Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

John Allotey,[1,2] Elena Stallings,[3,4] Mercedes Bonet,[5] Magnus Yap,[6] Shaunak Chatterjee,[6] Tania Kew,[6] Luke Debenham,[6] Anna Clavé Llavall,[6] Anushka Dixit,[6] Dengyi Zhou,[6] Rishab Balaji,[6] Siang Ing Lee,[1] Xiu Qiu,[7,8,9] Mingyang Yuan,[1,7] Dyuti Coomar,[1] Jameela Sheikh Yuan,[6] Heidi Lawson,[6] Kehkashan Ansari,[2] Madelon van Wely,[10] Elizabeth van Leeuwen,[11] Elena Kostova,[10] Heinke Kunst,[12,13] Asma Khalil,[14] Simon Tiberi,[12,13] Vanessa Brizuela,[5] Nathalie Broutet,[5] Edna Kara,[3] Caron Rahn Kim,[5] Anna Thorson,[5] Ramón Escuriet,[15] Olufemi T Oladapo,[5] Lynne Mofenson,[16] Javier Zamora,[2,3,4] Shakila Thangaratinam,[2,18] on behalf of the PregCOV-19 Living Systematic Review Consortium

For numbered affiliations see end of the article.

Correspondence to: S Thangaratinam s.thangaratinam.1@bham.ac.uk (or @thangaratinam on Twitter: ORCID 0000-0002-4254-460X)

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ABSTRACT

OBJECTIVE

To determine the clinical manifestations, risk factors, and maternal and perinatal outcomes in pregnant and recently pregnant women with suspected or confirmed coronavirus disease 2019 (covid-19).

DESIGN

Living systematic review and meta-analysis.

DATA SOURCES

Medline, Embase, Cochrane database, WHO COVID-19 database, China National Knowledge Infrastructure (CNKI), and Wanfang databases from 1 December 2019 to 6 October 2020, along with preprint servers, social media, and reference lists.

STUDY SELECTION

Cohort studies reporting the rates, clinical manifestations (symptoms, laboratory and radiological findings), risk factors, and maternal and perinatal outcomes in pregnant and recently pregnant women with suspected or confirmed covid-19.

DATA EXTRACTION

At least two researchers independently extracted the data and assessed study quality. Random effects meta-analysis was performed, with estimates pooled as odds ratios and proportions with 95% confidence intervals. All analyses will be updated regularly.

RESULTS

192 studies were included. Overall, 10% (95% confidence interval 7% to 12%; 73 studies, 67 271 women) of pregnant and recently pregnant women attending or admitted to hospital for any reason were diagnosed as having suspected or confirmed covid-19. The most common clinical manifestations of covid-19 in pregnancy were fever (40%) and cough (41%). Compared with non-pregnant women of reproductive age, pregnant and recently pregnant women with covid-19 were less likely to have symptoms (odds ratio 0.28, 95% confidence interval 0.13 to 0.62; I^2=42.9%) or report symptoms of fever (0.49, 0.38 to 0.63; I^2=40.8%), dyspnoea (0.76, 0.67 to 0.85; I^2=4.4%) and myalgia (0.53, 0.36 to 0.78; I^2=59.4%). The odds of admission to an intensive care unit (odds ratio 2.13, 1.53 to 2.95; I^2=71.2%), invasive ventilation (2.59, 2.28 to 2.94; I^2=0%) and need for extra corporeal membrane oxygenation (2.02, 1.22 to 3.34; I^2=0%) were higher in pregnant and recently pregnant than non-pregnant reproductive aged women. Overall, 339 pregnant women (0.02%, 59 studies, 41 664 women) with confirmed covid-19 died from any cause. Increased maternal age (odds ratio 1.83, 1.27 to 2.63; I^2=43.4%), high body mass index (2.37, 1.83 to 3.07; I^2=0%), any pre-existing maternal comorbidity (1.81, 1.49 to 2.20; I^2=0%), chronic hypertension (2.0, 1.14 to 3.48; I^2=0%), pre-existing diabetes (2.12, 1.62 to 2.78; I^2=0%), and pre-eclampsia (4.21, 1.27 to 14.0; I^2=0%) were associated with severe covid-19 in pregnancy. In pregnant women with covid-19, increased maternal age, high body mass index, non-white ethnicity, any pre-existing maternal comorbidity including chronic hypertension and diabetes, and pre-eclampsia were associated with serious complications such as admission to an intensive care unit, invasive

WHAT IS ALREADY KNOWN ON THIS TOPIC

Pregnant women are considered to be a high risk group for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and the potential adverse effects of the virus on maternal and perinatal outcomes are of concern

In non-pregnant populations admitted to hospital with coronavirus disease 2019 (covid-19) the most common symptoms are fever, cough, and dyspnoea, reported in more than two thirds of individuals

Advancing age, high body mass index, non-white ethnicity, and pre-existing comorbidities are risk factors for severe covid-19 in the general population

WHAT THIS STUDY ADDS

Pregnant and recently pregnant women with covid-19 diagnosed in hospital are less likely to have or manifest symptoms of fever, dyspnoea, and myalgia than non-pregnant women of reproductive age

Pregnant and recently pregnant women are at increased risk of admission to an intensive care unit, receiving invasive ventilation and extra corporeal membrane oxygenation treatment, compared with non-pregnant women of reproductive age

Risk factors for severe covid-19 in pregnancy include increasing maternal age, high body mass index, non-white ethnicity, pre-existing comorbidities, and pregnancy specific disorders such as gestational diabetes and pre-eclampsia

Pregnant women with covid-19 are more likely to experience preterm birth and their neonates are more likely to be admitted to a neonatal unit

ventilation and maternal death. Compared to pregnant women without covid-19, those with the disease had increased odds of maternal death (odds ratio 2.85, 1.08 to 7.52; I^2=0%), of needing admission to the intensive care unit (18.58, 7.53 to 45.82; I^2=0%), and of preterm birth (1.47, 1.14 to 1.91; I^2=18.6%). The odds of admission to the neonatal intensive care unit (4.89, 1.87 to 12.81, I^2=96.2%) were higher in babies born to mothers with covid-19 versus those without covid-19.

