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

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Demographic risk factors for COVID-19 infection, severity, ICU admission and death:

A meta-analysis of 59 studies.

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Abstract

Objective: We aimed to investigate the effect of age and sex on the risk of COVID-19 in different severity stages ranging from infection to death.

Methods: We searched Pubmed and Embase from December 2019 through May 4 2020 for studies that evaluated differences in age and sex on the risk of COVID-19 infection, disease severity, ICU admission and death. 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 (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 to 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.

Systematic review registration: PROSPERO 2020: CRD42020180085

Strengths and limitations of this study

- In SARS and other respiratory tract infections demographics such as sex and age have been identified as important risk factors for disease severity. However, a systematic review on the association between demographic factors and different severity stages of COVID-19 is lacking.
- This meta-analysis of 59 studies suggests that men are at an eight percent higher risk for infection with COVID-19 than women and when infected, they also had twenty to fifty percent higher risks for disease severity, ICU admission and death than women.
- Our study further suggests that patients aged 70 years and above had a 65% higher risk for infection with COVID-19 than patients younger than 70 years and when infected, they also had much higher risks for disease severity, ICU admission and death
- Now, that these associations have been quantified, they can serve as a reliable evidence-base for clinical and policy decision-making
- The main limitation of the current systematic review is that most included studies, n = 50, were still from China involving Chinese COVID-19 patients compared to n =9 studies from outside China, potentially limiting the generalizability of the findings.

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 at 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 COVID-19 patients and SARS patients, Jin et al, found that increased age and sex were associated with more severe disease and mortality.[4] 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, ICU admission and death may provide insight into the underlying pathophysiological mechanisms (immunity, coagulopathy and co-morbidities). This knowledge may also guide clinical decision making, especially when there is an impending shortage in health care resources such as ICU beds. Additionally, exploring demographic factors influencing COVID-19 outcomes may guide policy makers 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 be potentially be strong confounders. Therefore, the aim of this living systematic review is to determine 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 PRISMA statement and a protocol has been registered a priori at the Prospero registry (PROSPERO 2020: CRD42020180085)[6]

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 categorized into old age, defined as 70 years and older, and young age, defined as younger than 70 years. 70 years was chosen as a cut-off point for the main analyses, because this was the most commonly used cut-of in the first studies included. We also collected data on other cut-of points (60 years and 65 years) where possible. We considered 4 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) severe clinically/radiologically COVID-19 among hospitalized patients with a confirmed infection?

3) ICU admission among patients hospitalized for confirmed COVID-19 infection?

4) death among patients hospitalized 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 (GF) and the following databases were searched from December 2019 up to an including May 4 2020: Medline via PubMed and EMBASE. Additionally, EPPI Centre (COVID-19: a living systematic map of the evidence) was consulted up to March 31 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 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 (RD, AV or BP). A second reviewer (RD) re-did 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 2 reviewers (from: AR, SZ, AA, JD, 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 pre-specified 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 (e.g. kidney transplant patients, patients with fractured bones).

Data extraction and Quality Assessment

One reviewer (AR or SZ) extracted data from included studies regarding the severity stages of COVID-19, patient demographics and study characteristics in a pre-defined electronic data sheet that was designed during a pilot data extraction phase on the first eligible studies. A second reviewer (AA, JD or SH) double-checked the inclusion by the data extractors. Any disagreements were resolved by consensus or by consulting a referee (BP or MZ). We contacted authors of papers with data presented in a way that did not allow summarization in contingency tables by e-mail. We sent a reminder e-mail after one 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, JD 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 (i.e. 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% confidence intervals 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 pre-defined factors. These factors include: geographical region, study quality, study size, days into the pandemic, publication date, diagnostic modality (e.g. PCR test, CT signs, clinical symptoms and their combinations that led to the diagnosis of COVID-19) and clinical setting (e.g. nursing home, home, hospital, GP cohort). We carried out leave-one-out analyses to determine the influence of possible outlier studies on the pooled effect size.

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 was used to explore the magnitude and direction of publication bias.

Patient and public involvement statement

This systematic review and meta-analysis is part of the WHO Evidence Collaborative on COVID-19 answering on of 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 (PRIMSA flow chart).

Study characteristics

We included studies on the effect of age (70 years or more versus less than 70 years) and sex (men versus 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, three from the United States, one from Germany, one from Iran, one from Italy, one from Singapore, one from South-Korea and one from the United Kingdom. The included studies were published between 2nd January 2020 and 15th April 2020. The mean age of the patients in the included studies ranged between 7 and 73 years. The percentage of males in the included papers ranged from 35% to 81%. For details of individual studies, organized by exposure and outcome, see Appendix II.

Risk of bias

The methodological quality of the included papers was high with an average of 8.2 out of nine, as measured with the Newcastle Ottawa Scale (NOS). Case definition and case representativeness was acceptable in 55 out of 59 and 55 out of 59 studies respectively. Control selection and control definition was acceptable in 59 out of 59 and 55 out of 59 studies respectively. Exposure ascertainment and comparable ascertainment was 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, organized by exposure and outcome, is available in Appendix II.

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 from random effect 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 then women (RR: 1.08 (95%CI: 1.03 – 1.12), see Figure 2. When diagnosed, men also experienced more severe disease than women (RR = 1.18, 95%CI: 1.10 – 1.27) implying that the risk of severe disease of COVID-19 for men is 18% higher than that for women, see Figure 3. Moreover, the rate of admission to ICU in COVID-19 patients was higher among men as compared to women. The aggregated random effect was 1.38 with a 95%CI: 1.09 – 1.74, see Figure 4. Finally, we observed that men were at higher risk of death

from COVID-19 as compared to women (RR = 1.50, 95%CI: 1.18– 1.91, 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. 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, RR 2.70 95%CI 1.59 to 4.60 and RR 3.61 95%CI 2.70 to 4.84, 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 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 re-did 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 Appendix III. 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 evaluated the association between demographic factors and COVID-19 infection, severity, ICU admission and death. There was not enough data to report on pregnancy, SES or ethnicity. Our results showed that men are more severely affected by COVID-19 than women on all stages of the disease. Men appear to have a higher risk for COVID-19 infection. When infected, they appear to have a higher risk for severe COVID-19 disease and need for Intensive Care, ultimately leading to a higher risk of dying. We also found that patients affected by COVID-19 aged 70 years and above appear to have a higher risk of infection, severe disease, ICU admission and dying compared to 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 rigor 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 observation of higher risk of severe disease and higher risk of dying for men compared to 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 Severe Acute Respiratory Syndrome (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 points to an underlying biological mechanism. Aside from anatomic, 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. Aging, is among others, characterized by a chronic pro-inflammatory 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] Aging is also associated with a high prevalence of comorbidities and decreased reserve capacity of vital organs which may lead to increase 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 COVID-19 patients compared to n =9 studies from outside China, potentially limiting the generalizability 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) re-perform the data extraction.

Methodological limitations include the fact 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 upon hospitalization or during follow-up. This is additionally complicated by the fact that referral policy to dedicated hospitals in China obscures the severity upon 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 e.g. pre-hospitalization health status and co-morbidities. However, the observed differences in outcome for sex and age are consistent with other respiratory tract infections and there is a

pathophysiological basis (e.g. 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 determine the relation between age and sex as risk factors for COVID-19 infection, disease severity, ICU admission and death. Meta-analyses on 59 studies comprising 36.470 patients showed that men and patients aged 70 and above have a higher risk for infection, severe disease, ICU admission and death.

License statement

Conflicts of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author). All authors declare that they have no conflicts of interest.

Transparency declaration

The manuscript's guarantors (BP, SJ and MZ) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

Ethics committee approval

For this systematic review and meta-analysis approval by the ethics committee was not required.

Role of the funding source

There was no external funding for this work. All authors are volunteers on a research call from the Dutch epidemiological society and this study is part of the WHO Evidence Collaborative on COVID-19 answering on of their rapid review priority questions on risk factors for infection and disease severity

Hence, no sponsor took part in the design or conduct of the study; nor in the collection, management, analysis, or interpretation of the data; nor in the preparation, review, or the approval of 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.

Systematic review registration:

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

Data sharing statement

The study protocol is available online at the Prospero website: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=180085 . All relevant data are in the manuscript or online supplementary.

Dissemination declaration

This review will be disseminated via WHO, direct communication with national centres for disease control, international library organisation and via google search engine optimisation provided by Maastricht University

Authors' contributions

MZ conceived the study. All authors were involved in the study design during weekly meetings. GF designed and performed the search strategy. AV, RD and BP screened titles and abstracts for eligibility. AR and SZ extracted the data (quantitative data) and AA, SH and JD reviewed the study quality (qualitative data). SJ analysed the data. BP and SJ wrote the first draft. All authors revised this draft for critical content. All authors approve the final manuscript. MZ, BP and SJ are the guarantors. All persons listed as authors have contributed to preparing the manuscript and the International Committee of Medical Journal Editors criteria for authorship have been met. There are no person or persons other than the authors listed that have contributed significantly to the preparation of 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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Figures Legends

Figure 1: Prisma flow chart showing study selection

Figure 2: Forrest plot showing 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, R a = ref 32.

Figure 3: Forrest plot showing 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, J a = ref 67; Zhang, G a = ref 65; Zhang G, b = ref 64; Zhang, J b = ref 66; Liu, r b = ref 33.

Figure 4: Forrest plot showing 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, G a = ref 65.

Figure 5: Forrest plot showing 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.

Figure 6: Forrest plot showing association between age and risk of COVID-19 infection. Overall, patients 70 years or older have a 1.65 times higher risk of COVID-19 infection than patients younger than 70 years. Liu, R a = ref 32.

Figure 7: Forrest plot showing association between age and risk of severe COVID-19. Overall, patients 70 years or older have a 2.05 times higher risk of severe COVID-19 than patients younger than 70 years. Zhang, J a = ref 67; Zhang, G a = ref 65.

Figure 8: Forrest plot showing association between age and risk of ICU admission due to COVID-19. Overall, patients 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, G a = ref 65.

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

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

Table 2: summary of data synthesis

Exposure	Outcome	Number of studies	Number of patients	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	7.832	1.18	1.10 to 1.27	NA	15%
	ICU	11	1.493	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	1.102	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	9.222	3.61	2.70to 4.84	1.51 to 8.67	60%

RR = risk ratio

NA = not applicable

95%CI = 95% confidence interval

95%PI = 95% prediction interval

Table 3: Exclusion of possible overlaps

		All studies		Excluding possible overlap	
Exposure	Outcome	Number of studies	Pooled estimate (RR)	Number of studies	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.

RR = risk ratio

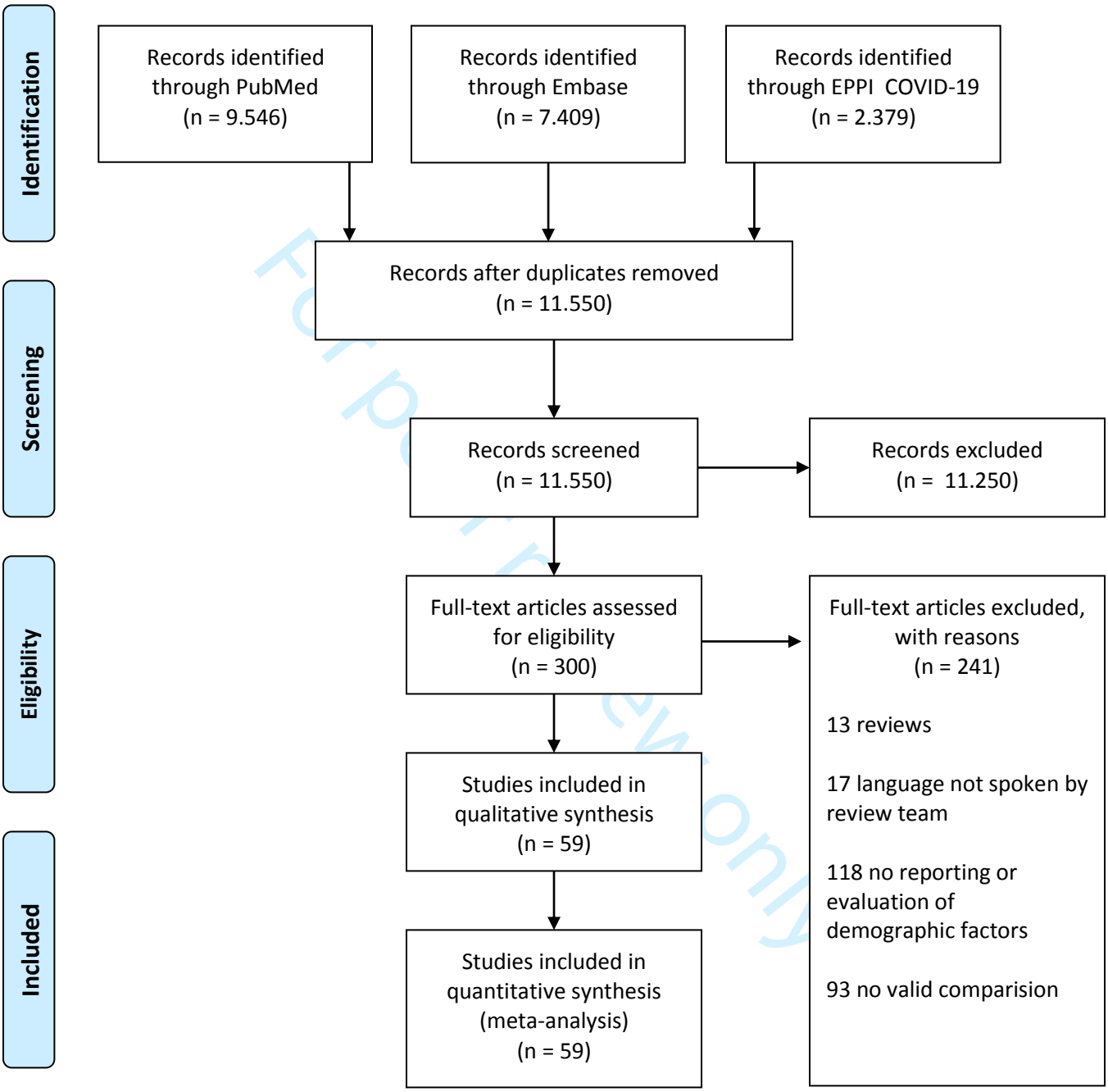
Appendix list:

Appendix I: search strategy

Appendix II: individual study characteristics (both data and quality)

