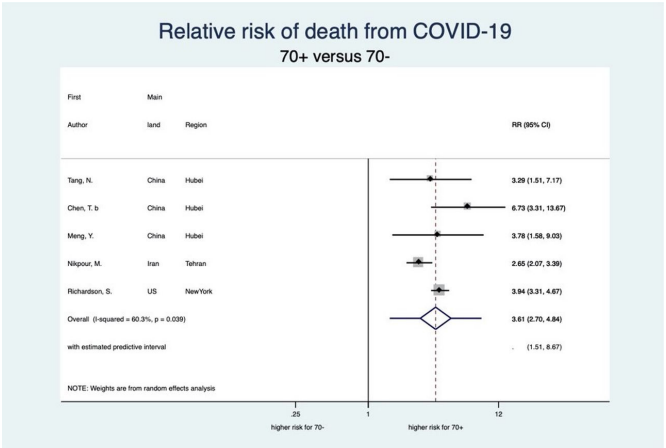

Figure 9 Forest plot showing the association between age and risk of death due to COVID-19. Overall, patients aged 70 years or older have a 3.61 times higher risk of death due to COVID-19 than patients younger than 70 years. RR, relative risk.

Table 3 Exclusion of possible overlaps

		All studies		Excluding possible overlap	
Exposure	Outcome	Studies (n)	Pooled estimate (RR)	Studies (n)	Pooled estimate (RR)
Sex (male vs female)	Infection	8	1.08	**6**	**1.09**
	Severe disease	35	1.18	**28**	**1.20**
	ICU	11	1.38	11	1.38
	Death	14	1.50	**11**	**1.34**
Age (70+ vs 70–)	Infection	4	1.65	4	1.65
	Severe disease	7	2.05	7	2.05
	ICU	5	2.70	5	2.70
	Death	5	3.61	**4**	**3.62**

Studies with possible overlap of patients were excluded from the analysis, results presented in bold. Possible overlap was assumed when studies were from the same region, recruitment period and hospital. In a group of studies with possible overlap only the largest study was included in the analysis. The results remained almost identical.
ICU, intensive care unit; RR, risk ratio.

resulting in death more often. We also found that patients aged 70 years and above affected by COVID-19 were more often observed to have confirmed COVID infection, severe disease, ICU admission and dying compared with patients younger than 70 years.

A living systematic review design was chosen because during the COVID-19 pandemic there is an urgent need for the most up-to-date evidence while maintaining scientific rigour and quality.[74 75] Additionally, studies relevant for these research questions will likely be continuously published in the foreseeable future. Moreover, traditional systematic reviews risk becoming rapidly outdated when new evidence is published almost on a daily basis, and it is not an option to wait until the pandemic is over to publish a systematic review on the full body of evidence.[76 77]

Possible explanations

This study looked at unadjusted risk ratios for the demographic factors age and sex for several COVID outcomes. Although some studies have reported adjusted risk ratios, this indicates a different goal. Adjustment is only relevant when attempting to look at causal effects, in which case the causal effect will be validly estimated after full adjustment for all confounders, while simultaneously avoiding adjustment for colliders and mediating factors. Given that the optimal adjustment factors are not yet known and also differ across various research questions, settings and, most importantly, across time and place, we consider this undesirable. For the purpose of the current study, unadjusted risk ratios were considered most appropriate.

This observation of higher risk of severe disease and higher risk of dying for men compared with women when affected by COVID-19 is in line with the fact that, in general, respiratory tract infectious diseases are more severe in men and subsequently tend to lead to higher mortality in men.[2] Moreover, during the SARS epidemic of 2003, mortality was also higher in men.[3] Thus, this increased severity of respiratory tract disease, including COVID-19, and increased mortality for men may point to an underlying biological mechanism. Aside from anatomical, lifestyle, behavioural, comorbidities and socioeconomic differences between men and women it has been suggested that differences in the immune system between men and women may, at least, partially explain the observed sex differences in the incidence and severity of respiratory tract infections.[2] Indeed, several groups have found sex differences in the immune response, including the innate immune response.[78 79] Regarding COVID-19, there are indications that immune response (inflammation) markers such as interleukin-6 (IL-6) are associated with severity and mortality.[80 81] In a broader perspective, immune response markers, such as IL-6, have also been associated with worse outcome and higher mortality in trauma patients.[82 83] Thus, in addition to differences in health and comorbidities between men and women, differences in the way the immune system responds to the COVID-19 infection may also play a role in the pathogenesis and the outcome of the disease.

Similar to sex differences in immune response, the immune system also changes with age. Ageing is, among others, characterised by a chronic proinflammatory status of the immune system with persistent low-grade innate immune activation that may increase tissue damage caused by infections in the elderly.[84 85] Ageing is also associated with a high prevalence of comorbidities and decreased reserve capacity of vital organs which may lead to increased frailty, and together with an aged immune system this may put elderly individuals at risk of a poor outcome and higher risk of mortality when infected with COVID-19.

Implications for clinicians, policymakers and researchers

Regardless of the underlying mechanism, the observed demographic differences in COVID-19 severity may contribute by informing clinical and policy guidelines in the prioritisation of non-pharmaceutical interventions and screening for COVID-19 in groups at risk of worse outcome. The observation that men and patients aged 70

years and above have a higher risk of severe disease, ICU admission and death when infected with COVID-19 may guide individual clinical decision-making. For instance, men and patients aged 70 and above may be advised to seek out medical consultation at an earlier stage of the disease, and when admission in hospital is required clinicians should be made aware of the higher risk of severe disease and mortality in these groups. For clinical trials and other human studies on COVID-19, in particular those evaluating possible treatments for COVID-19, it is especially important to control for age and sex as they are strong confounders.

Limitations and strengths

We should also consider some limitations. Most included studies, n=50, were still from China involving Chinese patients with COVID-19 compared with n=9 studies from outside China, potentially limiting the generalisability of the findings. Additional studies outside of China are expected and will be included in future updates of this living review. Additionally, the data extraction and quality assessment were performed by one reviewer. In future updates of this review, a second reviewer will (at least partially) reperform the data extraction.