CONCLUSION

Pregnant and recently pregnant women with covid-19 attending or admitted to the hospitals for any reason are less likely to manifest symptoms such as fever, dyspnoea, and myalgia, and are more likely to be admitted to the intensive care unit or needing invasive ventilation than non-pregnant women of reproductive age. Pre-existing comorbidities, non-white ethnicity, chronic hypertension, pre-existing diabetes, high maternal age, and high body mass index are risk factors for severe covid-19 in pregnancy. Pregnant women with covid-19 versus without covid-19 are more likely to deliver preterm and could have an increased risk of maternal death and of being admitted to the intensive care unit. Their babies are more likely to be admitted to the neonatal unit.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42020178076.

READERS' NOTE

This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication. This version is update 1 of the original article published on 1 September 2020 (*BMJ* 2020;370:m3320), and previous updates can be found as data supplements (https://www.bmj.com/content/370/bmj.m3320/related#datasupp). When citing this paper please consider adding the update number and date of access for clarity.

Introduction

Since the first report (December 2019) of the novel coronavirus disease 2019 (covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of confirmed cases and associated mortality and morbidity have increased rapidly.[1 2] Pregnant women are considered a high risk group because of concerns about the effect of covid-19 on them during and after pregnancy, and on their neonates.[3] Quantification of the rates of covid-19, its risk factors, clinical manifestations, and outcomes is key to planning clinical maternal care and management in an evolving pandemic scenario.[4]

Publications on covid-19 in pregnancy have risen steeply through individual case reports, case series, observational studies, and systematic reviews. Since the publication of our first version of the living systematic review on covid-19 in pregnancy,[5] over 150 reviews have been published in this area,[6-11] with many more registered in PROSPERO.[9 12] Early reviews mostly included case reports and case series that were often inappropriately meta-analysed providing biased estimates.[13] Subsequent reviews differed little from each other, often including similar primary studies, many with duplicate data. These reviews became quickly outdated as new evidence emerged. Moreover, the sampling frames in primary studies have varied, ranging from universal SARS-CoV-2 testing for all pregnant women admitted to hospital[14 15] to symptom based testing.[16 17] Testing strategies have also differed within and between countries, with diagnosis in many early studies based on epidemiological risk assessment and clinical features without confirmed SARS-CoV-2 infection, which need to be considered in the analysis.[18] Limitations in the external and internal validity of studies make it challenging for guideline developers and policy makers to make evidence based recommendations for the management of pregnant and recently pregnant women with covid-19.

We started this living systematic review in April 2020 to determine the clinical manifestations of covid-19 in pregnant and recently pregnant women, identify the risk factors for complications, and quantify maternal and perinatal outcomes. The systematic review is being updated on a regular basis.

Methods

Our systematic review is based on a prospectively registered protocol (PROSPERO CRD42020178076; registered 22 April 2020)[19] to evaluate a series of research questions on covid-19 during and after pregnancy. We report our findings on the rates, clinical manifestations, risk factors, and maternal and perinatal outcomes in women with covid-19 in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations (see appendix 1). As more relevant data become available, we shall address the research questions in our published protocol.[20] Each cycle of our living systematic review involves weekly search updates (rounds), with analysis performed every 2-4 months for reporting through a dedicated website, with early analysis if new definitive evidence emerges. We are regularly reviewing the planned frequency of updates.

Literature search

For the first publication of the review, we performed a systematic search of major databases: Medline, Embase, Cochrane database, WHO (World Health Organization) COVID-19 database, China National Knowledge Infrastructure (CNKI), and Wanfang databases from 1 December 2019 to 26 June 2020 for relevant studies on covid-19 in pregnant and recently pregnant women.[5] For this first update of the review, we searched databases up to 6 October 2020. To identify potential studies, we coordinated our search efforts with the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre), the WHO Library, and the Cochrane Gynaecology and Fertility group. Additional searches were conducted of preprint servers, blogs, websites that serve as repositories

for covid-19 studies, social media, guidelines, and reference lists of included studies and unpublished data. We also searched the Living Overview of the Evidence (LOVE) platform from June 2020.[21] We contacted established groups that were coordinating or conducting surveillance and studies in pregnant women with covid-19, such as the WHO Maternal, Newborn, Child and Adolescent health (MNCAH) covid-19 research network, the International Network of Obstetric Survey Systems (INOSS), the United States Centers for Disease Control and Prevention (CDC), and the European Centre for Disease Prevention and Control for information on published and upcoming data. No language restrictions were applied. Appendix 2 provides details of the search strategies and databases searched.

Study selection

Two reviewers independently selected studies using a two stage process: they first screened the titles and abstracts of studies and then assessed the full text of the selected studies in detail for eligibility. A total of 10 reviewers contributed to study selection. Disagreements were resolved through discussion with a third reviewer (ST or JA). We excluded studies if the duplicated data for all outcomes of interest were published elsewhere, as reported by the study authors, or when the characteristics of the mother or neonate matched the setting, characteristics, and duration of another study from the same geographical location. When we suspected an overlap of data between studies, the study that provided comparative data was included. If there was an overlap of data or suspicion of duplicates of participants in studies between the previous and current versions of the living systematic review, we included studies based on their study design (prioritising comparative cohorts), and sample size (larger study prioritised). When there was uncertainty about duplicate data, we contacted the authors of primary studies.

We defined women as having confirmed covid-19 if they had laboratory confirmation of SARS-CoV-2 infection irrespective of clinical signs and symptoms.[22] Women with a diagnosis based only on clinical or radiological findings were defined as having suspected covid-19. The recently pregnant group comprised women in the postpartum and post-abortion period. We included studies that compared covid-19 rates, clinical manifestations (symptoms, laboratory and radiological results), risk factors, and associated mortality and morbidity between pregnant and recently pregnant and non-pregnant women of reproductive age, and those that compared maternal and perinatal outcomes in pregnant women with and without covid-19. In studies comparing maternal and perinatal outcomes of pregnant women with covid-19 to those without, we classified the comparative controls as being historical if the cohort of pregnant women without covid-19 were pregnant before December 2019. Studies on non-comparative cohorts with a minimum of 10 participants were included if they reported on the rates and clinical manifestations of covid-19 and relevant outcomes in pregnant and recently pregnant women. We defined cohort studies as those that sampled participants on the basis of exposure, followed-up participants over time, and ascertained the outcomes.[23] The PROSPERO protocol provides a full list of the risk factors, clinical features, and outcomes evaluated.[19]

The sampling frames for detecting covid-19 included universal screening and testing, when all women were assessed for covid-19 using reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 or chest computed tomography; risk based testing on the basis of epidemiological history and clinical manifestations by National Health Commission of China (NHCC) guidelines[18]; and symptom based when testing was performed on women with symptoms and those with a history of contact with affected individuals. We defined the population as being selected when only specific groups of women were included, such as those undergoing caesarean section or in the third trimester. We categorised studies as a high risk group if only women with any pre-existing medical or obstetric risk factors were included, low risk if women did not have any risk factors, and any risk if all women were included.