Appendix III: sensitivity analyses

Appendix IV: Prospero Protocol



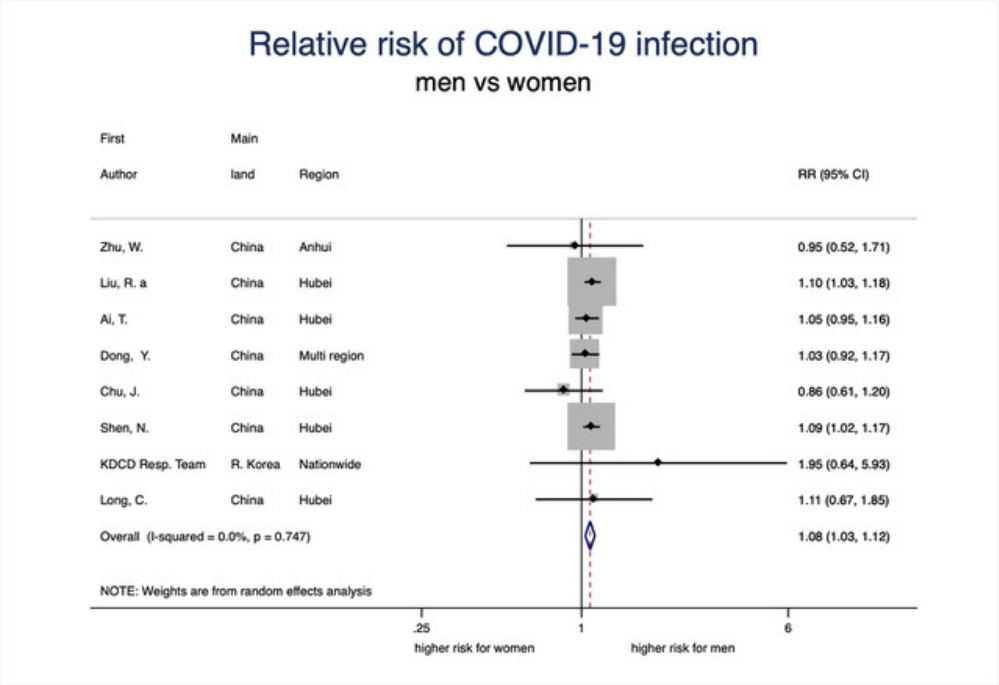


Figure 2: Forrest plot showing association between sex and risk of COVID-19 infection. Overall, men have a 1.08 times higher risk of COVID-19 infection than women. Liu, R a = ref 32.

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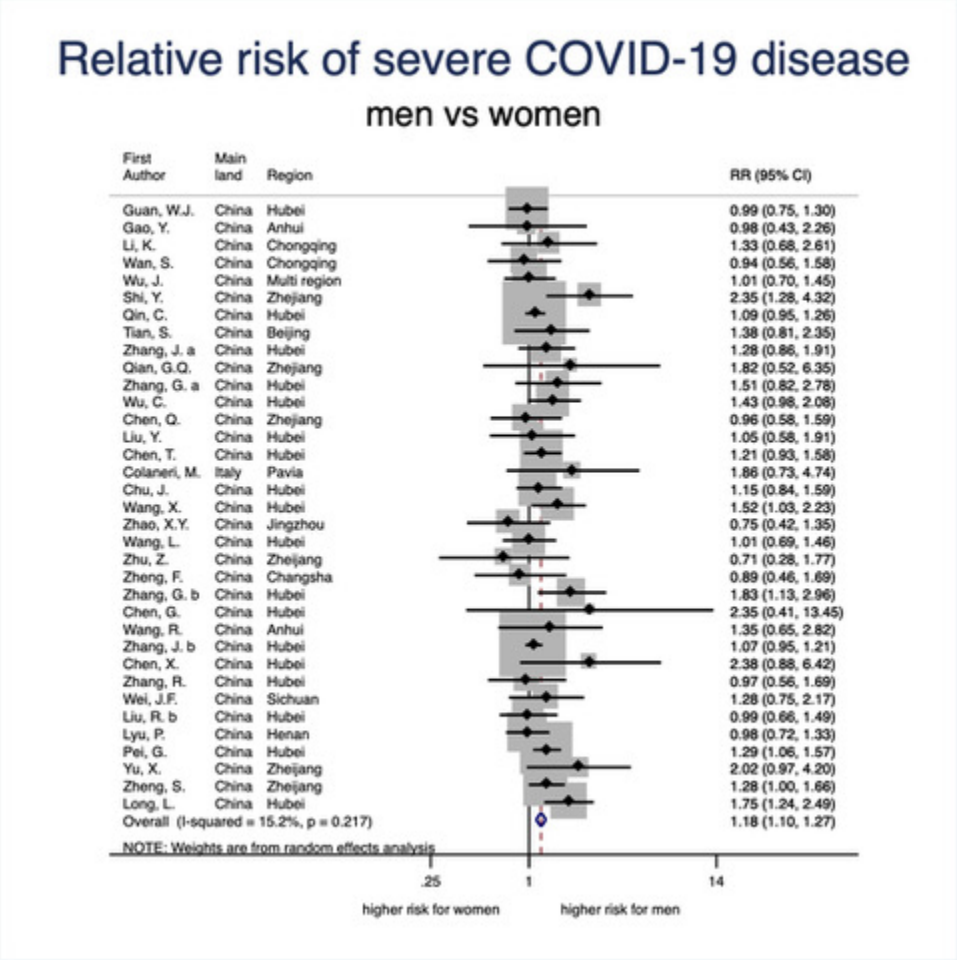

Figure 3: Forrest plot showing association between sex and risk of severe COVID-19. Overall, men have a 1.18 times higher risk of severe COVID-19 than women. Zhang, J a = ref 67; Zhang, G a = ref 65; Zhang G, b = ref 64; Zhang, J b = ref 66; Liu, r b = ref 33.

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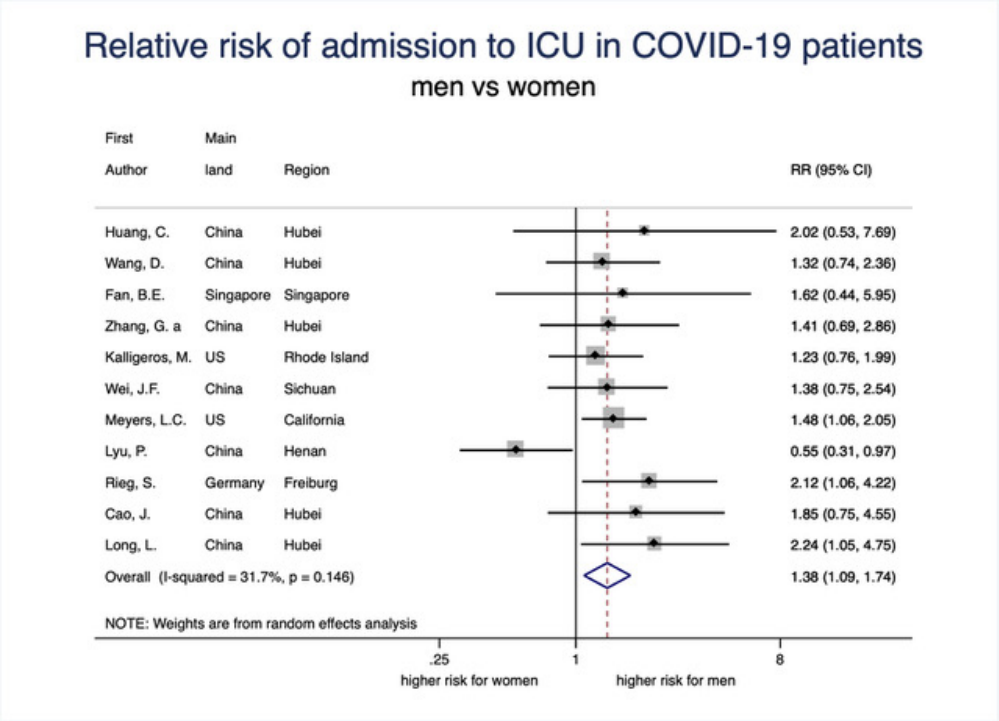

Figure 4: Forrest plot showing association between sex and risk of ICU admission due to COVID-19. Overall, men have a 1.38 times higher risk of ICU admission due to COVID-19 than women. Zhang, G a = ref 65.

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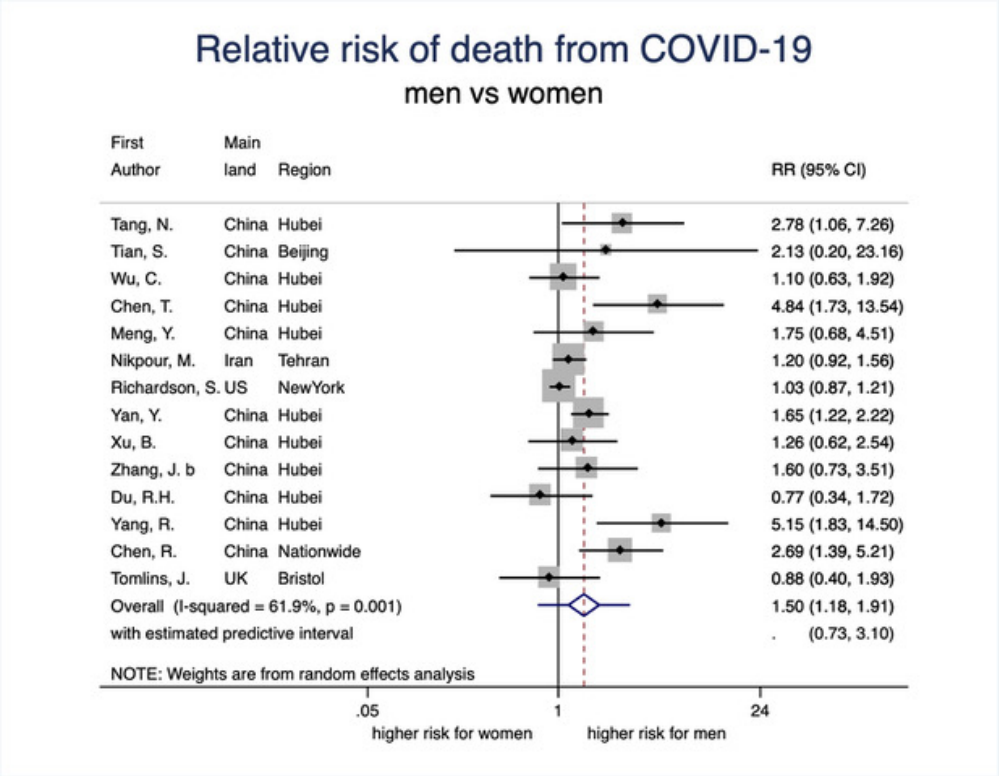

Figure 5: Forrest plot showing association between sex and risk of death due to COVID-19. Overall, men have a 1.50 times higher risk of death due to COVID-19 than women.

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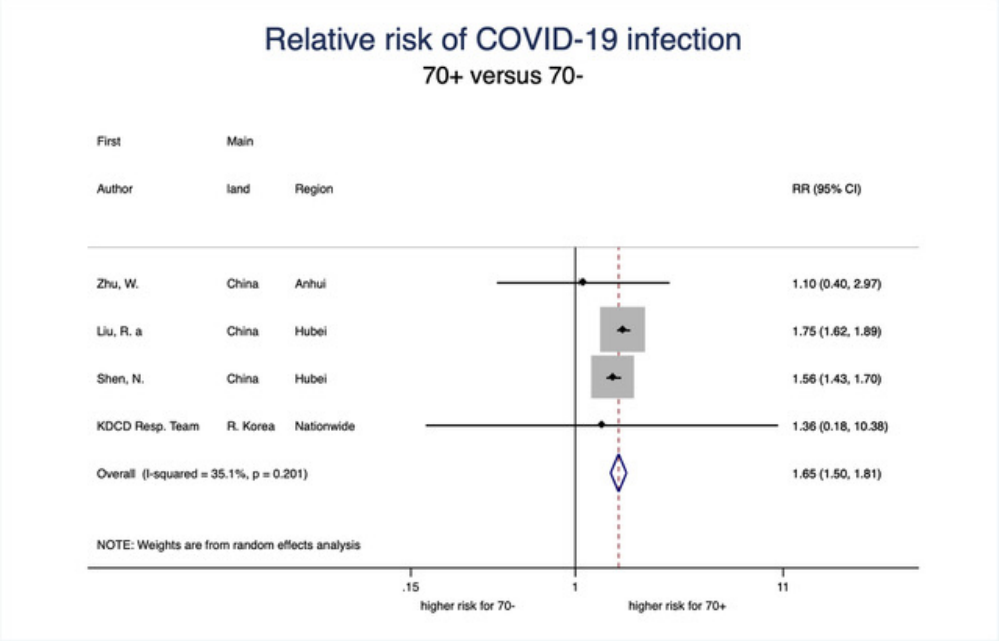

Figure 6: Forrest plot showing association between age and risk of COVID-19 infection. Overall, patients 70 years or older have a 1.65 times higher risk of COVID-19 infection than patients younger than 70 years. Liu, R a = ref 32.

112x72mm (144 x 144 DPI)

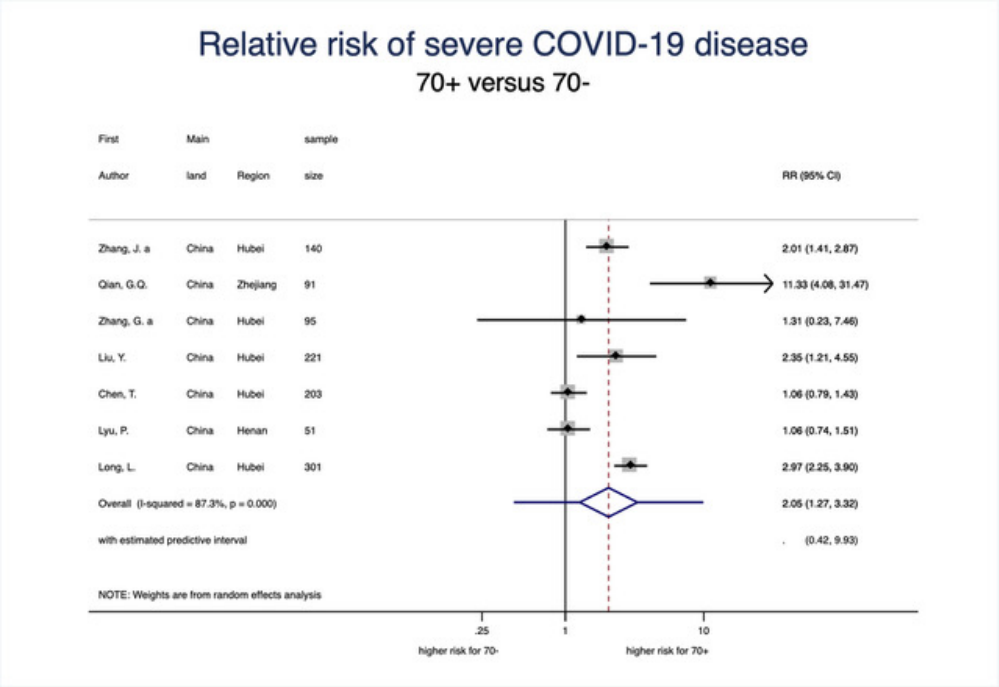

Figure 7: Forrest plot showing association between age and risk of severe COVID-19. Overall, patients 70 years or older have a 2.05 times higher risk of severe COVID-19 than patients younger than 70 years. Zhang, J a = ref 67; Zhang, G a = ref 65.