Methodological limitations include the fact that disease severity was in most papers defined according to the clinical stages of COVID-19 issued by China and WHO interim guidance,[7] but this was not always reported. Additionally, in some papers it was unclear whether severity was assessed on hospitalisation or during follow-up. This is additionally complicated by the fact that referral policy to dedicated hospitals in China obscures the severity on initial admission. Therefore, it was not always clear whether an RR or OR was the most appropriate risk measure. RRs were used to obtain conservative estimates.

Due to the observational design of the included studies, there may be confounding by differences in, for example, prehospitalisation health status and comorbidities. However, the observed differences in outcome for sex and age are consistent with other respiratory tract infections and there is a pathophysiological basis (eg, differences in immunity systems and response) that could explain the differences in outcome for sex and age that we observed.

Our review has the following strengths. Our search strategy was thorough and complete: we screened 11.550 individual records. After contacting corresponding authors, we were able to include additional data from 12 studies. The methodological quality as reflected by the NOS score was high and a thorough sensitivity analysis could not refute the conclusions. The possible influence of publication bias on our results was considered to be small: the time the included studies were published spans less than 4 months, almost all studies have a different research question than our questions and we were able to include extra (unpublished) data from 12 authors. This small influence of publication bias is confirmed by the small changes in effect size after the trim-and-fill analyses.

During the study selection phase we came across a number of studies that had to be excluded because of very short follow-up (days). As a consequence, the majority of included study subjects did not report on endpoints like recovery, discharge from hospital or mortality. Furthermore, information on the subjects without an endpoint was missing, so there was a high risk of non-differential misclassification that could lead to bias. For instance, in a particular study 20% had either recovered or diseased while 80% was still admitted in the hospital, and there was no information on the distribution of demographic factors for this 80%. When confronted with these studies we contacted the authors and, in some cases, received information that allowed the study to be included.

CONCLUSION

We systematically reviewed the literature to describe the relation between age and sex and COVID-19 infection, disease severity, ICU admission and death. Meta-analyses on 59 studies comprising 36.470 patients showed that infection, severe disease, ICU admission and death are more likely to occur among men and patients aged 70 and above.

Systematic review registration

PROSPERO 2020: CRD42020180085 and online supplemental appendix 4. Please note that we have prospectively reported when phases of the review started. However, these changes have not yet been made tothe online protocol. This delay in updates on the research protocol is probably due to the highworkload at Prospero.

Author affiliations
[1]Department of Orthopaedics, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Methodology and Statistics, Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands
[3]Department of Educational Research and Development, School of Health Professions Education, Maastricht University, Maastricht, The Netherlands
[4]Department of General Practice, Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands
[5]Amsterdam University Medical Center, location VUmc, Amsterdam, The Netherlands
[6]Maastricht University Library, Maastricht University, Maastricht, The Netherlands
[7]School of Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, The Netherlands
[8]Department of Research and Development, The Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands
[9]De Onderzoekerij, Leiden, The Netherlands
[10]UCB Pharma B.V, Breda, The Netherlands
[11]NUTRIM School of Translational Research in Metabolism, Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands

Contributors MPZ conceived the study. All authors were involved in the study design during weekly meetings. GHLF designed and performed the search strategy. AVJ, RTD and BGP screened the titles and abstracts for eligibility. AR and SZ extracted the data (quantitative data) and AA, SH and JIRD reviewed the study quality (qualitative data). SJ analysed the data. BGP and SJ wrote the first draft. All authors revised this draft for critical content. All authors approved the final manuscript. MPZ, BGP and SJ are the guarantors. All persons listed as authors have contributed to preparing the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs
Bart G Pijls http://orcid.org/0000-0001-5351-5057
Anke Richters http://orcid.org/0000-0002-1580-1543

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Appendix I: Search strategy;

PubMed

("COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR (("Coronavirus"[MeSH Terms] OR "Coronavirus Infections"[Mesh:NoExp] OR pneumonia virus*[tiab] OR cov[tiab]) AND (outbreak[tiab] OR wuhan[tiab] OR novel[all] OR 19[tiab] OR 2019[tiab] OR epidem*[tiab] OR epidemy[all] OR epidemic*[all] OR pandem*[all] OR new[tiab])) OR coronavirus*[tiab] OR corona virus*[tiab] OR ncov[tiab] OR 2019ncov[tiab] OR covid19[tiab] OR "covid 19"[tiab] OR "sars cov 2"[tiab] OR sars2[tiab] OR "ncov 2019"[tiab] OR "sars coronavirus 2"[tiab] OR "sars corona virus 2"[tiab] OR "severe acute respiratory syndrome cov 2"[tiab] OR "severe acute respiratory syndrome cov2"[tiab] OR severe acute respiratory syndrome cov*[tiab] OR cov2[tiab]) AND ("2019/12"[Date - Entrez] : "3000"[Date - Entrez])

Embase Ovid

1 exp Coronavirus/

2 exp Coronavirus Infections/

3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.

4 (or/1-3) and 20190101:20301231.(dc). [this set is the sensitive/broad part of the search]

5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. [line 5 removes noise in the search results]

6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.

7 (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp.

8 (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.