Study quality assessment and data extraction

The quality of the comparative cohort studies was assessed for selection, comparability, and outcome ascertainment bias using the Newcastle Ottawa scale.[24] Studies achieving four stars for selection, two for comparability, and three for ascertainment of the outcome were considered to have a low risk of bias. Studies achieving two or three stars for selection, one for comparability, and two for outcome ascertainment were considered to have a medium risk of bias, and any study achieving one star for selection or outcome ascertainment, or zero for any of the three domains, was regarded as having a high risk of bias. We assessed the quality of studies reporting on the prevalence of clinical manifestations or outcomes for internal and external validity using an existing tool.[25] The following were considered as low risk of bias for external validity: representative of national population for relevant variables (population), representative of target population (sampling frame), random selection (selection bias), and more than 75% response rate in individuals with and without the outcome (non-response bias).[25] Two independent reviewers extracted data using a pre-piloted form.

Statistical analysis

We pooled the comparative dichotomous data using random effects meta-analysis and summarised the findings as odds ratios with 95% confidence intervals. To combine comparative continuous data with dichotomous data we transformed standardised mean differences to logarithm odds ratios, assuming a normal underlying distribution.[26] We pooled the dichotomous non-comparative data for rates of clinical manifestations and maternal and perinatal outcomes

as proportions with 95% confidence intervals using Dersimonian and Laird random effects meta-analysis after transforming data using Freeman-Tukey double arcsin transformation. Heterogeneity was reported as I^2 statistics. We undertook subgroup analysis by country status (high income *v* low and middle income), sampling frame (universal, risk based, and symptom based testing, including not reported), and risk status of women in the studies (high, low, any). Sensitivity analysis was performed by restricting the analysis to women with confirmed covid-19, study quality (high, low), and population (unselected, selected). All analyses were done with Stata (version 16).

Patient and public involvement

The study was supported by Katie's Team, a dedicated patients and public involvement group in Women's Health. The team was involved in the conduct, interpretation, and reporting of this living systematic review through participation in virtual meetings.

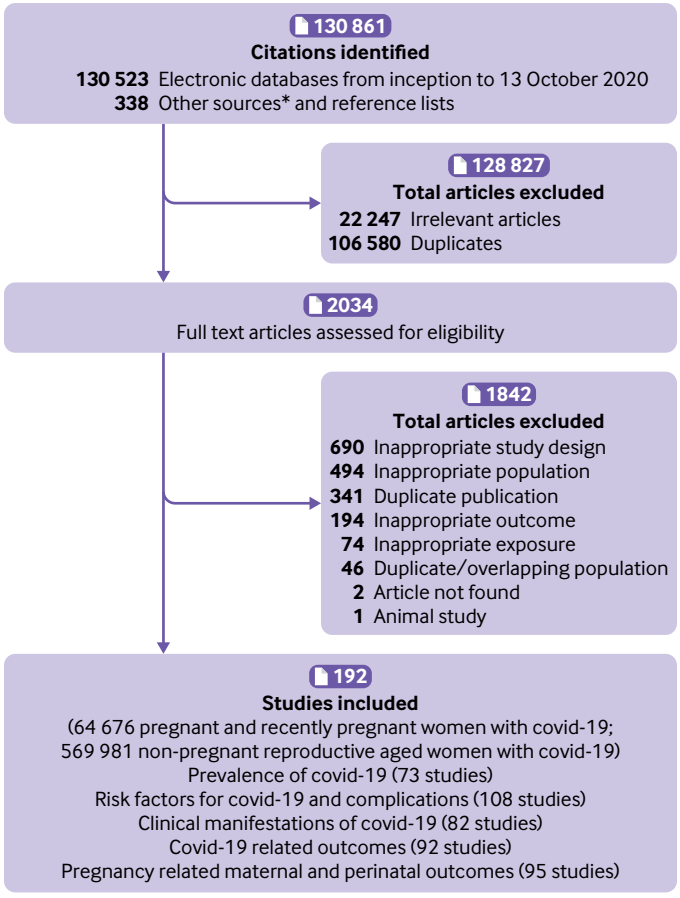

Fig 1 | Study selection process. *Twitter, national reports, blog by J Thornton, ObG Project, COVID-19 and Pregnancy Cases, www.obgproject.com/2020/04/07/covid-19-research-watch-with-dr-jim-thornton/; EPPI-Centre, COVID-19: a living systematic map of evidence, http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx; Norwegian Institute of Public Health, NIPH systematic and living map on COVID-19 evidence, www.nornesk.no/forskningskart/NIPH_mainMap.html; Johns Hopkins University Center for Humanitarian Health; COVID-19, Maternal and Child Health, Nutrition, http://hopkinshumanitarianhealth.org/empower/advocacy/covid-19/covid-19-children-and-nutrition/; ResearchGate, COVID-19 research community, www.researchgate.net/community/COVID-19; and Living Overview of the Evidence, Coronavirus disease (COVID-19), https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?population=5d062d5fc80dd41e58ba8459

Results

In the original review, 20 625 unique citations were identified after removing duplicates from 49 684 citations, with 77 cohort studies included in the review.[5] After removing duplicates from 130 861 citations, 24 281 unique citations were identified and 192 cohort studies (131 comparative, 61 non-comparative) were included in this update of the systematic review (fig 1). Two studies included in the original systematic review were excluded from the update because the information reported in those studies were reported in more recent and larger studies.[27 28]

Characteristics of included studies

Of 192 studies, 58 (30%) were from the United States; 31 from China (16%); 17 from Italy; 15 from Spain; eight from Turkey; seven each from the United Kingdom and India; five each from Brazil, France, and Mexico; three each from Iran and Portugal; two each from Belgium, Denmark, the Netherlands, Peru, and Sweden; and one each from Bangladesh, Chile, Estonia, Israel, Japan, Germany, Ireland, Kuwait, Pakistan, Qatar, Romania, Russia, and Switzerland. Most studies tested respiratory samples using RT-PCR to confirm the presence of SARS-CoV-2 (97%, 187/192); five studies tested for SARS-CoV-2 antibodies to confirm the diagnosis of covid-19; 43 studies additionally diagnosed covid-19 based only on clinical suspicion. Fourteen studies (602 565 women) compared pregnant populations with non-pregnant populations,[29-42] and 47 studies (26 017 women) compared pregnant women with covid-19 versus pregnant women without covid-19.[43-89] Eighty two cohort studies reported on clinical manifestations (41 396 pregnant, 434 348 non-pregnant women), 92 studies reported on covid-19 related maternal outcomes (49 443 pregnant, 568 386 non-pregnant women), and 95 studies reported on pregnancy related maternal (54 943 women) and perinatal outcomes (9466 neonates) (see appendix 3). The sampling frames included universal testing (89 studies), risk based NHCC guidelines (25 studies), and symptom based (32 studies) strategies. Forty six studies did not report the sampling strategy.