112x77mm (144 x 144 DPI)

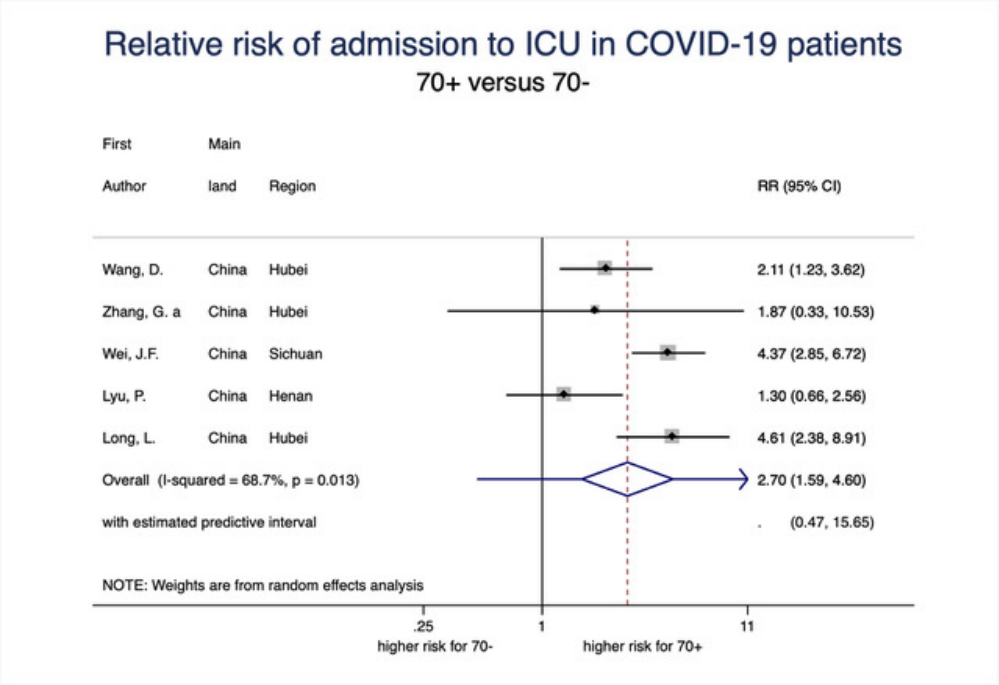

Figure 8: Forrest plot showing association between age and risk of ICU admission due to COVID-19. Overall, patients 70 years or older have a 2.70 times higher risk of ICU admission due to COVID-19 than patients younger than 70 years. Zhang, G a = ref 65.

112x77mm (144 x 144 DPI)

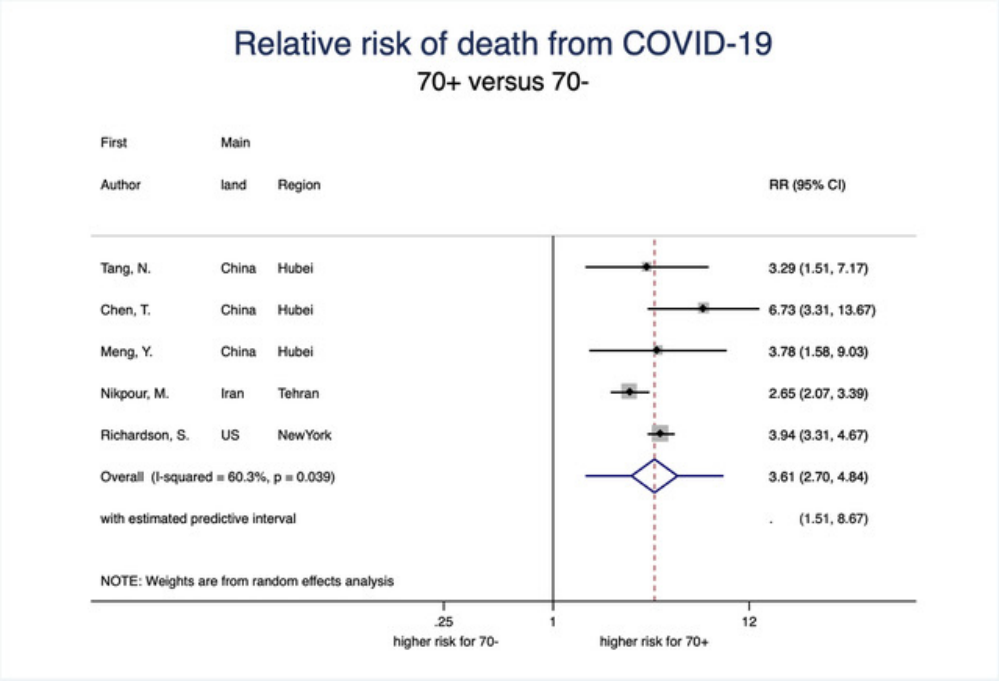

Figure 9: Forrest plot showing association between age and risk of death due to COVID-19. Overall, patients 70 years or older have a 3.61 times higher risk of death due to COVID-19 than patients younger than 70 years.

112x76mm (144 x 144 DPI)

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
Infection					
	Zhu W	0.95	China	Anhui	
	Liu R a	1.1	China	Hubei	Wuhan
	Ai T	1.05	China	Hubei	Wuhan
	Dong Y	1.03	China	multiple regions	
	Chu J	0.86	China	Hubei	Wuhan
	Shen N	1.09	China	Hubei	Wuhan
	KDC Resp Team	1.95	South Korea		
	Long C	1.11	China	Hubei	Yichang
severe					
	Guan W J	0.99	China	Multiple regions	
	Gao Y	0.98	China	Anhui	Fuyang
	Li K	1.33	China	Chongquing and Jinan	
	Wan S	0.94	China	Northeast Chongquing	
	Wu J	1.01	China	Jiangsu, Anhui	
	Shi Y	2.44	China	Zhejiang	
	Qin C	1.09	China	Hubei	Wuhan
	Tian S	1.38	China		Beijing
	Zhang J a	1.28	China	Hubei	Wuhan
	Qian GQ	1.82	China	Zhejiang	
	Zhang G a	1.51	China	Hubei	Wuhan
	Wu C	1.43	China	Wuhan	
	Chen Q	0.96	China	Zhejiang	Taizhou
	Liu Y	1.05	China		Shanghai
	Chen T b	1.21	China	Hubei	Wuhan
	Colaneri M	1.86	Italy	North Italy	
	Chu J	1.15	China	Wuhan	
	Wang X	1.52	China	Wuhan	Fangcang
	Zhao X Y	0.75	China	Jingzhou	
	Wang L	1.01	China	hubei	Wuhan
	Zhu Z	0.71	China	Zhejiang	Ningbo
	Zheng F	0.89	China		Changsha
	Zhang G b	1.83	China	Hubei	
	Chen G	2.35	China	Hubei	Wuhan
	Wang R	1.35	China	Anhui	Fuyang
	Zhang J b	1.07	China	Hubei	Wuhan
	Chen X	2.38	China	Hubei	Wuhan
	Zhang R	0.97	China	Hubei	Wuhan
	Wei J F	1.28	China	Sichuan	
	Liu R b	0.99	China	Hubei	
	Lyu P	0.98	China	Zhengzhou	
	Pei G	1.29	China	Hubei	Wuhan
	Yu X b	2.02	China	Zheijang	
	Zheng S	1.28	China	Zhejiang	
	Long L	1.75	China	Hubei	Jingzhou city and Xia
ICU					

Huang C	2.02	China	Hubei	Wuhan
Wang D	1.32	China		Wuhan
Bingwen E F	1.62	Singapore		
Zhang G a	1.41	China	Hubei	Wuhan
Kalligeros M	1.23	US	Rhode Island	
Wei J F	1.38	China	Sichuan	
Myers L C	1.48	US	California	
Lyu P	0.55	China	Henan	Zhengzhou
Rieg S	2.12	Germany		Freiburg
Cao J	1.85	China	Hubei	Wuhan
Long L	2.24	China	Hubei	Jingzhou city and Xia
death				
Tang N	2.78	China	Hubei	Wuhan
Tian S	2.13	China		Beijing
Wu C	1.1	China	Hubei	Wuhan
Chen T b	4.84	China	Hubei	Wuhan
Meng Y	1.56	China	Hubei	Wuhan
Nikpouraghdam	1.2	Iran		Teheran
Richardson	1.03	US	New York	
Yan, Y	1.65	China	Hubei	Wuhan
Xu B	1.26	China	Hubei	Wuhan
Zhang J b	1.6	China	Hubei	Wuhan
Du R H	0.77	China	Hubei	Wuhan
Yang R	5.15	China	Hubei	Wuhan
Chen R	2.69	China		
Tomlins J	0.88	UK		Bristol

n	publication type	publication date	Start	End
116	paper	10-Mar	24-Jan	20-Feb
4880	paper	7-Mar	22-Jan	14-Feb
1014	paper	26-Feb	6-Jan	6-Feb
2135	paper	1-Apr		8-Feb
54	paper	29-Mar	7-Jan	11-Feb
5630	paper	30-Apr	22-Jan	18-Feb
2370	paper			
87	paper	11-Mar	20-Jan	8-Feb
1096	paper	28-Feb	11-Dec	29-Jan
43	paper	13-Mar	23-Jan	2-Feb
83	paper	29-Feb	1-Jan	29-Feb
135	paper	22-Apr	23-Jan	8-Feb
280	paper	27-Mar	20-Jan	19-Feb
487	research letter	18-Mar		17-Feb
452	paper	12-Mar	10-Jan	12-Feb
262	paper	27-Feb	20-Jan	10-Feb
140	paper	18-Feb	16-Jan	3-Feb
91	paper	17-Mar	20-Jan	11-Feb
95	paper	26-Mar	16-Jan	25-Feb
201	paper	13-Mar	25-Dec	26-Jan
145	paper	28-Apr	1-Jan	11-Mar
221	paper	28-May		
203	paper	7-Apr	1-Jan	10-Feb
44	paper	23-Apr	21-Feb	28-Feb
54	paper	29-Mar	7-Jan	11-Feb
1012	paper	27-Mar	7-Feb	12-Feb
91	paper	29-Apr	16-Jan	10-Feb
116	paper	31-Mar	14-Jan	13-Feb
127	paper	17-Apr	23-Jan	20-Feb
161	paper		17-Jan	7-Feb
221	paper	5-Apr	2-Jan	10-Feb
21	paper	27-Mar	20-Dec	27-Jan
125	paper	24-Mar	20-Jan	8-Feb
663	paper	15-Apr	11-Jan	6-Feb
48	paper	17-Apr	1-Feb	19-Feb
120	paper	1-Apr	10-Jan	10-Feb
103	paper	6-Apr	16-Jan	10-Mar
119	paper	31-Mar	31-Jan	26-Feb
51	paper	17-Apr	15-Jan	24-Feb
333	paper	12-Apr	28-Jan	9-Feb
92	research letter	23-Apr	19-Jan	19-Mar
96	paper	6-Apr	19-Jan	15-Feb
301	letter	20-Apr	16-Jan	24-Feb

41	paper	24-Jan	16-Dec	2-Jan
138	paper	7-Feb	1-Jan	28-Jan
67	letter	3-Mar	23-Jan	28-Feb
95	paper	26-Mar	16-Jan	25-Feb
103	paper	30-Apr	17-Feb	5-Apr
103	paper	6-Apr	16-Jan	10-Mar
377	paper	24-Apr	1-Mar	31-Mar
51	paper	17-Apr	15-Jan	24-Feb
115	paper	28-Apr	25-Feb	31-Mar
102	letter	2-Mar	3-Jan	1-Feb
301	letter	20-Apr	16-Jan	24-Feb
183	paper	18-Feb	1-Jan	3-Feb
262	paper	27-Feb	20-Jan	10-Feb
201	paper	13-Mar	25-Dec	26-Jan
203	paper	7-Apr	1-Jan	10-Feb
168	paper	28-Apr	16-Jan	4-Feb
2968	paper	19-Apr	19-Feb	15-Apr
5700	paper	22-Apr	1-Mar	4-Apr
193	paper	6-Apr	10-Jan	24-Feb
187	paper	13-Apr	26-Dec	1-Mar
663	paper	15-Apr	11-Jan	6-Feb
179	paper	7-May	25-Dec	7-Feb
212	paper	24-Apr	11-Jan	16-Mar
1578	paper	15-Apr		
95	letter	30-Apr	10-Mar	20-Mar

recruitment window	FU	study or database	study desing	clinical setting
27		ED of the First Affilia	cohort	Hospital
23		Renmin Hospital	cohort	Hospital
31		(Tongji hopsital ethi	cohort	Hospital
			cohort	General population
35	35	Tongji Hospital	cohort	Hospital
27	27	Tongji Hospital	cohort	Hospital
	46		cohort	General population
19			cohort	Hospital
49	51	China Medical Treat	cohort	Hospital
10		Fuyangs Second Peo	cohort	Hospital
29		Second Affiliated Ho	cohort	Hospital
16	16	Chongqing Universit	cohort	Hospital
30	30	First People's Hospit	cohort	Hospital
		Zhejiang Province of	cohort	Hospital
33		Tongji Hospital	cohort	Hospital
21	21	Beijing Emergency M	cohort	Hospital
18		No. 7 Hospital of Wu	cohort	Hospital
22	27	five hospitals in Zhej	cohort	Hospital
40	46	Xinzhou District Peo	cohort	Hospital
32	50	Wuhan Jinyintan Ho	cohort	Hospital
70	70	Taizhou Public Healt	cohort	Hospital
		Shanghai Public Hea	cohort	Hospital
40	50	Zhongnan Hospital c	cohort	Hospital
7	12	Pavia teaching hospi	cohort	Hospital
35		Tongji Hospital	cohort	Hospital
5	15	Dongxihu Fangcang	cohort	Hospital
25	25	Jingzhou Central Ho	cohort	Hospital
30	30	Remin Hospital	cohort	Hospital
28	28	Hwa Mei Hospital	cohort	Hospital
21	21	North Hospital of Ch	cohort	Hospital
39	44	Zhongnan Hospital c	cohort	Hospital
38	38	Tongji Hospital	cohort	Hospital
19	29	NO.2 People's Hospi	cohort	Hospital
26		Renmin Hospital of W	cohort	Hospital
18	18	General Hospital of	cohort	Hospital
31	31	Renmin Hospital of W	cohort	Hospital
54		Public Health Clinica	cohort	Hospital
26	26	Renmin Hospital of W	cohort	Hospital
40	40	The First Affiliated H	cohort	Hospital
12	26		cohort	Hospital
60	56	First Affiliated Hospi	cohort	Hospital
27	27	First Affiliated Hospi	cohort	Hospital
39	45	irst People's Hospita	cohort	Hospital