9 (630575119 OR 630830186 OR 630941329 OR 631043694 OR 631260659 OR 631272428 OR 631272880 OR 631286076 OR 631290163 OR 631308782 OR 631324397 OR 631352500 OR 631416440 OR 631431802 OR 631452886 OR 631456079 OR 631457551 OR 631462438 OR 631462876 OR 631465538 OR 631465685 OR 631469310 OR 2004499662 OR 2004505338 OR 2005280837 OR 2005387675 OR 2005408544 OR 2005484987 OR 2005549151).an. [Articles not captured by this search when created in April 2020, pending further indexing by NLM/Elsevier]

10 (or/6-9) and 20191201:20301231.(dc). [Lines 5 to 8 are specific to Covid-19]

11 5 or 10

Males vs females														
	Author	RR	country	region	City	n	publication date	Start	End	recruitment window	FU	study desing	clinical setting	Diagnostic modality
Infection														
	Zhu W	0,95	China	Anhui		116	10-mrt	24-jan	20-feb	27		cohort	Hospital	PCR
	Liu R a	1,1	China	Hubei	Wuhan	4880	7-mrt	22-jan	14-feb	23		cohort	Hospital	PCR
	Ai T	1,05	China	Hubei	Wuhan	1014	26-feb	6-jan	6-feb	31		cohort	Hospital	PCR
	Dong Y	1,03	China	multiple regions		2135	1-apr		8-feb			cohort	General population	PCR
	Chu J	0,86	China	Hubei	Wuhan	54	29-mrt	7-jan	11-feb	35	35	cohort	Hospital	PCR
	Shen N	1,09	China	Hubei	Wuhan	5630	30-apr	22-jan	18-feb	27	27	cohort	Hospital	PCR
	KDC Resp Team	1,95	South Korea			2370					46	cohort	General population	
	Long C	1,11	China	Hubei	Yichang	87	11-mrt	20-jan	8-feb	19		cohort	Hospital	laboratory tests , CT findings
severe														
	Guan W J a	0,99	China	Multiple regions		1096	28-feb	11-dec	29-jan	49	51	cohort	Hospital	PCR
	Gao Y	0,98	China	Anhui	Fuyang	43	13-mrt	23-jan	2-feb	10		cohort	Hospital	PCR
	Li K	1,33	China	Chongquing and Jinan		83	29-feb	1-jan	29-feb	29		cohort	Hospital	PCR
	Wan S	0,94	China	Northeast Chongquing		135	22-apr	23-jan	8-feb	16	16	cohort	Hospital	PCR
	Wu J	1,01	China	Jiangsu, Anhui		280	27-mrt	20-jan	19-feb	30	30	cohort	Hospital	PCR
	Shi Y	2,44	China	Zhejiang		487	18-mrt		17-feb			cohort	Hospital	
	Qin C	1,09	China	Hubei	Wuhan	452	12-mrt	10-jan	12-feb	33		cohort	Hospital	PCR
	Tian S	1,38	China		Beijing	262	27-feb	20-jan	10-feb	21	21	cohort	Hospital	PCR
	Zhang J a	1,28	China	Hubei	Wuhan	140	18-feb	16-jan	3-feb	18		cohort	Hospital	PCR
	Qian GQ	1,82	China	Zhejiang		91	17-mrt	20-jan	11-feb	22	27	cohort	Hospital	PCR
	Zhang G a	1,51	China	Hubei	Wuhan	95	26-mrt	16-jan	25-feb	40	46	cohort	Hospital	PCR

	Wu C	1,43	China	Wuhan		201	13-mrt	25-dec	26-jan	32	50	cohort	Hospital	PCR
	Chen Q	0,96	China	Zhejiang	Taizhou	145	28-apr	1-jan	11-mrt	70	70	cohort	Hospital	PCR
	Liu Y	1,05	China		Shanghai	221	28-mei					cohort	Hospital	PCR
	Chen T b	1,21	China	Hubei	Wuhan	203	7-apr	1-jan	10-feb	40	50	cohort	Hospital	PCR
	Colaneri M	1,86	Italy	North Italy		44	23-apr	21-feb	28-feb	7	12	cohort	Hospital	PCR
	Chu J	1,15	China	Wuhan		54	29-mrt	7-jan	11-feb	35		cohort	Hospital	PCR
	Wang X	1,52	China	Wuhan	Fangcang	1012	27-mrt	7-feb	12-feb	5	15	cohort	Hospital	PCR
	Zhao X Y	0,75	China	Jingzhou		91	29-apr	16-jan	10-feb	25	25	cohort	Hospital	PCR
	Wang L b	1,01	China	hubei	Wuhan	116	31-mrt	14-jan	13-feb	30	30	cohort	Hospital	PCR
	Zhu Z	0,71	China	Zhejiang	Ningbo	127	17-apr	23-jan	20-feb	28	28	cohort	Hospital	PCR
	Zheng F	0,89	China		Changsha	161		17-jan	7-feb	21	21	cohort	Hospital	PCR
	Zhang G b	1,83	China	Hubei		221	5-apr	2-jan	10-feb	39	44	cohort	Hospital	PCR
	Chen G	2,35	China	Hubei	Wuhan	21	27-mrt	20-dec	27-jan	38	38	cohort	Hospital	PCR
	Wang R	1,35	China	Anhui	Fuyang	125	24-mrt	20-jan	8-feb	19	29	cohort	Hospital	PCR
	Zhang J c	1,07	China	Hubei	Wuhan	663	15-apr	11-jan	6-feb	26		cohort	Hospital	PCR
	Chen X	2,38	China	Hubei	Wuhan	48	17-apr	1-feb	19-feb	18	18	cohort	Hospital	PCR
	Zhang R	0,97	China	Hubei	Wuhan	120	1-apr	10-jan	10-feb	31	31	cohort	Hospital	PCR
	Wei J F	1,28	China	Sichuan		103	6-apr	16-jan	10-mrt	54		cohort	Hospital	PCR
	Liu R b	0,99	China	Hubei		119	31-mrt	31-jan	26-feb	26	26	cohort	Hospital	PCR
	Lyu P	0,98	China	Zhengzhou		51	17-apr	15-jan	24-feb	40	40	cohort	Hospital	PCR
	Pei G	1,29	China	Hubei	Wuhan	333	12-apr	28-jan	9-feb	12	26	cohort	Hospital	PCR
	Yu X b	2,02	China	Zheijang		92	23-apr	19-jan	19-mrt	60	56	cohort	Hospital	PCR
	Zheng S	1,28	China	Zhejiang		96	6-apr	19-jan	15-feb	27	27	cohort	Hospital	PCR