Quality of included studies

Overall, 56% (73/131) of the comparative cohort studies evaluated using the Newcastle Ottawa scale had an overall low risk of bias (see appendix 4a). Most (93%, 122/131) had a low risk of bias for study selection and nine (7%) had a medium risk. The risk of bias for comparability of cohorts was low in 59 of the studies (45%), medium in 71 (54%), and high in one (1%). For outcome assessment of the cohorts, 47 (36%) studies had a low risk of bias, 82 (63%) a medium risk, and two (2%) a high risk. Quality assessment of the prevalence studies for external validity showed a low risk of bias for representativeness in 15% (28/192) of

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the studies, sampling in 30% (57/192), selection in 82% (157/192), and non-response in 99% (191/192). For internal validity, there was low risk of bias for data collection in 96% (184/192) of the studies, case definition in 56% (108/192), measurement in 98% (189/192), differential verification in 95% (182/192), adequate follow-up in 35% (67/192), and appropriate numerator and denominator in 92% (177/192) (see appendix 4b).

Rates of covid-19 in pregnant and recently pregnant women

The overall rate of covid-19 diagnosis in pregnant and recently pregnant women attending or admitted to hospital for any reason was 10% (95% confidence interval 7% to 12%; 73 studies, 67 271 women; fig 2 and fig 3). Rates varied by sampling strategy: of the women sampled by universal screening, 7% (5% to 8%; 60 studies, 57 144 women) were diagnosed as having covid-19 compared with 28% (15% to 43%; 11 studies, 2436 women) of women sampled on the basis of symptoms. Most studies with a prevalence rate for covid-19 greater than 15% were from the US, except for two studies from the UK, and one each from Mexico, Turkey, France, and Iran.[90-95] One in 20 asymptomatic women (4%, 3% to 7%; 26 studies) attending or admitted to hospital had a diagnosis of covid-19 (see appendix 5a). Three quarters (73%, 62% to 82%; 38 studies) of the 906 pregnant women with covid-19 in the universal screening population were asymptomatic (see appendix 5b). Non-white ethnicity was associated with a diagnosis of covid-19 in pregnancy (odds ratio 1.66, 95% confidence interval 1.01 to 2.72; 11 studies; 8691 women); none of the other maternal factors assessed were associated with a diagnosis of covid-19 in pregnant women (see appendix 6a).

Clinical manifestations of covid-19 during pregnancy and after delivery

The most common symptoms reported by pregnant and recently pregnant women with suspected or confirmed covid-19 were fever (40%) and cough (41%); raised white cell count (26%), lymphopaenia (33%) and raised C reactive protein levels (49%) were the most common laboratory findings (fig 4). Compared with non-pregnant women of reproductive age with covid-19, pregnant and recently pregnant women with the disease were less likely to have symptoms (odds ratio 0.28, 95% confidence interval 0.13 to 0.62; 4 studies; 462 051 women), or manifest symptoms of fever (0.49, 0.38 to 0.63; 11 studies, 240 324 women), dyspnoea (0.76, 0.67 to 0.85; 11 studies; 240 324 women) and myalgia (0.53, 0.36 to 0.78; 8 studies, 240 105 women) (fig 5). Pregnant women with covid-19 had increased body mass index compared to non-pregnant women with the disease (1.98, 1.74 to 2.26; 2 studies, 461 897 women), and were more likely to have pre-existing diabetes (1.35, 1.24 to 1.46; 5 studies, 462 262 women) (see appendix 6b). Sensitivity analysis restricted to various sampling frames showed lower estimates of reported symptoms in the universal screening population and higher estimates of fever, cough, and dyspnoea in the symptom-based population (see appendix 7). The rates of clinical manifestations varied when the analysis was restricted to only women with RT-PCR confirmed covid-19, unselected populations, and women with any risk (see appendix 7).

Outcomes related to covid-19 in pregnant and recently pregnant women

Overall, 339 pregnant women (59 studies, 41 664 women) with confirmed covid-19 died from any cause (0.02%, 95% confidence interval 0.00% to 0.42%). Severe covid-19 infection as defined by the authors, was diagnosed in 10% (6% to 15%; 39 studies, 5621 women) of pregnant and recently pregnant women with suspected or confirmed covid-19; 4% (2% to 7%; 50 studies, 41 288 women) of pregnant women with covid-19 were admitted to an intensive care unit, 3% (1% to 5%; 31 studies, 42 026 women) required invasive ventilation, and 0.2% (0.0% to 0.7%; 13 studies, 33 521 women) required extracorporeal membrane oxygenation (ECMO) (fig 4). Appendix 8 provides the rates of complications by sampling strategy. Compared with non-pregnant women of reproductive age with covid-19, the odds of admission to the intensive care unit (odds ratio 2.13, 95% confidence interval 1.53 to 2.95; seven studies, 601 108 women) and need for invasive ventilation (2.59, 2.28 to 2.94; six studies, 601 044 women) and ECMO (2.02, 1.22 to 3.34; two studies, 461 936 women) were higher in pregnant and recently pregnant women (table 1).