	17		Jin Yin-tan Hospital	cohort	Hospital
	27	33	Zhongnan Hospital	cohort	Hospital
	36		National Centre for I	cohort	Hospital
	40	46	Xinzhou District Peo	cohort	Hospital
	48	48	Rhode island Hospit	cohort	Hospital
	54		Public Health Clinica	cohort	Hospital
	30	39		cohort	Hospital
	40	40		cohort	Hospital
	35	35	Freiburg University I	cohort	Hospital
	29	43	Wuhan University Zł	cohort	Hospital
	39	45	irst People's Hospita	cohort	Hospital
	33	43	Tongji Hospital of Hu	cohort	Hospital
	21	21	Beijing Emergency M	cohort	Hospital
	32	50	Wuhan Jinyintan Ho	cohort	Hospital
	40	50	Zhongnan Hospital c	cohort	Hospital
	19	64	Tongji Hospital	cohort	Hospital
	56	73	Baqiyatallah Hospita	cohort	Hospital
	34	34	12 Northwell Health	cohort	Hospital
	45		Tongji Hospital	cohort	Hospital
	66	66	Hubei Provincial Hos	cohort	Hospital
	26		Renmin Hospital of V	cohort	Hospital
	44		Wuhan Pulmonary H	cohort	Hospital
	65	65	Renmin Hospital of V	cohort	Hospital
			hospitalized patient	cohort	Hospital
	10	27	North Bristol NHS Tr	cohort	Hospital

Diagnostic modality	% comorbidities	% males	mean age	% BMI > 25
PCR		56	40	23
PCR		46		
PCR		46	51	
PCR		57	7	
PCR		67	54	
PCR		47	49	
		45		
laboratory tests , CT findings		53		
PCR	24	58	47	
PCR		61	43	
PCR	18	53	45	
PCR	32	53	47	
PCR		54	43	
		53	46	
PCR	44	51	58	
PCR		49	48	
PCR	64	51	57	
PCR		41	50	
PCR		56	49	
PCR	33	64	51	
PCR		55	48	
PCR		52		
PCR	42	53	55	
PCR	64	64	60	
PCR		67	54	
PCR	11	52	51	
PCR	23	54	46	
PCR	44	58	54	
PCR	41	35	51	24
PCR	21	50	45	
PCR	35	49	54	
PCR	33	81	61	
PCR	27	57	37	
PCR	37	48	56	
PCR		77	65	
PCR	73	43	61	
PCR		54	49	
PCR		52		
PCR	33	56	54	
PCR		55	56	
PCR		62	55	
PCR		60	55	
PCR		50	50	

PCR	32	73	49	
PCR	46	54	57	
PCR		55	42	
PCR		56	49	
PCR		61	60	81.6
PCR		54	49	
PCR		56	61	
PCR	33	57	54	
PCR		63	56	
PCR	46	52	53	24
PCR		50	50	
PCR	41	54	54	
PCR		49	48	
PCR	33	64	51	
PCR	42	53	55	
PCR	34	51	57	
PCR	11	66	56	
PCR	94	60	63	
PCR	49	59	63	
PCR		55	61	
PCR	37	48	56	
		54	58	
PCR	42	51	55	
PCR		57		
		63	73	

NOS

Case definition	Case representativeness	Control selection	control definition
Acceptable	Acceptable	Acceptable	Acceptable
Acceptable	Acceptable	Acceptable	Not acceptable
Acceptable	Acceptable	Acceptable	Acceptable
Acceptable	Acceptable	Acceptable	Acceptable
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Acceptable	Acceptable	Acceptable	Acceptable
Not Acceptable	Acceptable	Acceptable	Acceptable
Acceptable	Not acceptable	Acceptable	Not acceptable
Acceptable	Acceptable	Acceptable	Acceptable
Unknown	Acceptable	Acceptable	Acceptable
Acceptable	Acceptable	Acceptable	Acceptable
Acceptable	Acceptable	Acceptable	Acceptable
Acceptable	Acceptable	Acceptable	Acceptable
Acceptable	Acceptable	Acceptable	Acceptable
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Acceptable	Acceptable	Acceptable	Acceptable
Acceptable	not acceptable	Acceptable	Not Acceptable
Acceptable	Acceptable	Acceptable	Not Acceptable

exposure ascertainment	comparable ascertainment	non response rate	overall quality
Acceptable	Acceptable	NA	9
Acceptable	Acceptable	NA	7
Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Unknown	8
Acceptable	Acceptable	acceptable	9
Acceptable	Acceptable	acceptable	9
Acceptable	Acceptable	NA	7
Acceptable	Acceptable	NA	6
Acceptable	Acceptable	NA	9
Unknown	Acceptable	NA	6
Acceptable	Acceptable	NA	9
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Acceptable	Acceptable	NA	9
Unknown	unknown	NA	5
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Acceptable	Acceptable	NA	9
Acceptable	Acceptable	NA	8
Acceptable	Acceptable	NA	9
Acceptable	Acceptable	NA	9
Acceptable	Acceptable	NA	9
Acceptable	Acceptable	NA	7
Acceptable	Acceptable	na	7
Acceptable	Acceptable	NA	8

Included for ICU (so different outcome)

70 and above versus less than 70

	Author	RR	country	region	city	n	publication	publication
Infection								
	Zhu W	1.1	China	Anhui		116	paper	10-Mar
	Liu R a	1.75	China	Hubei	Wuhan	4880	paper	7-Mar
	Shen N	1.56	China	Hubei	Wuhan	5630	paper	30-Apr
	KDC Resp T	1.36	South Korea			2370	paper	
severe								
	Zhang J a	2.01	China	Hubei	Wuhan	140	paper	18-Feb
	Qian GQ	11.33	China	Zhejiang		91	paper	17-Mar
	Zhang G a	1.31	China	Hubei	Wuhan	95	paper	26-Mar
	Liu Y	2.35	China		Shanghai	221	paper	28-May
	Chen T	1.06	China	Hubei	Wuhan	203	paper	7-Apr
	Lyu P	1.06	China	Henan	Zhengzhou	51	paper	17-Apr
	Long L	2.97	China	Hubei	Jingzhou cit	301	letter	20-Apr
ICU								
	Wang D	2.11	China		Wuhan	138	paper	7-Feb
	Zhang G a	1.87	China	Hubei	Wuhan	95	paper	26-Mar
	Wei J F	4.37	China	Sichuan		103	paper	6-Apr
	Lyu P	1.3	China	Henan	Zhengzhou	51	paper	17-Apr
	Long L	4.61	China	Hubei	Jingzhou cit	301	letter	20-Apr
death								
	Tang N	3.29	China	Hubei	Wuhan	183	paper	18-Feb
	Chen T	6.73	China	Hubei	Wuhan	203	paper	7-Apr
	Meng Y	3.78	China	Hubei	Wuhan	168	paper	28-Apr
	Nikpouragh	3.94	Iran		Teheran	2968	paper	19-Apr
	Richardson	3.38	US	New York		5700	paper	22-Apr

Start	End	recruitmen	FU	study or database	study desin	clinical sett	Diagnostic
24-Jan	20-Feb	27		ED of the First Affili	cohort	Hospital	PCR
22-Jan	14-Feb	23		Renmin Hospital	cohort	Hospital	PCR
22-Jan	18-Feb		27	Tongji Hospital	cohort	Hospital	PCR
			46		cohort	General population	
16-Jan	3-Feb	18		No. 7 Hospital of W	cohort	Hospital	PCR
20-Jan	11-Feb	22	27	five hospitals in Zhe	cohort	Hospital	PCR
16-Jan	25-Feb	40	46	Xinzhou District Pec	cohort	Hospital	PCR
				Shanghai Public He	cohort	Hospital	PCR
1-Jan	10-Feb	40	50	Zhongnan Hospital	cohort	Hospital	PCR
15-Jan	24-Feb	40	40		cohort	Hospital	PCR
16-Jan	24-Feb	39	45	irst People's Hospit	cohort	Hospital	PCR
1-Jan	28-Jan	27	33	Zhongnan Hospital	cohort	Hospital	PCR
16-Jan	25-Feb	40	46	Xinzhou District Pec	cohort	Hospital	PCR
16-Jan	10-Mar	54		Public Health Clinic	cohort	Hospital	PCR
15-Jan	24-Feb	40	40		cohort	Hospital	PCR
16-Jan	24-Feb	39	45	irst People's Hospit	cohort	Hospital	PCR
1-Jan	3-Feb	33	43	Tongji Hospital of H	cohort	Hospital	PCR
1-Jan	10-Feb	40	50	Zhongnan Hospital	cohort	Hospital	PCR
16-Jan	4-Feb	19	64	Tongji Hospital	cohort	Hospital	PCR
19-Feb	15-Apr	56	73	Baqiyatallah Hospit	cohort	Hospital	PCR
1-Mar	4-Apr	34	34	12 Northwell Health	cohort	Hospital	PCR

% comorbic	% males	mean age	% BMI > 25	NOS Case defini	Case repres
	56	40	23	Acceptable	Acceptable
	46			Acceptable	Acceptable
	47	49		Acceptable	Acceptable
	45			Not Accept	Acceptable
64	51	57		Acceptable	Acceptable
	41	50		Acceptable	Acceptable
	56	49		Acceptable	Acceptable
	52			Not accept	Acceptable
42	53	55		Acceptable	Acceptable
33	57	54		Acceptable	Acceptable
	50	50		Acceptable	Acceptable
46	54	57		Acceptable	Acceptable
	56	49		Acceptable	Acceptable
	54	49		Acceptable	Acceptable
33	57	54		Acceptable	Acceptable
	50	50		Acceptable	Acceptable
41	54	54		Acceptable	Acceptable
42	53	55		Acceptable	Acceptable
34	51	57		Acceptable	Acceptable
11	66	56		Acceptable	Acceptable
94	60	63		Acceptable	Acceptable

Control sel	control def	exposure a	comparabl	non respon	overall quality
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Not accept	Acceptable	Acceptable	NA	7
Acceptable	Acceptable	Acceptable	Acceptable	acceptable	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	7
Acceptable	Acceptable	Acceptable	Acceptable	acceptable	8
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	6
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	6
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	8
Acceptable	Acceptable	Acceptable	Acceptable	NA	9
Acceptable	Acceptable	Acceptable	Acceptable	NA	9

Study	country	region	City	n	publication	publication	Start	End
Ai T	China	Hubei	Wuhan	1014	paper	26-Feb	6-Jan	6-Feb
Bingwen E I	Singapore			67	letter	3-Mar	23-Jan	28-Feb
Cao J	China	Hubei	Wuhan	102	letter	2-Mar	3-Jan	1-Feb
Chen G	China	Hubei	Wuhan	21	paper	27-Mar	20-Dec	27-Jan
Chen Q	China	Zhejiang	Taizhou	145	paper	28-Apr	1-Jan	11-Mar
Chen R	China			1578	paper	15-Apr		
Chen T b	China	Hubei	Wuhan	203	paper	7-Apr	1-Jan	10-Feb
Chen X	China	Hubei	Wuhan	48	paper	17-Apr	1-Feb	19-Feb
Chu J	China	Hubei	Wuhan	54	paper	29-Mar	7-Jan	11-Feb
Colaneri M	Italy	North Italy		44	paper	23-Apr	21-Feb	28-Feb
Dong Y	China	multiple regions		2135	paper	1-Apr		8-Feb
Du R H	China	Hubei	Wuhan	179	paper	7-May	25-Dec	7-Feb
Gao Y	China	Anhui	Fuyang	43	paper	13-Mar	23-Jan	2-Feb
Guan W J a	China	Multiple regions		1096	paper	28-Feb	11-Dec	29-Jan
Huang C	China	Hubei	Wuhan	41	paper	24-Jan	16-Dec	2-Jan
Kalligeros M	US	Rhode Island		103	paper	30-Apr	17-Feb	5-Apr
KDC Resp T	South Korea			2370	paper			
Li K	China	Chongquing and Jinan		83	paper	29-Feb	1-Jan	29-Feb
Liu R a	China	Hubei	Wuhan	4880	paper	7-Mar	22-Jan	14-Feb
Liu R b	China	Hubei		119	paper	31-Mar	31-Jan	26-Feb
Liu Y	China		Shanghai	221	paper	28-May		
Long C	China	Hubei	Yichang	87	paper	11-Mar	20-Jan	8-Feb
Long L	China	Hubei	Jingzhou cit	301	letter	20-Apr	16-Jan	24-Feb
Lyu P	China	Zhengzhou		51	paper	17-Apr	15-Jan	24-Feb
Meng Y	China	Hubei	Wuhan	168	paper	28-Apr	16-Jan	4-Feb
Myers L C	US	California		377	paper	24-Apr	1-Mar	31-Mar
Nikpouragh	Iran		Teheran	2968	paper	19-Apr	19-Feb	15-Apr
Pei G	China	Hubei	Wuhan	333	paper	12-Apr	28-Jan	9-Feb
Qian GQ	China	Zhejiang		91	paper	17-Mar	20-Jan	11-Feb
Qin C	China	Hubei	Wuhan	452	paper	12-Mar	10-Jan	12-Feb
Richardson	US	New York		5700	paper	22-Apr	1-Mar	4-Apr
Rieg S	Germany		Freiburg	115	paper	28-Apr	25-Feb	31-Mar
Shen N	China	Hubei	Wuhan	5630	paper	30-Apr	22-Jan	18-Feb
Shi Y	China	Zhejiang		487	research let	18-Mar		17-Feb
Tang N	China	Hubei	Wuhan	183	paper	18-Feb	1-Jan	3-Feb
Tian S	China		Beijing	262	paper	27-Feb	20-Jan	10-Feb
Tomlins J	UK		Bristol	95	letter	30-Apr	10-Mar	20-Mar
Wan S	China	Northeast Chongquing		135	paper	22-Apr	23-Jan	8-Feb
Wang D a	China		Wuhan	138	paper	7-Feb	1-Jan	28-Jan
Wang L b	China	hubei	Wuhan	116	paper	31-Mar	14-Jan	13-Feb
Wang R	China	Anhui	Fuyang	125	paper	24-Mar	20-Jan	8-Feb
Wang X	China	Wuhan	Fangcang	1012	paper	27-Mar	7-Feb	12-Feb
Wei J F	China	Sichuan		103	paper	6-Apr	16-Jan	10-Mar
Wu C	China	Wuhan		201	paper	13-Mar	25-Dec	26-Jan
Wu J	China	Jiangsu, Anhui		280	paper	27-Mar	20-Jan	19-Feb
Xu B	China	Hubei	Wuhan	187	paper	13-Apr	26-Dec	1-Mar
Yan, Y	China	Hubei	Wuhan	193	paper	6-Apr	10-Jan	24-Feb