	Long L	1,75	China	Hubei	Jingzhou city and Xiangyang city	301	20-apr	16-jan	24-feb	39	45	cohort	Hospital	PCR
ICU														
	Huang C	2,02	China	Hubei	Wuhan	41	24-jan	16-dec	2-jan	17		cohort	Hospital	PCR
	Wang D a	1,32	China		Wuhan	138	7-feb	1-jan	28-jan	27	33	cohort	Hospital	PCR
	Bingwen E F	1,62	Singapore			67	3-mrt	23-jan	28-feb	36		cohort	Hospital	PCR
	Zhang G a	1,41	China	Hubei	Wuhan	95	26-mrt	16-jan	25-feb	40	46	cohort	Hospital	PCR
	Kalligeros M	1,23	US	Rhode Island		103	30-apr	17-feb	5-apr	48	48	cohort	Hospital	PCR
	Wei J F	1,38	China	Sichuan		103	6-apr	16-jan	10-mrt	54		cohort	Hospital	PCR
	Myers L C	1,48	US	California		377	24-apr	1-mrt	31-mrt	30	39	cohort	Hospital	PCR
	Lyu P	0,55	China	Henan	Zhengzhou	51	17-apr	15-jan	24-feb	40	40	cohort	Hospital	PCR
	Rieg S	2,12	Germany		Freiburg	115	28-apr	25-feb	31-mrt	35	35	cohort	Hospital	PCR
	Cao J	1,85	China	Hubei	Wuhan	102	2-mrt	3-jan	1-feb	29	43	cohort	Hospital	PCR
	Long L	2,24	China	Hubei	Jingzhou city and Xiangyang city	301	20-apr	16-jan	24-feb	39	45	cohort	Hospital	PCR
death														
	Tang N	2,78	China	Hubei	Wuhan	183	18-feb	1-jan	3-feb	33	43	cohort	Hospital	PCR
	Tian S	2,13	China		Beijing	262	27-feb	20-jan	10-feb	21	21	cohort	Hospital	PCR
	Wu C	1,1	China	Hubei	Wuhan	201	13-mrt	25-dec	26-jan	32	50	cohort	Hospital	PCR
	Chen T b	4,84	China	Hubei	Wuhan	203	7-apr	1-jan	10-feb	40	50	cohort	Hospital	PCR
	Meng Y	1,56	China	Hubei	Wuhan	168	28-apr	16-jan	4-feb	19	64	cohort	Hospital	PCR
	Nikpouraghdam	1,2	Iran		Teheran	2968	19-apr	19-feb	15-apr	56	73	cohort	Hospital	PCR
	Richardson	1,03	US	New York		5700	22-apr	1-mrt	4-apr	34	34	cohort	Hospital	PCR
	Yan, Y	1,65	China	Hubei	Wuhan	193	6-apr	10-jan	24-feb	45		cohort	Hospital	PCR

	Xu B	1,26	China	Hubei	Wuhan	187	13-apr	26-dec	1-mrt	66	66	cohort	Hospital	PCR
	Zhang J c	1,6	China	Hubei	Wuhan	663	15-apr	11-jan	6-feb	26		cohort	Hospital	PCR
	Du R H	0,77	China	Hubei	Wuhan	179	7-mei	25-dec	7-feb	44		cohort	Hospital	
	Yang R	5,15	China	Hubei	Wuhan	212	24-apr	11-jan	16-mrt	65	65	cohort	Hospital	PCR
	Chen R	2,69	China			1578	15-apr					cohort	Hospital	PCR
	Tomlins J	0,88	UK		Bristol	95	30-apr	10-mrt	20-mrt	10	27	cohort	Hospital	

Males vs females					NOS							
Author	% comorbidities	% males	mean age	% BMI > 25	Case definition	Case representativeness	Control selection	control definition	exposure ascertainment	comparable ascertainment	non response rate	Overal quality
Infection												
Zhu W		56	40	23	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Liu R a		46			Acceptable	Acceptable	Acceptable	Not acceptable	Acceptable	Acceptable	NA	7
Ai T		46	51		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Dong Y		57	7		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Unknown	8
Chu J		67	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	acceptable	9
Shen N		47	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	acceptable	9
KDC Resp Team		45			Not Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	7
Long C		53			Acceptable	Not acceptable	Acceptable	Not acceptable	Acceptable	Acceptable	NA	6
Severe												
Guan W J a	24	58	47		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Gao Y		61	43		Unknown	Acceptable	Acceptable	Acceptable	Unknown	Acceptable	NA	6
Li K	18	53	45		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Wan S	32	53	47		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Wu J		54	43		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Shi Y		53	46		Acceptable	Acceptable	Acceptable	Acceptable	Unknown	unknown	NA	5
Qin C	44	51	58		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	acceptable	9
Tian S		49	48		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zhang J a	64	51	57		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	acceptable	8
Qian GQ		41	50		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zhang G a		56	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9

Wu C	33	64	51		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Chen Q		55	48		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Liu Y		52			Not acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Chen T b	42	53	55		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Colaneri M	64	64	60		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Chu J		67	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	acceptable	9
Wang X	11	52	51		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zhao X Y	23	54	46		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	7
Wang L b	44	58	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	unknown	8
Zhu Z	41	35	51	24	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zheng F	21	50	45		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zhang G b	35	49	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Chen G	33	81	61		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	7
Wang R	27	57	37		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	unknown	9
Zhang J c	37	48	56		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Chen X		77	65		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	7
Zhang R	73	43	61		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Wei J F		54	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Liu R b		52			Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	6
Lyu P	33	56	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	6
Pei G		55	56		Acceptable	Not Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Yu X b		62	55		Not acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	5
Zheng S		60	55		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Long L		50	50		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
ICU												
Huang C	32	73	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Wang D a	46	54	57		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Bingwen E F		55	42		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zhang G a		56	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Kalligeros M		61	60	81,6	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Wei J F		54	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Myers L C		56	61		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	9
Lyu P	33	57	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	6
Rieg S		63	56		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Cao J	46	52	53	24	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Long L		50	50		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9