Maternal risk factors associated with severe covid-19 were increasing age (odds ratio 1.83, 95% confidence interval 1.27 to 2.63; seven studies, 3561 women), high body mass index (2.37, 1.83 to 3.07; five studies, 3367 women), any pre-existing maternal comorbidity (1.81, 1.49 to 2.20; 3 studies; 2634 women), chronic hypertension (2.0, 1.14 to 3.48; two studies, 858 women), pre-eclampsia (4.21, 1.27 to 14.0; 4 studies; 274 women), and pre-existing diabetes (2.12, 1.62 to 2.78; 3 studies, 3333 women) (fig 6). Increasing maternal age (2.11, 1.69 to 2.63; 7 studies, 31 710 women), high body mass index (2.71, 1.10 to 6.63; 4 studies, 31 456 women), non-white ethnicity (1.66, 1.20 to 2.29; 4 studies, 31 543 women), pre-existing maternal comorbidity (1.70, 1.34 to 2.15; 5 studies, 31 512 women), chronic hypertension (4.72, 2.37 to 9.41; 5 studies, 31 433 women), pre-existing diabetes (4.67, 1.94 to 11.22; 6 studies, 31 473 women), and gestational diabetes (3.27, 1.55 to 6.89; 2 studies, 777 women), were associated with admission to an intensive care unit. Risk factors associated with maternal death and the need for invasive ventilation included: non-white ethnicity (1.61, 1.05 to 2.47; 3 studies, 31 469 women; 2.23, 1.25 to 3.97; 1 study, 669 women; respectively), and high body mass index (2.27, 1.20 to 4.31; 3 studies, 31 085 women; 6.61, 1.98 to 22.02; 2 studies, 485 women; respectively; table 2).

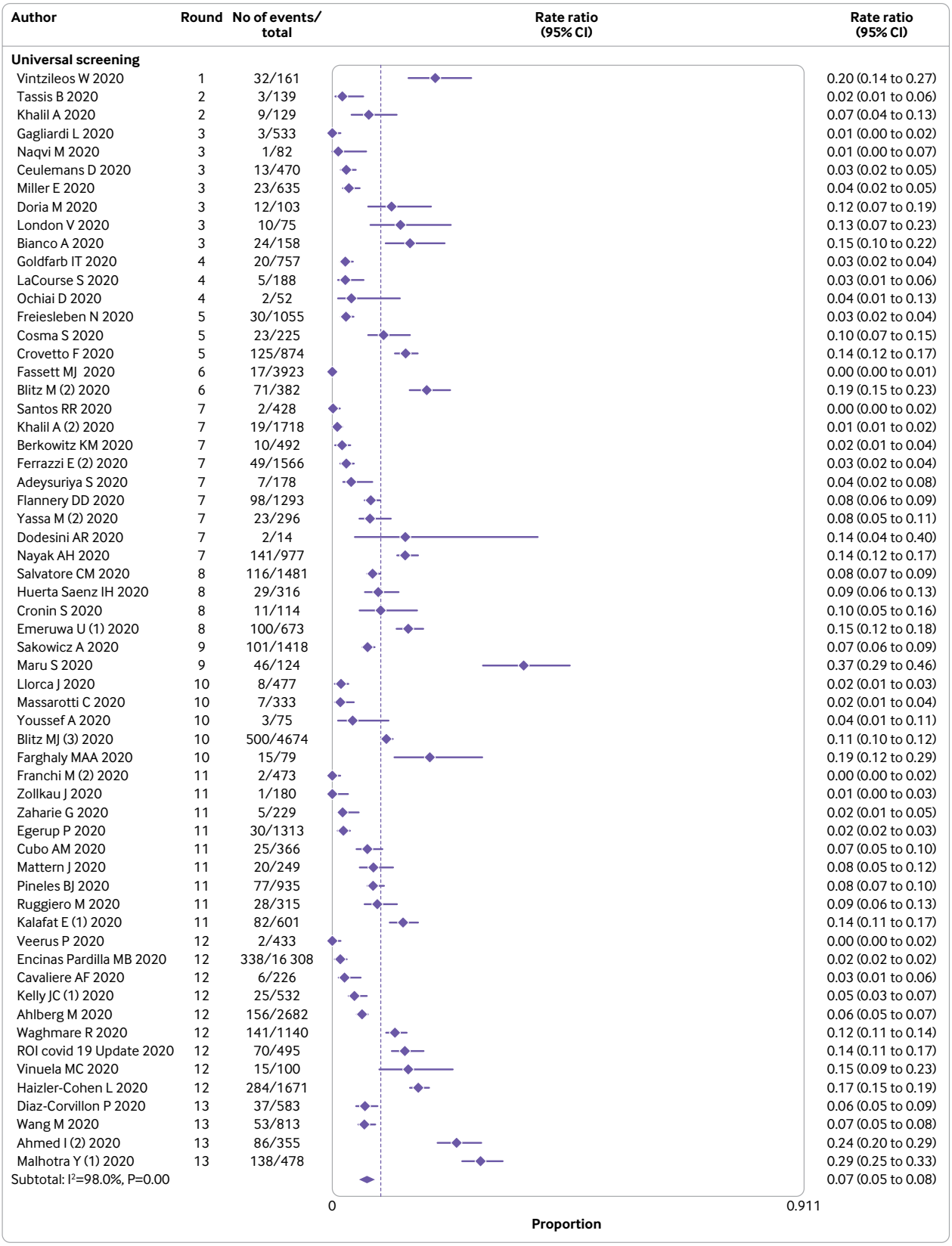

Fig 2 | Prevalence of severe acute respiratory syndrome coronavirus 2 in pregnant and recently pregnant women identified by universal screening. Meta-analysis includes one study (Liao 2020)[46] screened using National Health Commission China criteria with no events. Round number represents search strategy updates in the living systematic review. Overall estimate for sampling strategies can be found in figure 3

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Maternal and perinatal outcomes in pregnant and recently pregnant women with covid-19

In pregnant and recently pregnant women with covid-19 compared with pregnant and recently pregnant women without the disease, the odds of all cause mortality (odds ratio 2.85, 95% confidence interval 1.08 to 7.51; 8 studies, 4820 women), and admission to the intensive care unit (18.58, 95% confidence interval 7.53 to 45.82; 7 studies, 4990 women) were higher (table 1). In pregnant and recently pregnant women with covid-19, the overall rate of preterm birth was 17% (95% confidence interval 14% to 19%; 70 studies, 9369 women) and of spontaneous preterm birth was 6% (4% to 9%; 17 studies, 1629 women) (fig 4). Seventy two stillbirths (47 studies; 9020 offspring) and 41 neonatal deaths (51 studies; 8263 neonates) occurred among these women (fig 4). Compared to pregnant and recently pregnant women without the disease, pregnant women with covid-19 were at higher risk of any preterm birth (odds ratio 1.47, 95% confidence interval 1.14 to 1.91; 18 studies, 8549 women) and stillbirth (2.84, 95% confidence interval 1.25 to 6.45; 9 studies, 5794 women), although the overall number of stillbirth was small (only nine events in the covid-19 group).