Yang R	China	Hubei	Wuhan	212	paper	24-Apr	11-Jan	16-Mar
Yu X b	China	Zheijang		92	research let	23-Apr	19-Jan	19-Mar
Zhang G a	China	Hubei	Wuhan	95	paper	26-Mar	16-Jan	25-Feb
Zhang G b	China	Hubei		221	paper	5-Apr	2-Jan	10-Feb
Zhang J a	China	Hubei	Wuhan	140	paper	18-Feb	16-Jan	3-Feb
Zhang J b	China	Hubei	Wuhan	663	paper	15-Apr	11-Jan	6-Feb
Zhang R	China	Hubei	Wuhan	120	paper	1-Apr	10-Jan	10-Feb
Zhao X Y	China	Jingzhou		91	paper	29-Apr	16-Jan	10-Feb
Zheng F	China		Changsha	161	paper		17-Jan	7-Feb
Zheng S	China	Zhejiang		96	paper	6-Apr	19-Jan	15-Feb
Zhu W	China	Anhui		116	paper	10-Mar	24-Jan	20-Feb
Zhu Z	China	Zhejiang	Ningbo	127	paper	17-Apr	23-Jan	20-Feb

recruitmen	FU	study or da	study desin	clinical sett	Diagnostic	% comorbic	% males	mean age
31		(Tongji hop	cohort	Hospital	PCR		46	51
36		National Ce	cohort	Hospital	PCR		55	42
29	43	Wuhan Uni	cohort	Hospital	PCR	46	52	53
38	38	Tongji Hosp	cohort	Hospital	PCR	33	81	61
70	70	Taizhou Pul	cohort	Hospital	PCR		55	48
		hospitalize	cohort	Hospital	PCR		57	
40	50	Zhongnan H	cohort	Hospital	PCR	42	53	55
18	18	General Ho	cohort	Hospital	PCR		77	65
35	35	Tongji Hosp	cohort	Hospital	PCR		67	54
7	12	Pavia teach	cohort	Hospital	PCR	64	64	60
			cohort	General po	PCR		57	7
44		Wuhan Pul	cohort	Hospital			54	58
10		Fuyangs Se	cohort	Hospital	PCR		61	43
49	51	China Medi	cohort	Hospital	PCR	24	58	47
17		Jin Yin-tan I	cohort	Hospital	PCR	32	73	49
48	48	Rhode islan	cohort	Hospital	PCR		61	60
	46		cohort	General population			45	
29		Second Affi	cohort	Hospital	PCR	18	53	45
23		Renmin Ho	cohort	Hospital	PCR		46	
26	26	Renmin Ho	cohort	Hospital	PCR		52	
		Shanghai Pu	cohort	Hospital	PCR		52	
19			cohort	Hospital	laboratory tests , CT fir		53	
39	45	irst People'	cohort	Hospital	PCR		50	50
40	40	The First Af	cohort	Hospital	PCR	33	56	54
19	64	Tongji Hosp	cohort	Hospital	PCR	34	51	57
30	39		cohort	Hospital	PCR		56	61
56	73	Baqiyatallal	cohort	Hospital	PCR	11	66	56
12	26		cohort	Hospital	PCR		55	56
22	27	five hospita	cohort	Hospital	PCR		41	50
33		Tongji Hosp	cohort	Hospital	PCR	44	51	58
34	34	12 Northwe	cohort	Hospital	PCR	94	60	63
35	35	Freiburg Ur	cohort	Hospital	PCR		63	56
27	27	Tongji Hosp	cohort	Hospital	PCR		47	49
		Zhejiang Pr	cohort	Hospital			53	46
33	43	Tongji Hosp	cohort	Hospital	PCR	41	54	54
21	21	Beijing Eme	cohort	Hospital	PCR		49	48
10	27	North Brist	cohort	Hospital			63	73
16	16	Chongqing	cohort	Hospital	PCR	32	53	47
27	33	Zhongnan H	cohort	Hospital	PCR	46	54	57
30	30	Remin Hosp	cohort	Hospital	PCR	44	58	54
19	29	NO.2 Peopl	cohort	Hospital	PCR	27	57	37
5	15	Dongxihu F	cohort	Hospital	PCR	11	52	51
54		Public Heal	cohort	Hospital	PCR		54	49
32	50	Wuhan Jiny	cohort	Hospital	PCR	33	64	51
30	30	First People	cohort	Hospital	PCR		54	43
66	66	Hubei Provi	cohort	Hospital	PCR		55	61
45		Tongji Hosp	cohort	Hospital	PCR	49	59	63

	65	65	Renmin Ho	cohort	Hospital	PCR	42	51	55
	60	56	First Affiliat	cohort	Hospital	PCR		62	55
	40	46	Xinzhou Dis	cohort	Hospital	PCR		56	49
	39	44	Zhongnan H	cohort	Hospital	PCR	35	49	54
	18		No. 7 Hospi	cohort	Hospital	PCR	64	51	57
	26		Renmin Ho	cohort	Hospital	PCR	37	48	56
	31	31	Renmin Ho	cohort	Hospital	PCR	73	43	61
	25	25	Jingzhou Ce	cohort	Hospital	PCR	23	54	46
	21	21	North Hosp	cohort	Hospital	PCR	21	50	45
	27	27	First Affiliat	cohort	Hospital	PCR		60	55
	27		ED of the Fi	cohort	Hospital	PCR		56	40
	28	28	Hwa Mei H	cohort	Hospital	PCR	41	35	51

	NOS				
% BMI > 25	Case defini	Case repres	Control sel	control defi	exposure as
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
24	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	not accepta	Acceptable	Not Accept	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Unknown	Acceptable	Acceptable	Acceptable	Unknown
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
81.6	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Not Accept	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Not accepta	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Not accepta	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Not accepta	Acceptable	Not accepta	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
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	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Unknown
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
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	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	not accepta	Acceptable	Acceptable	Acceptable

	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Not accept	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
23	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
24	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable

comparable	non respon	overall	quality
Acceptable	NA	10	9
Acceptable	NA	10	9
Acceptable	NA	10	9
Acceptable	NA	8	7
Acceptable	NA	10	9
Acceptable	na	8	7
Acceptable	NA	10	9
Acceptable	NA	8	7
Acceptable	acceptable	10	9
Acceptable	NA	9	8
Acceptable	Unknown	9	8
Acceptable	NA	10	9
Acceptable	NA	7	6
Acceptable	NA	10	9
Acceptable	NA	10	9
Acceptable	NA	9	8
Acceptable	NA	8	7
Acceptable	NA	10	9
Acceptable	NA	8	7
Acceptable	NA	7	6
Acceptable	NA	9	8
Acceptable	NA	7	6
Acceptable	NA	10	9
Acceptable	NA	7	6
Acceptable	NA	9	8
Acceptable	Acceptable	10	9
Acceptable	NA	10	9
Acceptable	NA	9	8
Acceptable	NA	10	9
Acceptable	acceptable	10	9
Acceptable	NA	10	9
Acceptable	NA	9	8
Acceptable	acceptable	10	9
unknown	NA	6	5
Acceptable	NA	9	8
Acceptable	NA	10	9
Acceptable	NA	9	8
Acceptable	NA	10	9
Acceptable	NA	10	9
Acceptable	unknown	9	8
Acceptable	unknown	10	9
Acceptable	NA	10	9
Acceptable	NA	10	9
Acceptable	NA	10	9
Acceptable	NA	10	9
Acceptable	NA	10	9
Acceptable	NA	9	8

Acceptable NA	8	7
Acceptable NA	6	5
Acceptable NA	10	9
Acceptable NA	9	8
Acceptable acceptable	9	8
Acceptable NA	10	9
Acceptable NA	9	8
Acceptable NA	8	7
Acceptable NA	10	9
Acceptable NA	10	9
Acceptable NA	10	9
Acceptable NA	10	9

Included fo

ır ICU (so different outcome)

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.

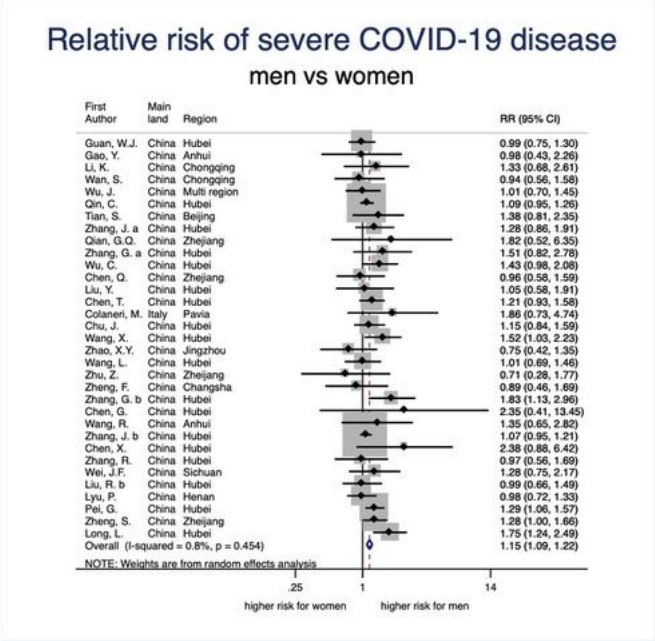

Figure A1

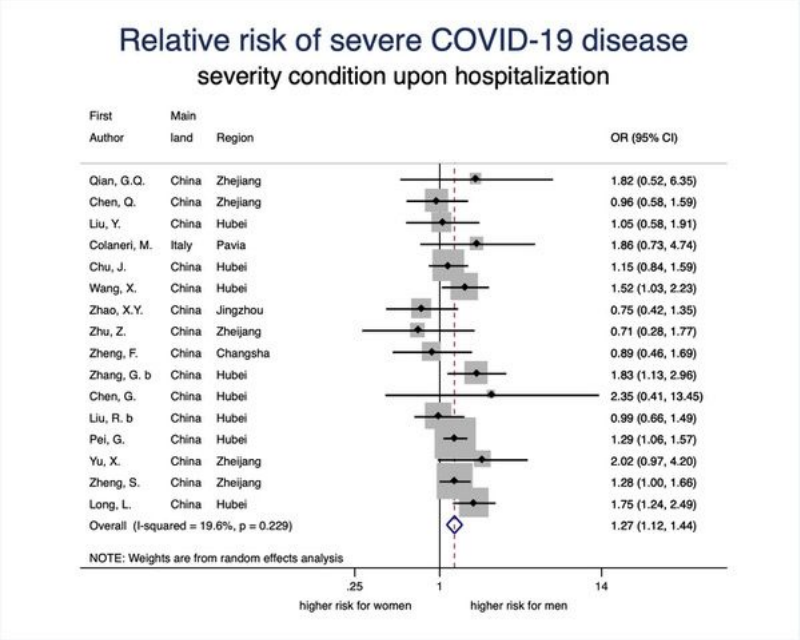

Figure A2

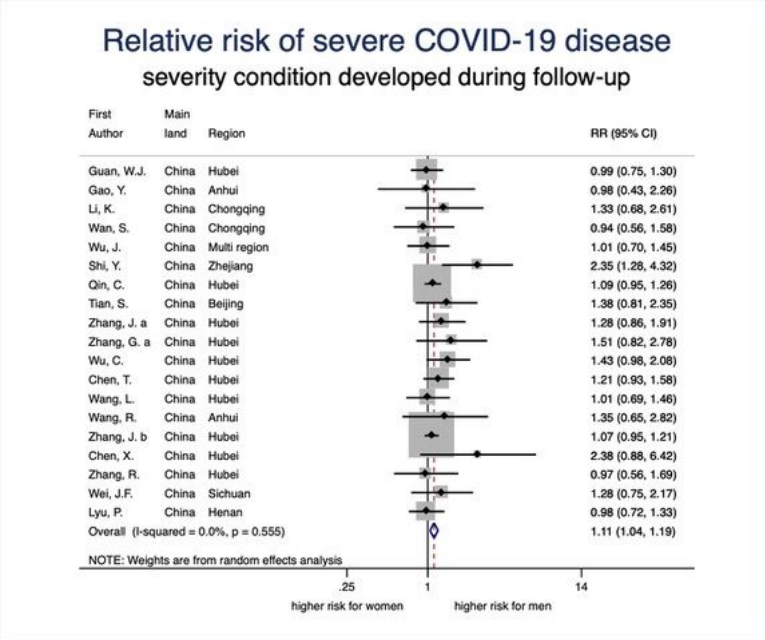

Figure A3

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.

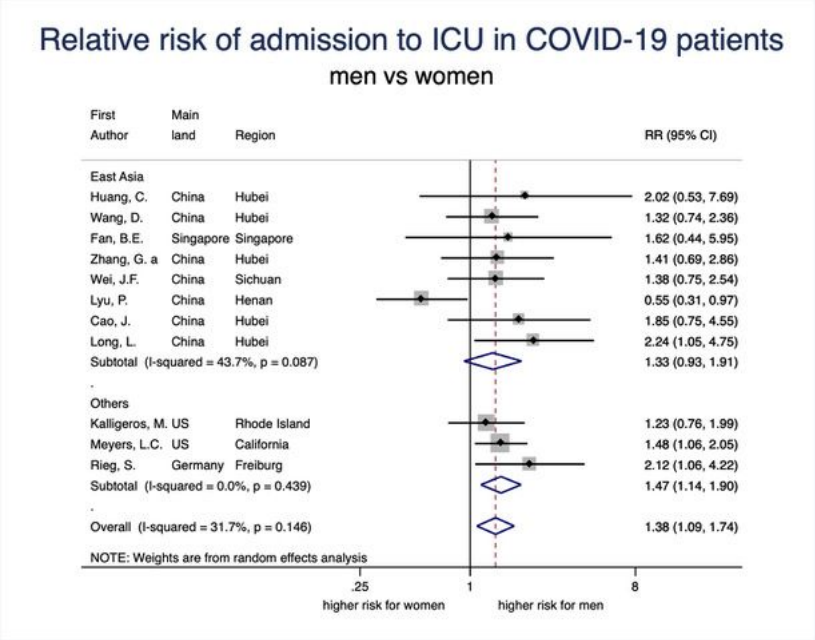

Figure A4

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.