Death												
Tang N	41	54	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Tian S		49	48		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Wu C	33	64	51		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Chen T b	42	53	55		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Meng Y	34	51	57		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Nikpouraghdam	11	66	56		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Richardson	94	60	63		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Yan, Y	49	59	63		Acceptable	not acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Xu B		55	61		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zhang J c	37	48	56		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Du R H		54	58		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Yang R	42	51	55		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	7
Chen R		57			Acceptable	not acceptable	Acceptable	Not Acceptable	Acceptable	Acceptable	na	7
Tomlins J		63	73		Acceptable	Acceptable	Acceptable	Not Acceptable	Acceptable	Acceptable	NA	8

70 and above versus less than 70														
	Author	RR	country	region	city	n	publication date	Start	End	recruitment window	FU	study desing	clinical setting	Diagnostic modality
Infection														
	Zhu W	1,1	China	Anhui		116	10-mrt	24-jan	20-feb	27		cohort	Hospital	PCR
	Liu R a	1,75	China	Hubei	Wuhan	4880	7-mrt	22-jan	14-feb	23		cohort	Hospital	PCR
	Shen N	1,56	China	Hubei	Wuhan	5630	30-apr	22-jan	18-feb		27	cohort	Hospital	PCR
	KDC Resp Team	1,36	South Korea			2370					46	cohort	General population	
severe														
	Zhang J a	2,01	China	Hubei	Wuhan	140	18-feb	16-jan	3-feb	18		cohort	Hospital	PCR
	Qian GQ	11,33	China	Zhejiang		91	17-mrt	20-jan	11-feb	22	27	cohort	Hospital	PCR
	Zhang G a	1,31	China	Hubei	Wuhan	95	26-mrt	16-jan	25-feb	40	46	cohort	Hospital	PCR
	Liu Y	2,35	China		Shanghai	221	28-mei					cohort	Hospital	PCR
	Chen T b	1,06	China	Hubei	Wuhan	203	7-apr	1-jan	10-feb	40	50	cohort	Hospital	PCR
	Lyu P	1,06	China	Henan	Zhengzhou	51	17-apr	15-jan	24-feb	40	40	cohort	Hospital	PCR
	Long L	2,97	China	Hubei	Jingzhou city and Xiangyang city	301	20-apr	16-jan	24-feb	39	45	cohort	Hospital	PCR
ICU														
	Wang D a	2,11	China		Wuhan	138	7-feb	1-jan	28-jan	27	33	cohort	Hospital	PCR
	Zhang G a	1,87	China	Hubei	Wuhan	95	26-mrt	16-jan	25-feb	40	46	cohort	Hospital	PCR
	Wei J F	4,37	China	Sichuan		103	6-apr	16-jan	10-mrt	54		cohort	Hospital	PCR

	Lyu P	1,3	China	Henan	Zhengzhou	51	17-apr	15-jan	24-feb	40	40	cohort	Hospital	PCR
	Long L	4,61	China	Hubei	Jingzhou city and Xiangyang city	301	20-apr	16-jan	24-feb	39	45	cohort	Hospital	PCR
death														
	Tang N	3,29	China	Hubei	Wuhan	183	18-feb	1-jan	3-feb	33	43	cohort	Hospital	PCR
	Chen T b	6,73	China	Hubei	Wuhan	203	7-apr	1-jan	10-feb	40	50	cohort	Hospital	PCR
	Meng Y	3,78	China	Hubei	Wuhan	168	28-apr	16-jan	4-feb	19	64	cohort	Hospital	PCR
	Nikpouraghdam M	3,94	Iran		Teheran	2968	19-apr	19-feb	15-apr	56	73	cohort	Hospital	PCR
	Richardson S	3,38	US	New York		5700	22-apr	1-mrt	4-apr	34	34	cohort	Hospital	PCR

70 and above versus less than 70					NOS							
Author	% comorbidities	% males	mean age	% BMI > 25	Case definition	Case representativeness	Control selection	control definition	exposure ascertainment	comparable ascertainment	non response rate	overal quality
Infection												
Zhu W		56	40	23	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Liu R a		46			Acceptable	Acceptable	Acceptable	Not acceptable	Acceptable	Acceptable	NA	7
Shen N		47	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	acceptable	9
KDC Resp Team		45			Not Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	7
severe												
Zhang J a	64	51	57		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	acceptable	8
Qian GQ		41	50		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zhang G a		56	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Liu Y		52			Not acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Chen T b	42	53	55		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Lyu P	33	57	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	6
Long L		50	50		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
ICU												

Wang D a	46	54	57		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Zhang G a		56	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Wei J F		54	49		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Lyu P	33	57	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	6
Long L		50	50		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Death												
Tang N	41	54	54		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Chen T b	42	53	55		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Meng Y	34	51	57		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Nikpouraghdam M	11	66	56		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Richardson S	94	60	63		Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	NA	9

Appendix III: Sensitivity analysis

In order to investigate potential sources of observed heterogeneity in primary outcomes, we performed several subgroup and meta-regression analyses provided enough information was available.

For sex outcome severe disease, the first subgroup analysis included studies with quality scores 7 or above. This allows having only high-quality studies in the meta-analysis. Although the I^2 statistics dropped to below 1% (form 15.2%), the effect size remained unaffected (RR 1.15, 95%CI 1.09 to 1.22), see Figure A1. As an additional analysis, we partitioned studies based on whether critical condition of severity was upon hospitalization or developed during follow-up. The former showed a slight increase (RR 1.27, 95%CI 1.12 to 1.44 – Figure A2) while the latter a slight decrease (RR 1.11, 95%CI 1.04 to 1.19 – Figure A3). However, both were fairly close to that of base analysis (RR 1.18, 95%CI 1.10 to 1.27). Finally, we performed meta-regression on study size, total quality score, study duration and study start date, but none were significant.