Overall, 33% (95% confidence interval 24% to 43%; 41 studies, 3323 women) of neonates born to women with covid-19 were admitted to the neonatal intensive care unit (NICU) (fig 4), with a higher risk of NICU admission (odds ratio 4.89, 95% confidence interval 1.87 to 12.81; 10 studies, 5873 neonates) than neonates born to women without the disease. No differences were observed for other perinatal outcomes. Appendix 9 provides the rates of covid-19 related and pregnancy related outcomes for the individual studies.

Discussion

Compared with the original version of our living systematic review, the findings in this update remain consistent for prevalence of covid-19, rates of clinical manifestations, and outcomes in pregnant and recently pregnant women. One in 10 pregnant or recently pregnant women who are attending or admitted to hospital for any reason were diagnosed as having suspected or confirmed covid-19, although the rates vary by sampling strategy. Pregnant and recently pregnant women were more likely to be asymptomatic than non-pregnant women of reproductive age, and showed covid-19 related symptoms of fever, dyspnoea, and myalgia less often than non-pregnant women with covid-19. Whereas testing for SARS-CoV-2 in non-pregnant women is based on symptoms or contact history, testing in pregnant women is usually done when they are in hospital for reasons that might not be related to covid-19. Pregnant or recently pregnant women with covid-19 seem to be at increased risk of requiring admission to an intensive care unit, invasive ventilation, and extra corporeal membrane oxygenation compared to non-pregnant, reproductive

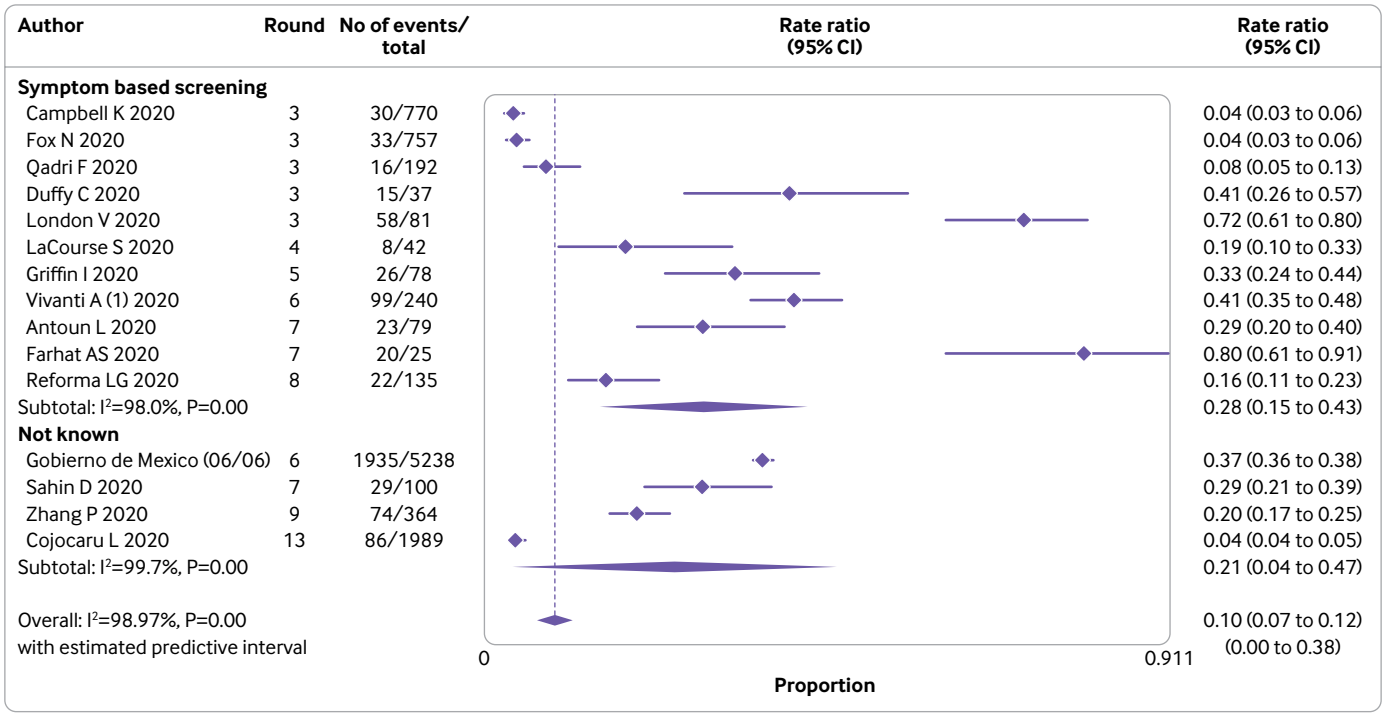

Fig 3 | Prevalence of severe acute respiratory syndrome coronavirus 2 in pregnant and recently pregnant women identified by symptom based screening and unknown sampling strategies. Meta-analysis includes one study (Liao 2020)[46] screened using National Health Commission China criteria with no events. Symptom based screening includes screening based on symptoms or history of contact with individuals with covid-19. Round number represents search strategy updates in the living systematic review. Overall estimate for sampling strategies also includes prevalence data identified by universal screening, which are shown in figure 2

aged women with covid-19. Increased maternal age, high body mass index, non-white ethnicity, and pre-existing comorbidities are associated with severe disease. Compared to pregnant women without covid-19, pregnant women with covid-19 are at increased risk of death, admission to the intensive care unit, delivering preterm, and their babies being admitted to the neonatal unit. The overall rates of stillbirth and neonatal death are low in women with suspected or confirmed covid-19. Substantial heterogeneity was observed in the estimates for rates of clinical manifestations and outcomes, which varied by sampling frames, participant selection, and risk status of the participants.