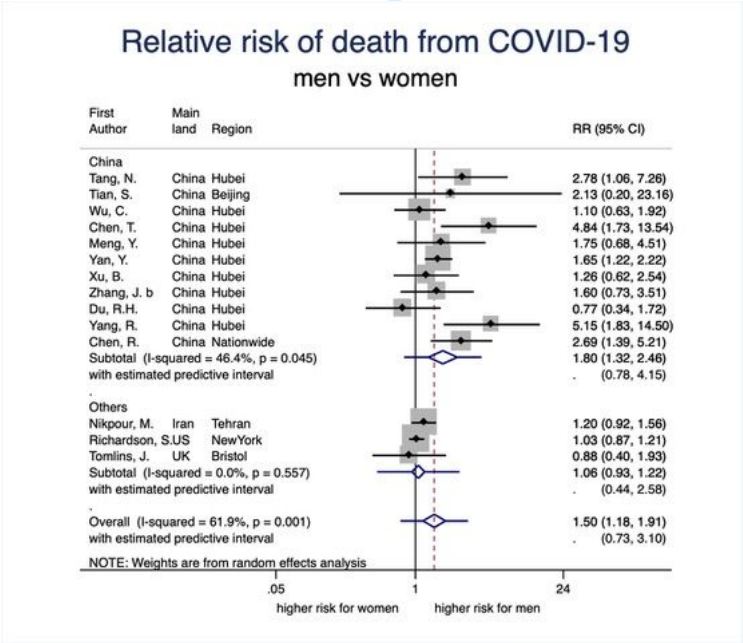

Figure A5

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

.
```

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

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

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

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 τ^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.

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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

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

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

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Demographic risk factors for COVID-19 infection, severity, ICU admission and death:

A meta-analysis of 59 studies.

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J-11-S

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 May 4 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, 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 (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 to 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 on 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 COVID-19 patients compared to 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 at 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 COVID-19 patients and SARS patients, Jin et al, found that increased age and sex were associated with more severe disease and mortality.[4] 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, ICU admission and death may provide insight into the underlying pathophysiological mechanisms (immunity, coagulopathy and co-morbidities). This knowledge may also guide clinical decision making, especially when there is an impending shortage in health care resources such as ICU beds. Additionally, exploring demographic factors influencing COVID-19 outcomes may guide policy makers 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 be 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 PRISMA statement and a protocol has been registered a priori at the Prospero registry (PROSPERO 2020: CRD42020180085)[6] For this review we focused on the early phase in 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 categorized into old age, defined as 70 years and older, and young age, defined as younger than 70 years. 70 years was chosen as a cut-off point for the main analyses, because this was the most commonly used cut-of in the first studies included. We also collected data on other cut-of points (60 years and 65 years) where possible. We considered 4 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) severe clinically/radiologically COVID-19 among hospitalized patients with a confirmed infection?

3) ICU admission among patients hospitalized for confirmed COVID-19 infection?

4) death among patients hospitalized 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 (GF) and the following databases were searched from December 2019 up to an including May 4 2020: Medline via PubMed and EMBASE. Additionally, EPPI Centre (COVID-19: a living systematic map of the evidence) was consulted up to March 31 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 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 (RD, AV or BP). A second reviewer (RD) re-did 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 2 reviewers (from: AR, SZ, AA, JD, 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 pre-specified 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 (e.g. kidney transplant patients, patients with fractured bones).

Data extraction and Quality Assessment

Observed frequencies of outcomes and controls per level of the determinants were extracted from text, tables or figures (i.e. 2x2 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 pre-defined electronic data sheet that was designed during a pilot data extraction phase on the first eligible studies. A second reviewer (AA, JD or SH) double-checked the inclusion by the data extractors. Any disagreements were resolved by consensus or by consulting a referee (BP or MZ). We contacted authors of papers with data presented in a way that did not allow summarization in contingency tables by e-mail. We sent a reminder e-mail after one 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, JD 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 (i.e. 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% confidence intervals 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 pre-defined factors. These factors include: geographical region, study quality, study size, days into the pandemic, publication date, diagnostic modality (e.g. PCR test, CT signs, clinical symptoms and their combinations that led to the diagnosis of COVID-19) and clinical setting (e.g. nursing home, home, hospital, GP 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 was used to explore the magnitude and direction of publication bias.

Patient and public involvement statement

This systematic review and meta-analysis is part of the WHO Evidence Collaborative on COVID-19 answering on of 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 (PRIMSA flow chart).

Study characteristics

We included studies on the effect of age (70 years or more versus less than 70 years) and sex (men versus 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, three from the United States, one from Germany, one from Iran, one from Italy, one from Singapore, one from South-Korea and one from the United Kingdom. The included studies were published between 2nd January 2020 and 15th April 2020. The mean age of the patients in the included studies ranged between 7 and 73 years. The percentage of males in the included papers ranged from 35% to 81%. The follow-up ranged from 12 days to 73 days. For details of individual studies, organized by exposure and outcome, see Appendix II.

Risk of bias