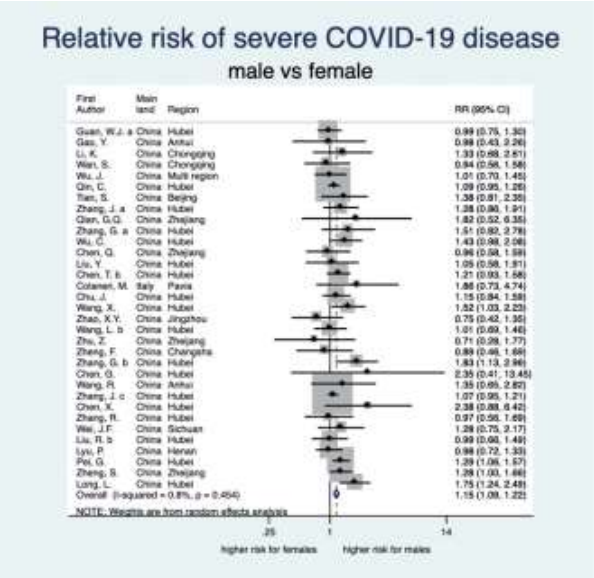

Figure A1

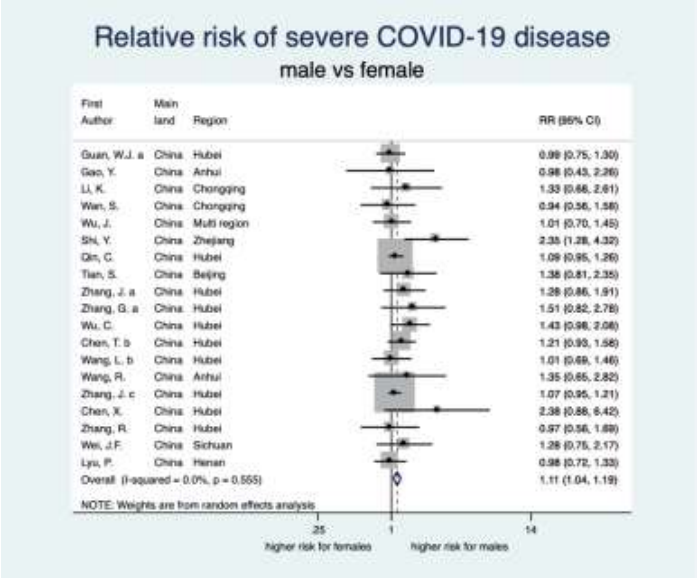

Figure A2

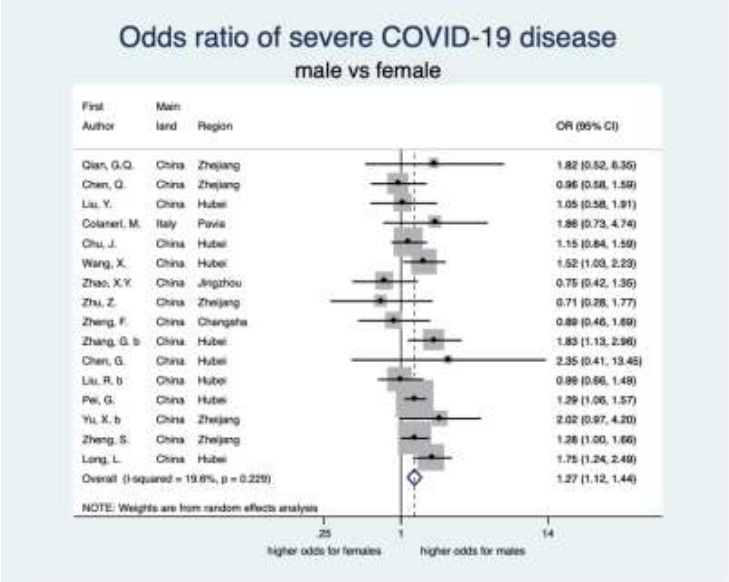

Figure A3

For sex outcome ICU admission, we conducted a subgroup analysis based on geographical location (Asia versus outside Asia), but the overall conclusion remained the same (RR 1.33, 95%CI 0.93 to 1.91 and RR 1.47, 95%CI 1.14 to 1.90 for Asia and outside Asia, respectively), see Figure A4. There was also no evidence for the effect of study size, total quality score, study duration and study start date from meta-regression.

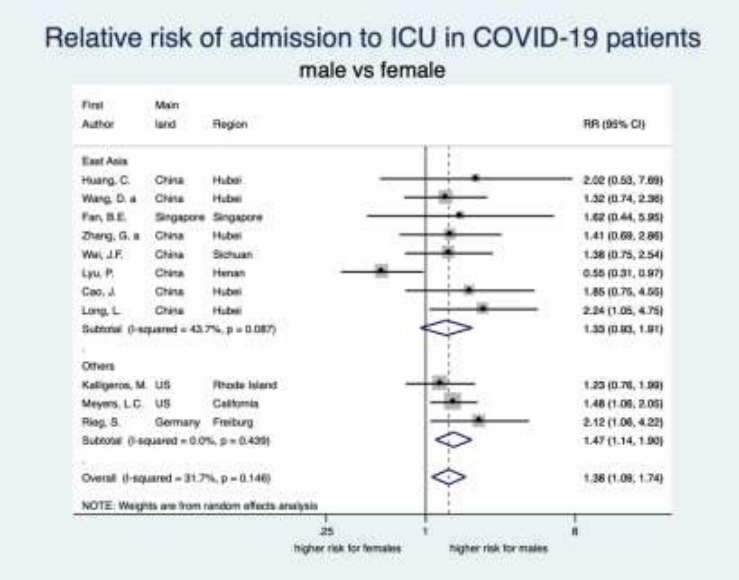

Figure A4

For sex outcome death, we also conducted a subgroup analysis based on geographical location (east Asia versus outside east Asia). In the group of east Asia, the effect size was substantially increased (RR 1.8, 95%CI: 1.32 to 2.46), while it largely dropped to RR 1.06, 95%CI: 0.93 to 1.22 in the group of outside east Asia, which consists of only 3 studies (see, Figure A5). The results from meta-regression on study start date revealed that this factor can explain about 40% of heterogeneity, see Table 1.