This update of the living systematic review includes more than double the number of studies included in the original version, and five times more pregnant women with covid-19. In addition to an increase in precision of the estimates for previously identified risk factors (age, body mass index, and comorbidities such as diabetes and chronic hypertension) for serious complications in pregnant and recently pregnant women with covid-19,

Clinical manifestation	Studies	No of events/ total	Proportion (95% CI)	Proportion (95% CI)	I^2 (%) (P value)	Range
Clinical manifestations						
Symptoms						
Fever	53	8033/39 429		0.40 (0.31 to 0.49)	99.2 (0.00)	(0.05-0.78)
Cough	53	10 379/39 641		0.41 (0.33 to 0.50)	99.1 (0.00)	(0.03-0.83)
Dyspnoea	42	5408/39 014		0.21 (0.15 to 0.28)	98.7 (0.00)	(0.00-0.62)
Myalgia	22	5196/34 663		0.19 (0.12 to 0.27)	98.4 (0.00)	(0.00-0.67)
Ageusia	10	83/776		0.14 (0.06 to 0.24)	89.6 (0.00)	(0.03-0.55)
Diarrhoea	29	2236/38 206		0.08 (0.06 to 0.10)	93.4 (0.00)	(0.00-0.53)
Laboratory findings						
Raised WCC	13	159/580		0.26 (0.14 to 0.40)	90.9 (0.00)	(0.00-0.65)
Lymphopaenia	27	659/1833		0.33 (0.25 to 0.41)	90.4 (0.00)	(0.00-0.90)
Thrombocytopaenia	13	91/1383		0.06 (0.02 to 0.10)	86.3 (0.00)	(0.00-0.35)
Abnormal LFTs	12	99/641		0.13 (0.06 to 0.21)	84.8 (0.00)	(0.00-0.36)
Raised PCT	5	60/261		0.21 (0.00 to 0.59)	96.6 (0.00)	(0.00-0.97)
Raised CRP	10	298/637		0.49 (0.36 to 0.62)	89.5 (0.00)	(0.10-0.71)
Radiological findings						
Ground glass appearance	14	338/569		0.69 (0.46 to 0.87)	96.3 (0.00)	(0.09-1.00)
Any CT abnormality	24	694/2120		0.64 (0.47 to 0.80)	98.2 (0.00)	(0.02-1.00)
Maternal and perinatal outcomes						
Clinical outcomes						
Covid-19 related outcomes						
All cause mortality	59	339/41 664		0.00 (0.00 to 0.00)	91.8 (0.00)	(0.00-0.08)
Admission to ICU	50	1373/41 288		0.04 (0.02 to 0.07)	97.5 (0.00)	(0.00-0.29)
Severe covid-19	39	633/5621		0.10 (0.06 to 0.15)	94.4 (0.00)	(0.00-1.00)
Invasive ventilation	31	668/42 026		0.03 (0.01 to 0.05)	97.5 (0.00)	(0.00-0.13)
ECMO	13	37/33 521		0.00 (0.00 to 0.00)	76.0 (0.00)	(0.00-0.01)
Oxygen/cannula	17	261/1522		0.22 (0.12 to 0.36)	96.2 (0.00)	(0.02-1.00)
ARDS	15	315/2348		0.07 (0.01 to 0.17)	97.8 (0.00)	(0.00-0.51)
Pneumonia	36	1257/7198		0.35 (0.26 to 0.45)	97.9 (0.00)	(0.00-1.00)
Cardiac/liver/renal failure	13	15/2046		0.00 (0.00 to 0.00)	28.3 (0.16)	(0.00-0.13)
Pregnancy related outcomes						
Preterm birth <37 weeks	70	1406/9396		0.17 (0.14 to 0.19)	79.6 (0.00)	(0.00-0.57)
Spontaneous preterm birth	17	104/1629		0.06 (0.04 to 0.09)	67.2 (0.00)	(0.00-0.31)
PPROM <37 weeks	18	58/993		0.05 (0.03 to 0.07)	29.7 (0.11)	(0.00-0.21)
Caesarean section	75	3760/9725		0.54 (0.49 to 0.58)	93.4 (0.00)	(0.00-1.00)
Vaginal delivery	74	5410/9708		0.46 (0.42 to 0.50)	91.8 (0.00)	(0.00-1.00)
Postpartum haemorrhage	15	91/908		0.08 (0.03 to 0.14)	86.7 (0.00)	(0.00-0.30)
Offspring outcomes						
Stillbirth	47	72/9020		0.00 (0.00 to 0.00)	31.2 (0.02)	(0.00-0.24)
Neonatal death	51	41/8263		0.00 (0.00 to 0.00)	33.0 (0.01)	(0.00-0.13)
Admission to neonatal unit	41	934/3323		0.33 (0.24 to 0.43)	96.8 (0.00)	(0.00-1.00)
Neonatal sepsis	6	9/499		0.01 (0.00 to 0.03)	22.6 (0.26)	(0.01-0.06)
Abnormal Apgar score	31	42/1479		0.01 (0.00 to 0.02)	34.8 (0.03)	(0.00-0.26)
Fetal distress	17	65/553		0.11 (0.08 to 0.15)	40.2 (0.04)	(0.04-0.50)

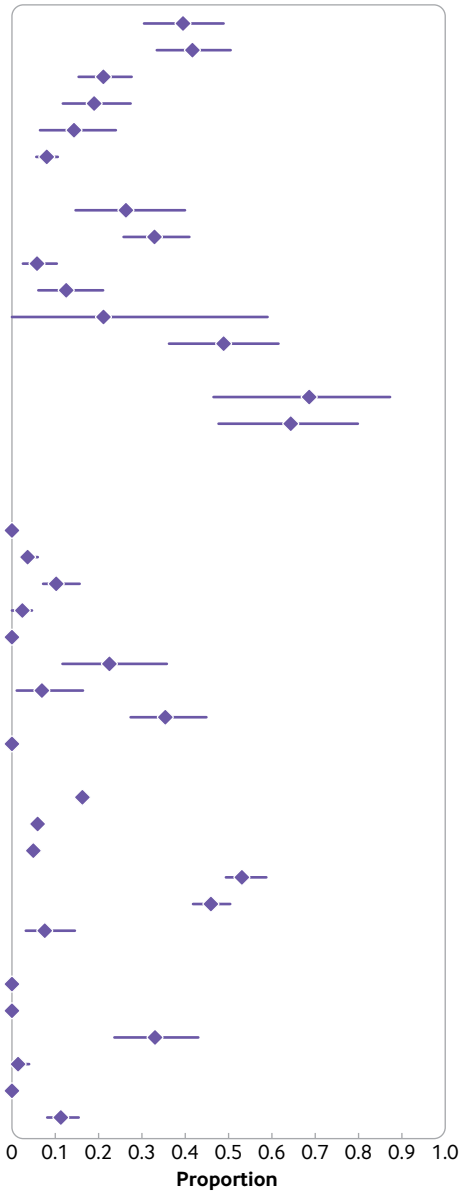

Fig 4 | Rates of clinical manifestations of coronavirus disease 2019 (covid-19) in pregnant women and recently pregnant women with suspected or confirmed covid-19 and associated maternal and perinatal outcomes. ECMO=extracorporeal membrane oxygenation; ARDS=acute respiratory distress syndrome; PPROM=preterm premature rupture of membranes; WCC=white cell count; LFT=liver function test; PCT=procalcitonin; CRP=C reactive protein; CT=computed tomography; ICU=intensive care unit

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in this update, we identified additional risk factors such as non-white ethnicity, and potential association with pregnancy specific conditions such as gestational diabetes and pre-eclampsia, and increased risk of adverse outcomes in pregnant women with covid-19 than without the disease.