The methodological quality of the included papers was high with an average of 8.2 out of nine, as measured with the Newcastle Ottawa Scale (NOS). Case definition and case representativeness was acceptable in 55 out of 59 and 55 out of 59 studies respectively. Control selection and control definition was acceptable in 59 out of 59 and 55 out of 59 studies respectively. Exposure ascertainment and comparable ascertainment was 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, organized by exposure and outcome, is available in Appendix II.

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 from random effect 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 then women (RR: 1.08 95%CI: 1.03 – 1.12; 8 studies), see Figure 2. When diagnosed, men also experienced more severe disease than women (RR = 1.18, 95%CI: 1.10 – 1.27; 35 studies) implying that the risk of severe disease of COVID-19 for men is 18% higher than that for women, see Figure 3. Moreover, the rate of admission to ICU in COVID-19 patients was higher among men as compared to women. The aggregated random effect was 1.38 (95%CI: 1.09 – 1.74; 11 studies), see Figure 4. Finally, we

observed that men were at higher risk of death from COVID-19 as compared to women (RR = 1.50, 95%CI: 1.18– 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. 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 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 re-did 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 Appendix III. 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 was not enough data to report on pregnancy, SES 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 hada higher risk for COVID-19 infection. When ihospitalized with COVID, men more often developed severe COVID-19 disease and more often required Intensive Care admission, ultimately resulting in death more often . We also found that patients affected by COVID-19 aged 70 years and above were more often observed to have confirmed COVID-infection, severe disease, ICU admission and dying compared to 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 rigor 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 to 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 Severe Acute Respiratory Syndrome (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 points to an underlying biological mechanism. Aside from anatomic, 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. Aging, is among others, characterized by a chronic pro-inflammatory 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] Aging is also associated with a high prevalence of comorbidities and

decreased reserve capacity of vital organs which may lead to increase 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 COVID-19 patients compared to n =9 studies from outside China, potentially limiting the generalizability 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) re-perform the data extraction.

Methodological limitations include the fact 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 upon hospitalization or during follow-up. This is additionally complicated by the fact that referral policy to dedicated hospitals in China obscures the severity upon 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 e.g. pre-hospitalization health status and co-morbidities. However, the observed differences in outcome for sex and age are consistent with other respiratory tract infections and there is a pathophysiological basis (e.g. 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..

License statement

Conflicts of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author). All authors declare that they have no conflicts of interest.

Transparency declaration

The manuscript's guarantors (BP, SJ and MZ) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

Ethics committee approval

For this systematic review and meta-analysis approval by the ethics committee was not required.

Role of the funding source

There was no external funding for this work. All authors are volunteers on a research call from the Dutch epidemiological society and this study is part of the WHO Evidence Collaborative on COVID-19 answering on of their rapid review priority questions on risk factors for infection and disease severity

Hence, no sponsor took part in the design or conduct of the study; nor in the collection, management, analysis, or interpretation of the data; nor in the preparation, review, or the approval of 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.

Systematic review registration:

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

Data sharing statement

The study protocol is available online at the Prospero website: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=180085 . All relevant data are in the manuscript or online supplementary.

Dissemination declaration

This review will be disseminated via WHO, direct communication with national centres for disease control, international library organisation and via google search engine optimisation provided by Maastricht University

Authors' contributions

MZ conceived the study. All authors were involved in the study design during weekly meetings. GF designed and performed the search strategy. AV, RD and BP screened titles and abstracts for eligibility. AR and SZ extracted the data (quantitative data) and AA, SH and JD reviewed the study quality (qualitative data). SJ analysed the data. BP and SJ wrote the first draft. All authors revised this draft for critical content. All authors approve the final manuscript. MZ, BP and SJ are the guarantors. All persons listed as authors have contributed to preparing the manuscript and the International Committee of Medical Journal Editors criteria for authorship have been met. There are no person or persons other than the authors listed that have contributed significantly to the preparation of 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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Figures Legends