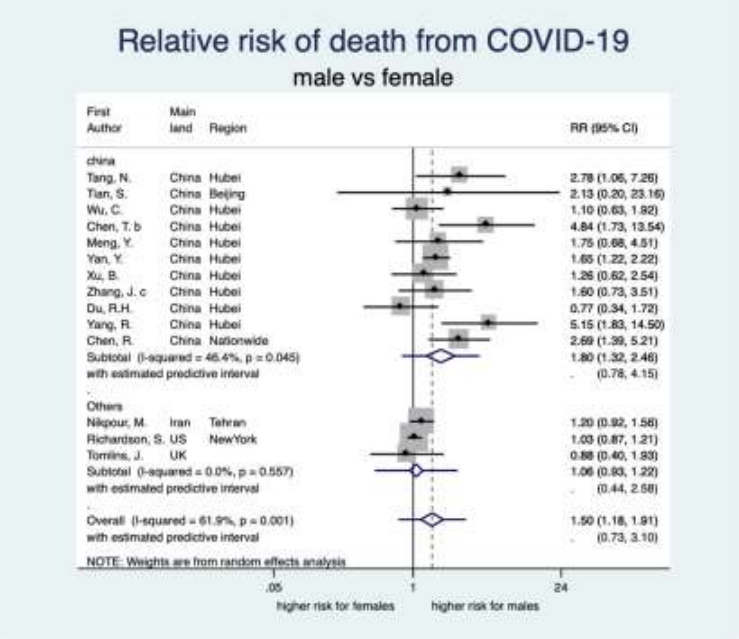

Figure A5

Table 1

```
. metareg logES startdate, wsse(_selogES) eform tau

Meta-regression                                 Number of obs  =      13
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =  40.99%
Proportion of between-study variance explained  Adj R-squared  = 100.00%
With Knapp-Hartung modification
------------------------------------------------------------------------------
       logES |     exp(b)   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   startdate |   .9927859   .0029568    -2.43   0.033     .9862992    .9993152
       _cons |   1.33e+69   8.67e+70     2.43   0.033      4133904    4.3e+131
------------------------------------------------------------------------------
Test for residual between-study variance (of tau2=0)  Q_res (11 df)  =   18.64
                                                      Prob > Q_res   =  0.0679
Likelihood-ratio test of tau2=0: chibar2(01) =  0.00  Prob > chibar2 =  1.0000

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For age outcomes severe disease, ICU admission, and death, insufficient number of studies were available preventing obtaining meaningful results from sensitivity analysis.

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PROSPERO
International prospective register of systematic reviews

Demographic factors and COVID-19: a rapid and living systematic review and meta-analysis

Anique Atherley, Raissa Derckx, Janna Dijkstra, Gregor Franssen, Stevie Hendriks, Shahab Jolani, Bart Pijls, Anke Richters, Annemarie Venemans, Saurabh Zalpuri, Maurice Zeegers

Citation

Anique Atherley, Raissa Derckx, Janna Dijkstra, Gregor Franssen, Stevie Hendriks, Shahab Jolani, Bart Pijls, Anke Richters, Annemarie Venemans, Saurabh Zalpuri, Maurice Zeegers. Demographic factors and COVID-19: a rapid and living systematic review and meta-analysis. PROSPERO 2020 CRD42020180085 Available from:
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020180085

Review question

What is the association between demographic factors* and COVID-19 in:
1) patients diagnosed with COVID-19 compared to patients not diagnosed with COVID-19?
2) COVID-19 patients admitted to hospital compared to COVID-19 patients not admitted to hospital?
3) Patients with severe COVID-19 (clinical / radiological) compared to patients with non-severe COVID-19?
4) COVID-19 patients admitted to ICU compared to COVID-19 patients not admitted to ICU?
5) COVID-19 patients who died compared to COVID-19 patients who survived?
*demographic factors include: age, sex, social economic status (education level), pregnancy and ethnicity.
Rationale for the rapid and living systematic review design: in the midst of a pandemic there is an urgent need for the most up-to-date evidence while maintaining scientific rigor and quality. Additionally, studies relevant for these research questions will likely be continuously published in the foreseeable future. Moreover, traditional systematic reviews risk becoming rapidly outdated when new evidence is published almost on a daily basis and it is not an option to wait untill the pandemic is over to publish a systematic review on the full body of evidence. Hence a rapid systematic review that is continuously updated (aka living) is necessary.

Searches

The search strategy will be devised with an information specialist and the following databases will be searched from 2019-12 onwards: PubMed, EMBASE and Web of Science. Additionally, EPPI Centre (COVID-19: a living systematic map of the evidence) will be consulted.
We will also search preprint repositories medRxiv and bioRxiv from 2019-12 onwards.
No language restrictions will be applied during the search strategy. Studies reported in languages spoken by the research team will be included. These are at least English, Dutch, German, French and Russian. Studies published in any other language will be excluded and listed seperately in the appendix.

Types of study to be included

Studies that provide information on the 5 research questions mentioned above.
Inclusion criteria:
1) Human study on COVID-19 or SARS-CoV-2 coronavirus
2) Comparison of patients diagnosed with COVID-19 with patients not diagnosed with COVID-19 regarding age, sex, social economic status, pregnancy or ethnicity
3) Comparison of COVID-19 patients admitted to hospital to COVID-19 patients not admitted to hospital regarding age, sex, social economic status, pregnancy or ethnicity
4) Comparison of patients with severe COVID-19 (clinically / radiologically) to patients with non-severe COVID-19 regarding age, sex, social economic status, pregnancy or ethnicity
5) Comparison of COVID-19 patients admitted to ICU to COVID-19 patients not admitted to ICU regarding age, sex, social economic status, pregnancy or ethnicity
6) Comparison of COVID-19 patients who died to COVID-19 patients whu survived, regarding age, sex, social economic status, pregnancy or ethnicity

Exclusion criteria:
1) No reporting/evaluation of demographic factors (age, sex, social economic status, pregnancy or ethnicity)
2) No comparison of diagnosis-positive versus diagnosis-negative, admitted to hospital versus not admitted to hospital, severe COVID-19 versus not severe COVID-19, admitted to ICU versus not admitted to ICU, deaths versus alive

Condition or domain being studied
COVID-19 or the disease caused by SARS-CoV-2 coronavirus.

Participants/population
Patients or individuals subjected to diagnosis of COVID-19.

Intervention(s), exposure(s)
The exposure is COVID-19 or the disease caused by the SARS-CoV-2 coronavirus. As cases we consider:
1) patients diagnosed with COVID-19
2) COVID-19 patients admitted to hospital
3) COVID-19 patients with severe COVID-19 (clinically / radiologically)
4) COVID-19 patients admitted to the ICU
5) COVID-19 patients who died
demographic factors for the analysis include age, sex, social economic status (education level), pregnancy and ethnicity.

Comparator(s)/control
As the controls we consider:
1) patients not diagnosed with COVID-19
2) COVID-19 patients not admitted to hospital
3) COVID-19 patients with non-severe COVID-19 (clinically / radiologically)
4) COVID-19 patients not admitted to ICU
5 COVID-19 patients who survived

Main outcome(s)
1) COVID-19 diagnosis
2) hospital admittance due to COVID-19
3) severity of COVID-19 (clinically / radiologically)
4) ICU admittance due to COVID-19
5) mortality as a result of COVID-19

* Measures of effect

These outcomes are expressed as the number of patients or individuals for each outcome or the ratio of the probabilities of the 5 outcomes between the exposed and unexposed groups regarding demographic factors, mentioned above, expressed as Relative Risk, Odds Ratio, Hazard Ratio or Risk Difference.

Additional outcome(s)
None.

* Measures of effect

Not applicable.

Data extraction (selection and coding)
For this rapid and living systematic review design we consider two phases which may alternate periodically when new evidence becomes available: rapid phase and quality assurance phase.
During the rapid phase emphasis is put on timely availability of up-to-date analyses, so one reviewer (from a pool of reviewers) will perform study selection and data extraction. During the quality assurance phase, a

second reviewer (from a pool of reviewers) will re-do the full study selection procedure. Both reviewers will record their findings in an electronic database. Any disagreements will be resolved by either consensus or by consulting a referee.
During the rapid phase one reviewer (from a pool of reviewers) will extract data from included studies regarding the outcomes, patient demographics, and study characteristics. During the quality assurance phase, a second reviewer (from a pool of reviewers) will re-do the data extraction for at least 20 studies (randomly selected). Both reviewers will record their findings in an electronic database. Any disagreements will be resolved by either consensus or by consulting a referee. In case the data extraction from the second reviewer leads to more than 10% change in the results from the meta-analysis, the second reviewer will re-do the whole data extraction.

Risk of bias (quality) assessment

The risk of bias of the included studies will be appraised by one reviewer (from a pool of reviewers) during the rapid phase using the Newcastle Ottawa Scale (NOS) http:/www.ohri.ca/programs/clinical_epidemiology/oxford.asp. During the quality assurance phase, a second reviewer (from a pool of reviewers) will re-do the risk of bias assessment for at least 20 studies (randomly selected). Both reviewers will record their findings in an electronic database. Any disagreements will be resolved by either consensus or by consulting a referee. In case the risk of bias assessment from the second reviewer leads to a different quality score in more than 10% of the studies, the second reviewer will re-do the whole risk of bias assessment.

Strategy for data synthesis

The data from the included studies will be pooled in a meta-analysis with the random effects model according to DerSimonian and Laird to determine the pooled effect sizes with corresponding 95% confidence intervals and (in case of heterogeneity) corresponding 95% prediction intervals. The amount of statistical heterogeneity will be assessed through visual inspection of the Forest plots and by calculating the $?^2$ statistics and I^2 statistics. In case of statistical heterogeneity and if data allow, potential sources of statistical heterogeneity will be explored through subgroup analyses (e.g. geographical region/countries and items from NOS) and with random effects meta-regression (e.g. study size, inclusion period or publication data).
To assess for publication bias we will construct a funnel plot. In case of asymmetry in the funnel plot, a trim-and-fill method and cumulative meta-analyses will be used to explore the magnitude and direction of publication bias.

Analysis of subgroups or subsets

See also strategy for data synthesis. Subgroup analyses will be performed, if data permit, on pre-defined factors:
* geographical region/country\
* items from NOS (separately, not total score)
* study size
* start inclusion period
* publication date
* diagnostic modality (e.g. PCR test, CT signs, clinical symptoms and their combinations that led to the diagnosis of COVID-19)
* clinical setting (e.g. nursing home, home, hospital, GP cohort)
If considered appropriate sensitivity analyses will explore the effect of other non pre-defined items/factors. These will be labellled as "non pre-defined" in the results.

Contact details for further information

Dr. Bart G Pijls
b.g.c.w.pijls@lumc.nl

Organisational affiliation of the review

Maastricht University, the Netherlands

Review team members and their organisational affiliations

Dr Anique Atherley. School of Health Professions Education, Dept of Educational Research and

Development, Maastricht University
Ms Raissa Derckx. Care and Public Health Research Institute (CAPHRI), Dept of General Practice, Maastricht University
Ms Janna Dijkstra. Amsterdam University Medical Centers, location VUmc
Mr Gregor Franssen. Maastricht University Library
Ms Stevie Hendriks. School of Mental Health and Neuroscience (MNeNS), Maastricht University
Dr Shahab Jolani. Maastricht University, Dept of Methodology and Statistics
Dr Bart Pijls. Leiden University Medical Center, Dept of Orthopaedics
Dr Anke Richters. The Netherlands Comprehensive Cancer Organisation, Dept of Research and Development
Dr Annemarie Venemans. De Onderzoekerij
Dr Saurabh Zalpuri. Real World Evidence, UCB Pharmaceutical BV
Dr Maurice Zeegers. Care and Public Health Research Institute (CAPHRI), Maastricht University

Type and method of review
Epidemiologic, Meta-analysis, Systematic review

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13 April 2020

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Conflicts of interest

Language
English

Country
Netherlands

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
COVID-19; Demography; Humans; severe acute respiratory syndrome coronavirus 2

Date of registration in PROSPERO
20 April 2020

Date of first submission
16 April 2020

Stage of review at time of this submission

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

20 April 2020