Figure 1: Prisma flow chart showing study selection

Figure 2: Forrest plot showing 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, R a = ref 32.

Figure 3: Forrest plot showing 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, J a = ref 67; Zhang, G a = ref 65; Zhang G, b = ref 64; Zhang, J b = ref 66; Liu, r b = ref 33.

Figure 4: Forrest plot showing 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, G a = ref 65.

Figure 5: Forrest plot showing 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.

Figure 6: Forrest plot showing association between age and risk of COVID-19 infection. Overall, patients 70 years or older have a 1.65 times higher risk of COVID-19 infection than patients younger than 70 years. Liu, R a = ref 32.

Figure 7: Forrest plot showing association between age and risk of severe COVID-19. Overall, patients 70 years or older have a 2.05 times higher risk of severe COVID-19 than patients younger than 70 years. Zhang, J a = ref 67; Zhang, G a = ref 65.

Figure 8: Forrest plot showing association between age and risk of ICU admission due to COVID-19. Overall, patients 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, G a = ref 65.

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

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

Table 2: summary of data synthesis

Exposure	Outcome	Number of studies	Number of patients	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	7.832	1.18	1.10 to 1.27	NA	15%
	ICU	11	1.493	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	1.102	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	9.222	3.61	2.70to 4.84	1.51 to 8.67	60%

RR = risk ratio

NA = not applicable

95%CI = 95% confidence interval

95%PI = 95% prediction interval

Table 3: Exclusion of possible overlaps

		All studies		Excluding possible overlap	
Exposure	Outcome	Number of studies	Pooled estimate (RR)	Number of studies	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.

RR = risk ratio

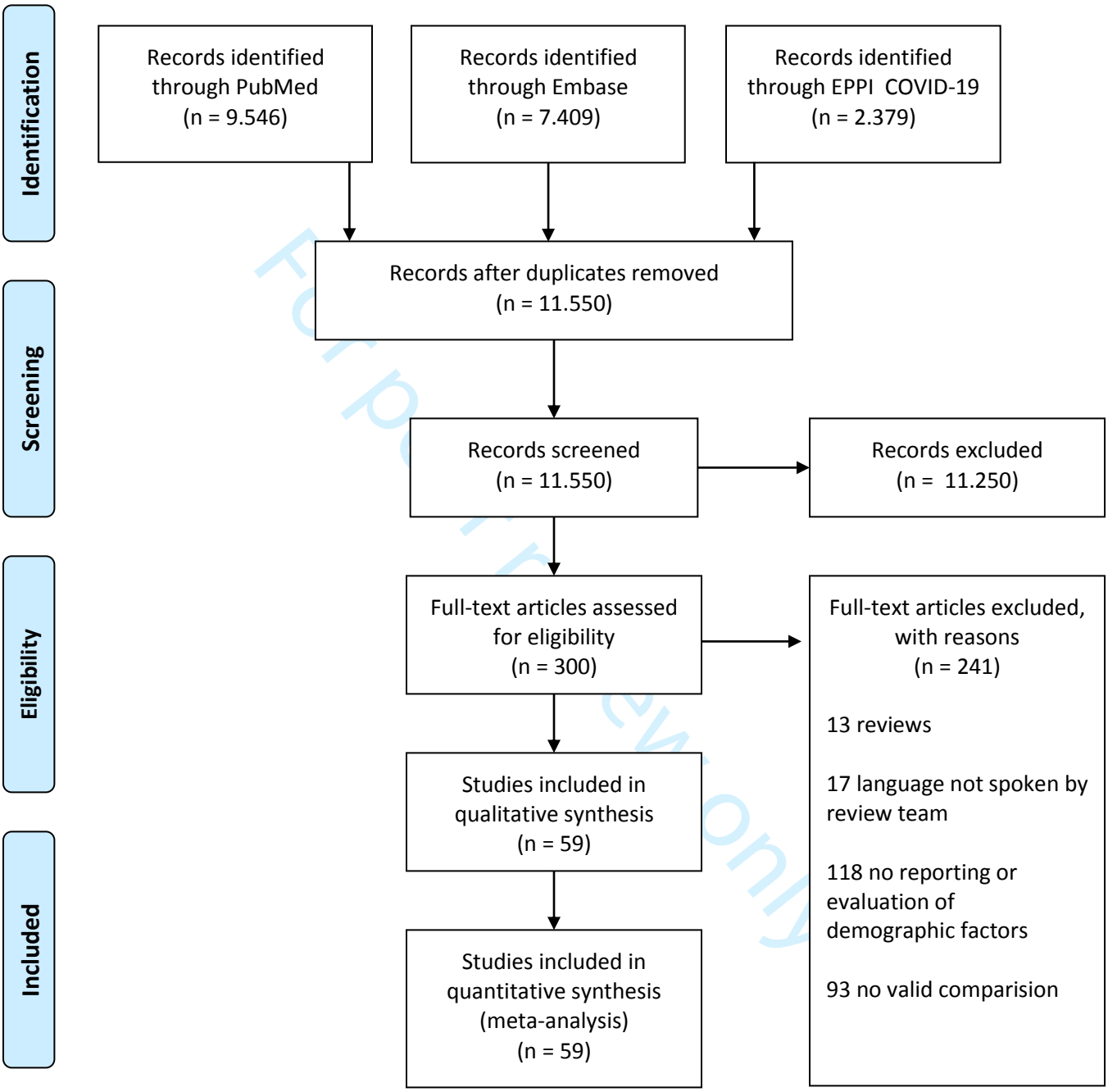
Appendix list:

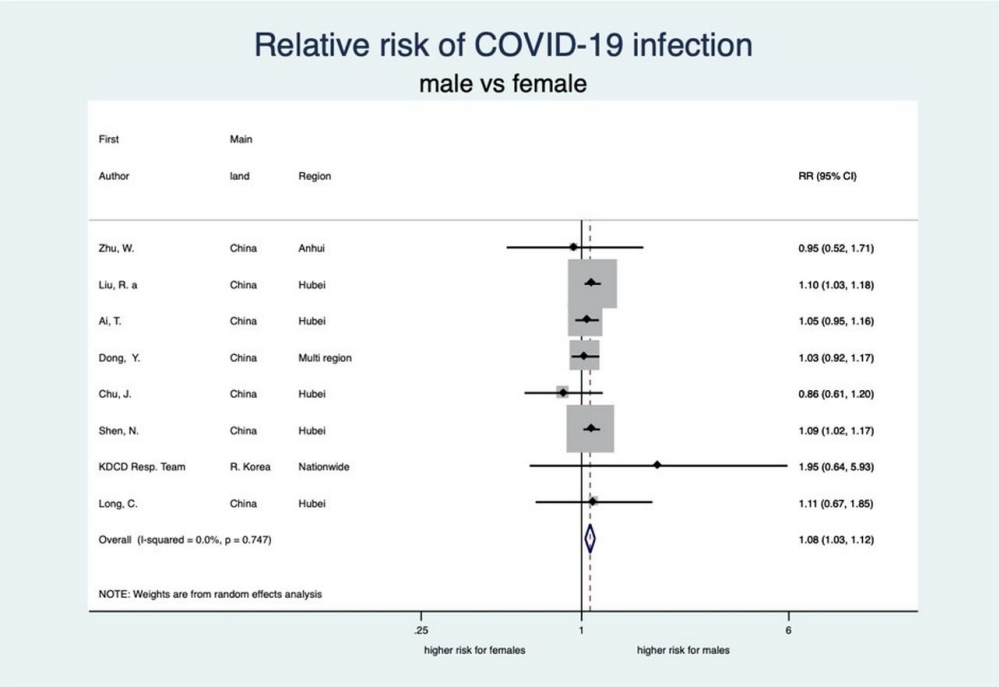
Appendix I: search strategy

Appendix II: individual study characteristics (both data and quality)

Appendix III: sensitivity analyses

Appendix IV: Prospero Protocol





Caption : Figure 2: Forrest plot showing 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, R a = ref 32.

Link text : Figure 2

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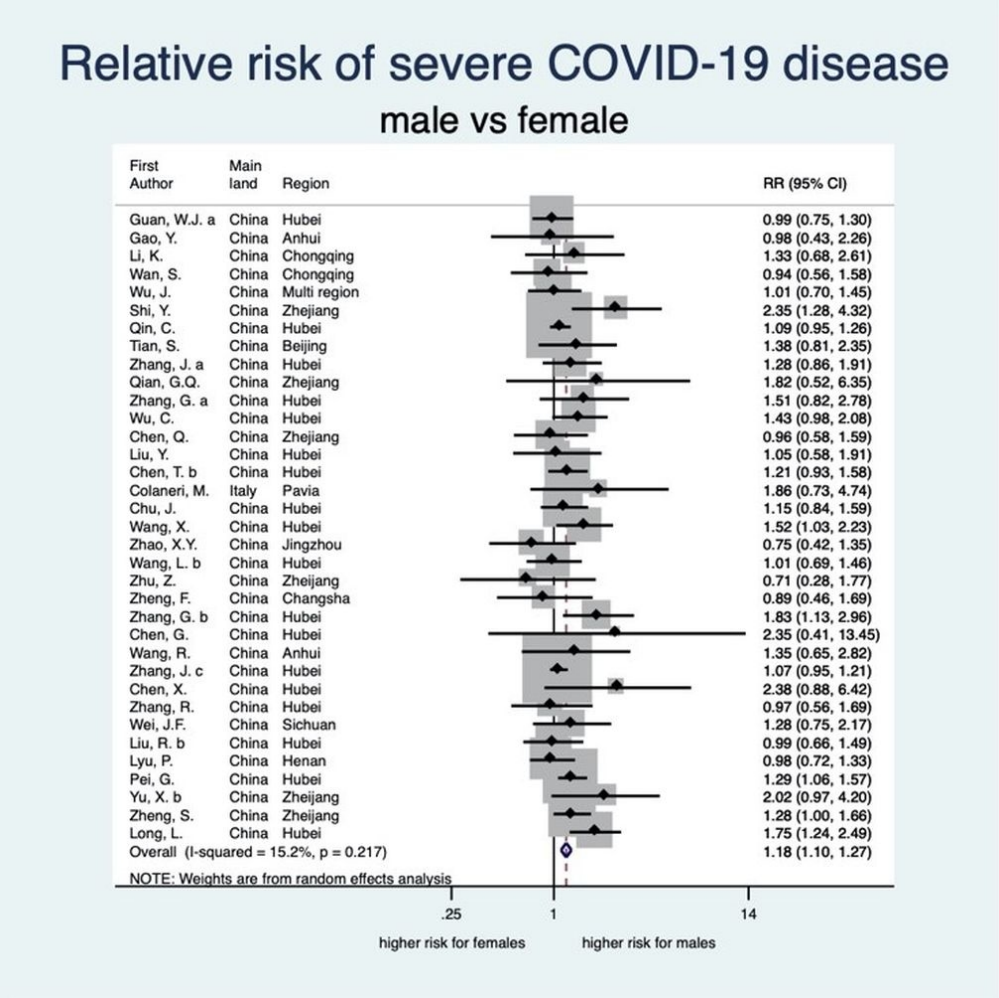

Caption : Figure 3: Forrest plot showing association between sex and risk of severe COVID-19. Overall, men have a 1.18 times higher risk of severe COVID-19 than women. Zhang, J a = ref 67; Zhang, G a = ref 65; Zhang G, b = ref 64; Zhang, J b = ref 66; Liu, r b = ref 33.

Link text : Figure 3

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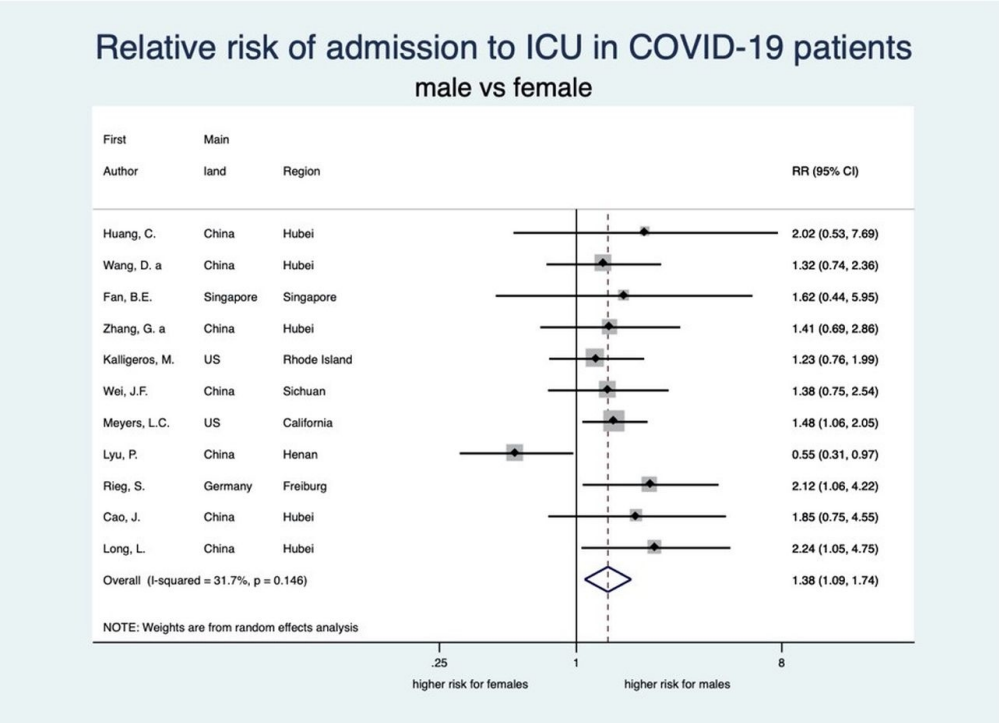

Caption : Figure 4: Forrest plot showing association between sex and risk of ICU admission due to COVID-19. Overall, men have a 1.38 times higher risk of ICU admission due to COVID-19 than women. Zhang, G a = ref 65.

Link text : Figure 4

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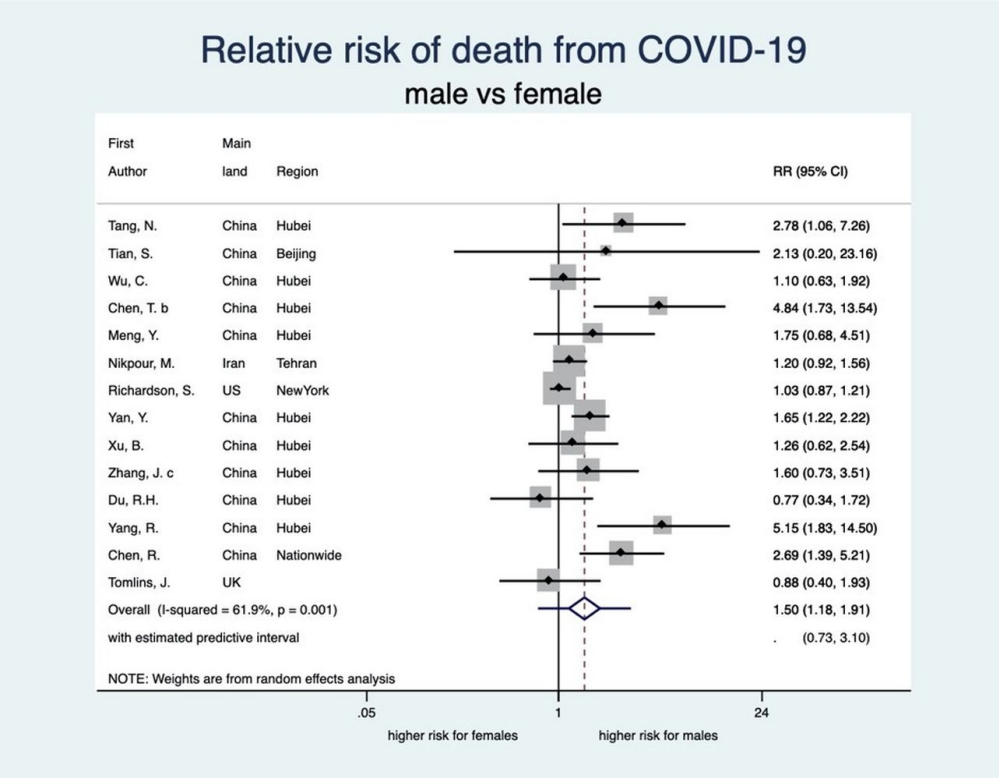

Caption : Figure 5: Forrest plot showing association between sex and risk of death due to COVID-19. Overall, men have a 1.50 times higher risk of death due to COVID-19 than women.

Link text : Figure 5

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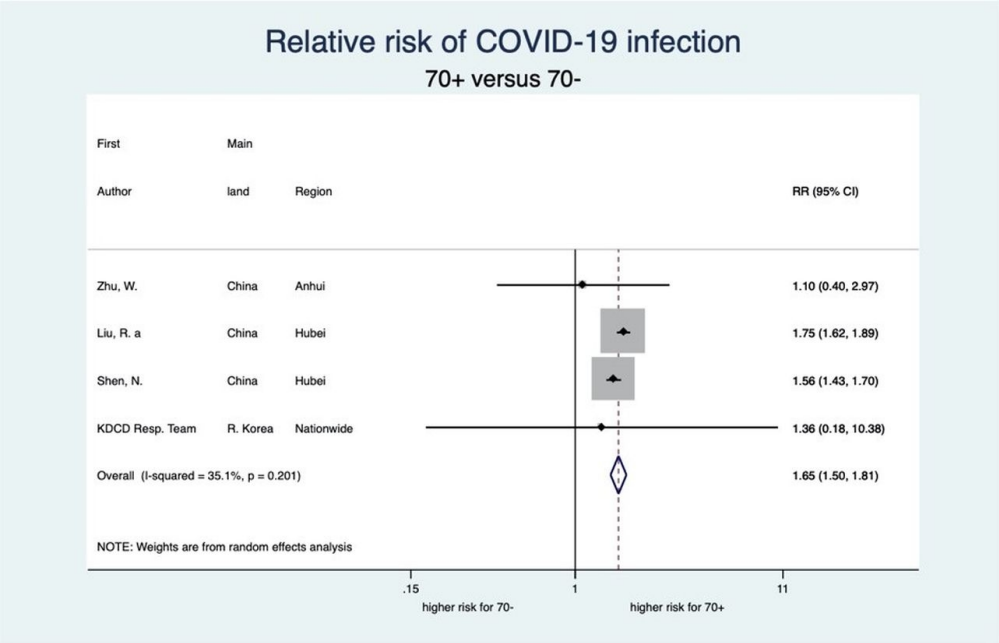

Caption : Figure 6: Forrest plot showing association between age and risk of COVID-19 infection. Overall, patients 70 years or older have a 1.65 times higher risk of COVID-19 infection than patients younger than 70 years. Liu, R a = ref 32.

Link text : Figure 6

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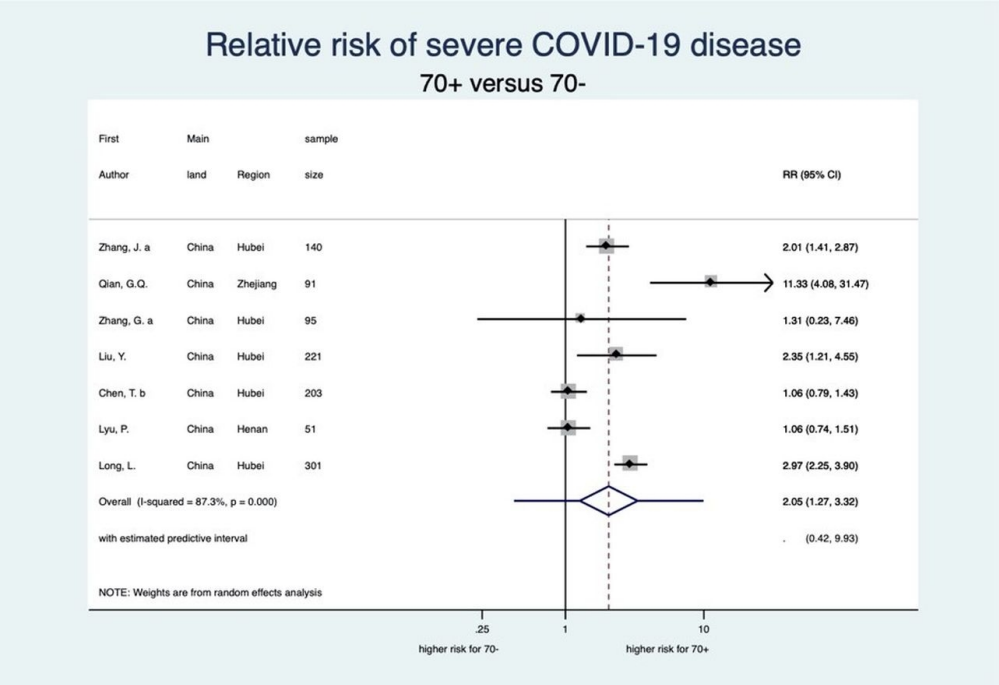

Caption : Figure 7: Forrest plot showing association between age and risk of severe COVID-19. Overall, patients 70 years or older have a 2.05 times higher risk of severe COVID-19 than patients younger than 70 years. Zhang, J a = ref 67; Zhang, G a = ref 65.

Link text : Figure 7

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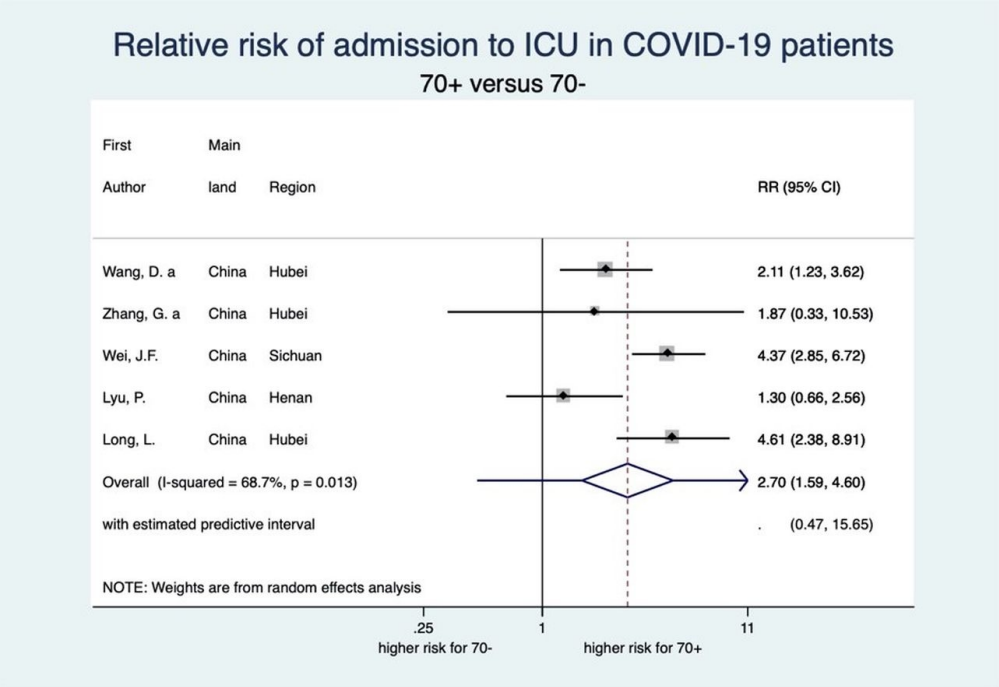

Caption : Figure 8: Forrest plot showing association between age and risk of ICU admission due to COVID-19. Overall, patients 70 years or older have a 2.70 times higher risk of ICU admission due to COVID-19 than patients younger than 70 years. Zhang, G a = ref 65.

Link text : Figure 8

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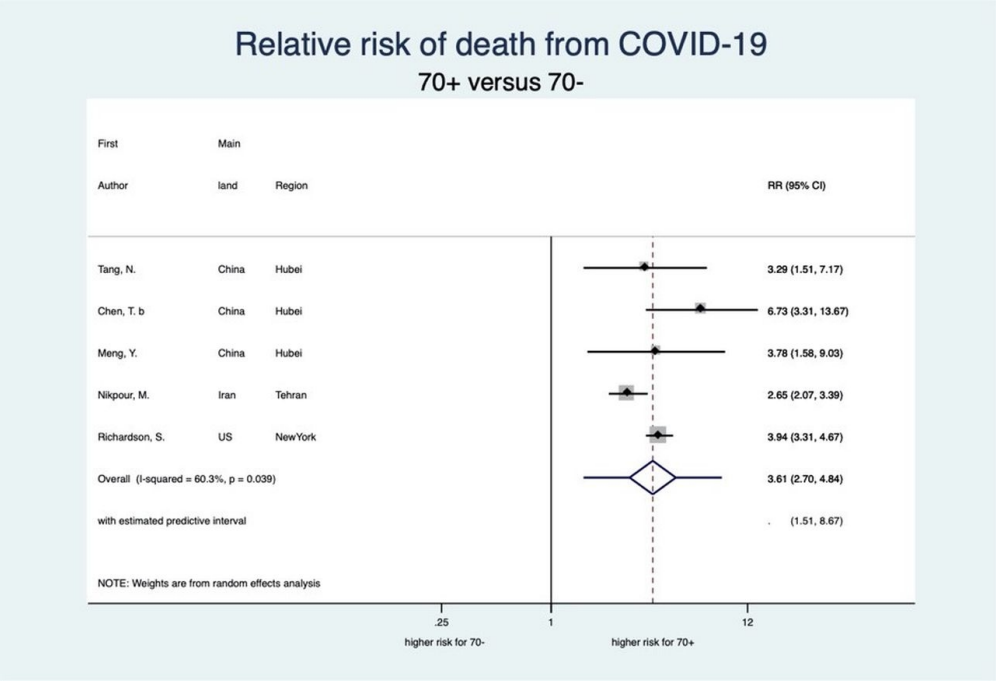

Caption : Caption : Figure 2: Forrest plot showing association between sex and risk of COVID-19 infection. Overall, men have a 1.08 times higher risk of COVID-19 infection than women. Liu, R a = ref 32.Link text : Figure 2

Link text : Figure 2

108x73mm (300 x 300 DPI)

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.

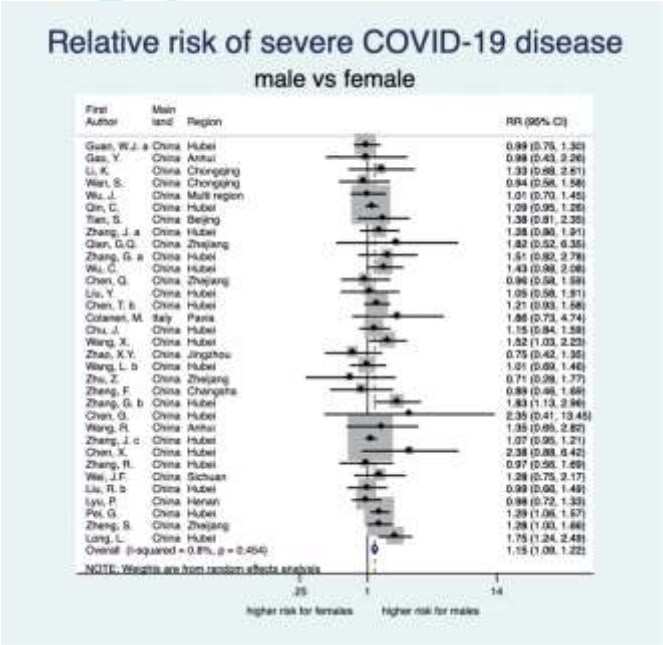

Figure A1

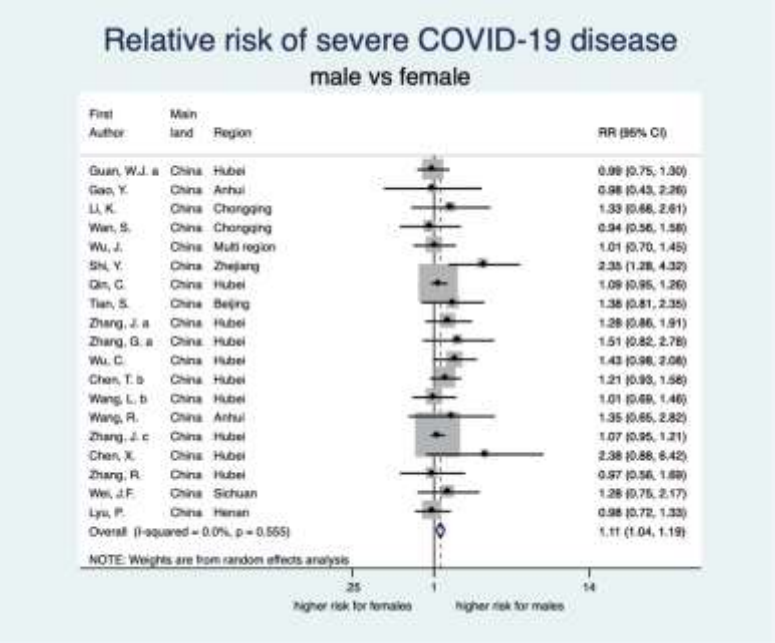

Figure A2

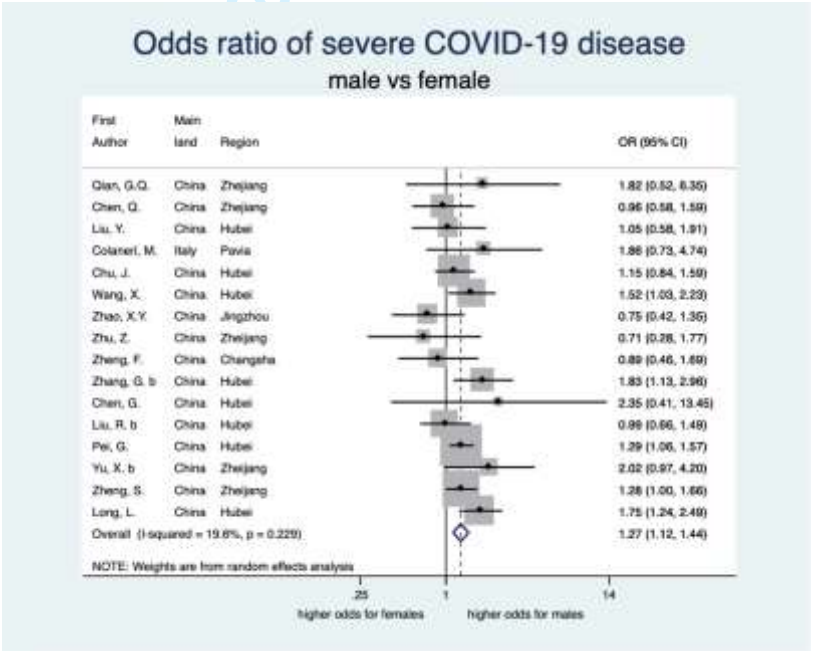

Figure A3

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.

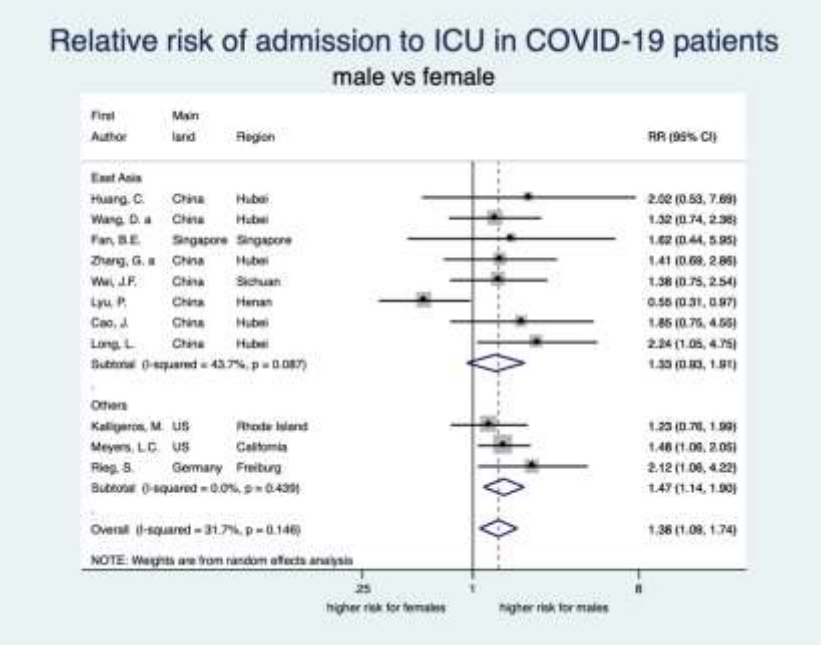

Figure A4

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.

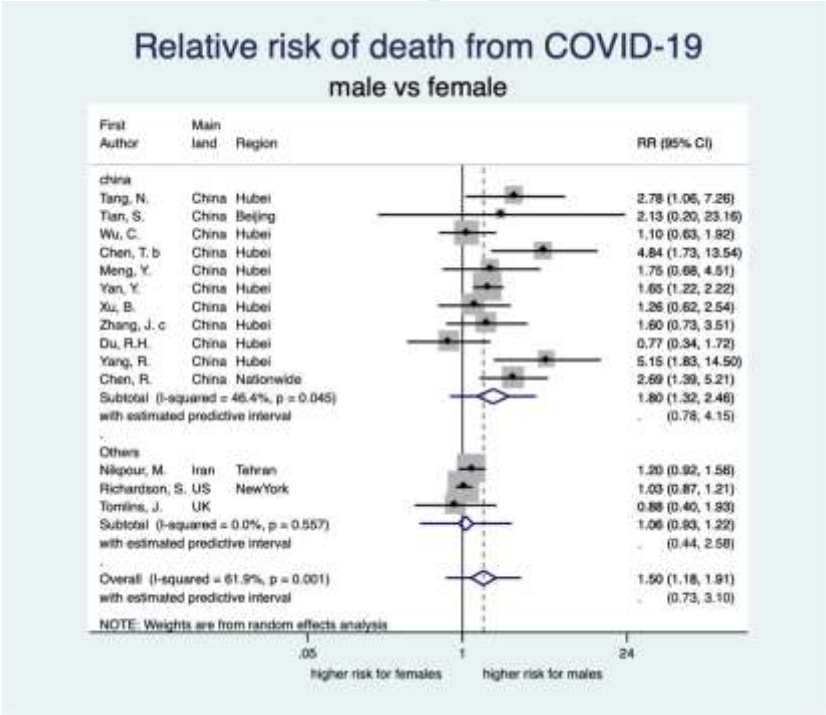

Figure A5

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

.
```

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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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

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13 April 2020

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Conflicts of interest

Language
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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

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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