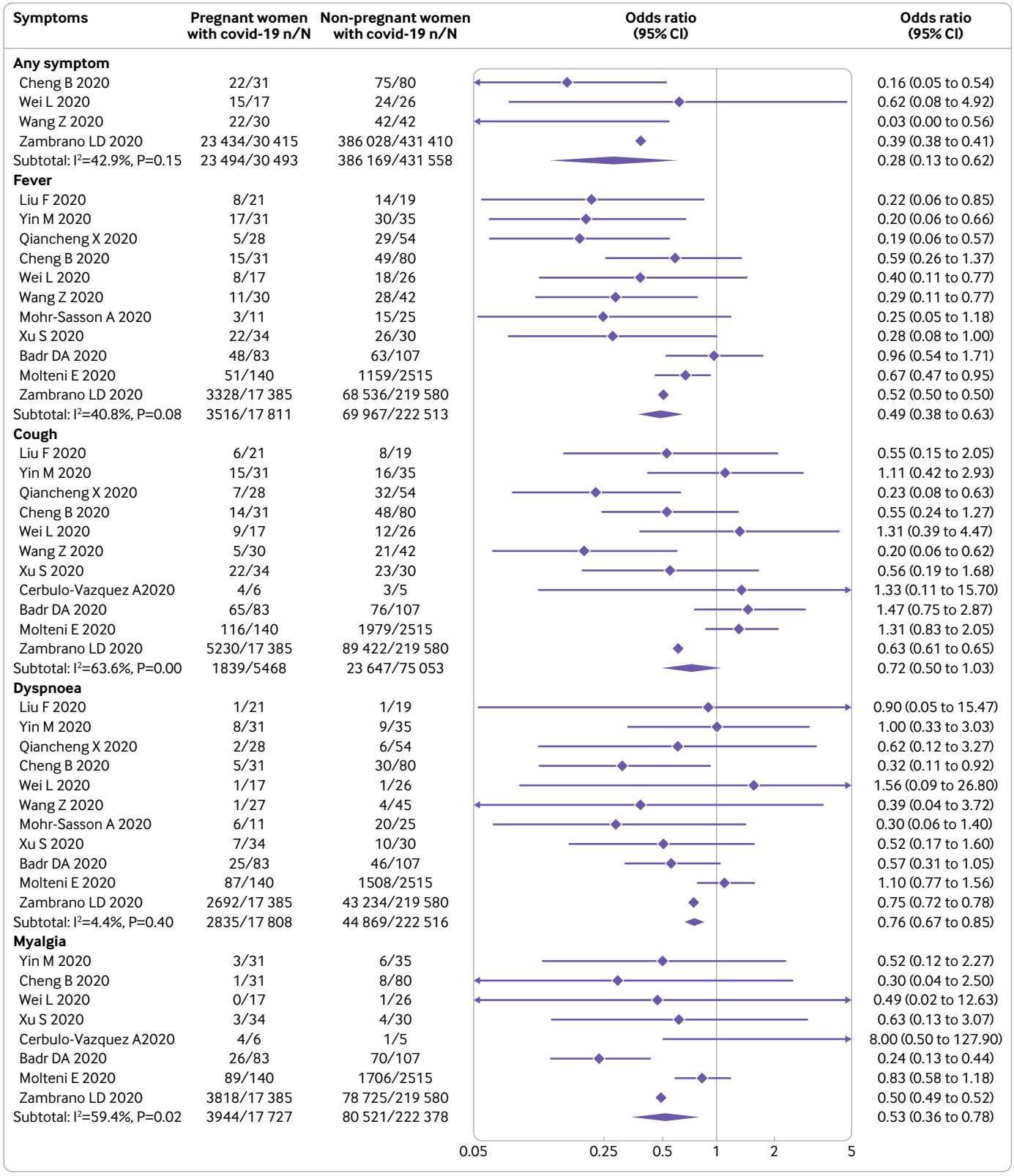

Fig 5 | Clinical manifestations of coronavirus disease 2019 (covid-19) in pregnant and recently pregnant women compared with non-pregnant women of reproductive age with covid-19

Strengths and limitations of this review

In this unprecedented pandemic situation, where evidence is rapidly produced and published in various formats, our living systematic review underpinned by robust methods and continually updated at regular intervals is relevant for several reasons. Firstly, it addresses important research questions relevant to clinical decision making and policies. Secondly, uncertainties remain for key outcomes that require further evidence. Thirdly, the rapid turnover of evidence in various formats requires assessments of study quality and regular updating of the findings. Finally, our living systematic review is producing strong evidence base for living guidelines on covid-19 and pregnancy.

We undertook a comprehensive search and coordinated our efforts with key organisations and research groups, such as WHO, the Cochrane Centre, and EPPI-Centre. To minimise risk of bias we restricted our meta-analysis to cohort studies, and we reported the quality of the included studies. By contacting the authors and obtaining reports not published in PubMed, we minimised the risk of missing relevant studies. Our systematic review has a large sample size and it is continuously increasing. Our living meta-analyses framework will enable us to rapidly update the findings as new data emerge. We undertook extensive work to ensure that duplicate data are not included. Our various comparative analyses allowed us to comprehensively assess the association between pregnancy and covid-19 related outcomes, covid-19 and pregnancy outcomes, risk factors for SARS-CoV-2 infection, and complications. Our review helps to understand the variations in estimates through sensitivity analyses by sampling strategies, population characteristics, and risk factors, and it provides confidence in the rates of reported outcomes. The update has allowed us to seamlessly incorporate new evidence from 115 studies and more than half a million women, published since our original review in June 2020.

Our systematic review also has limitations. The primary studies used varied sampling frames to identify women with covid-19, comprised women with suspected and confirmed covid-19, and primarily reported on pregnant women who required visits to hospital, including for childbirth, thereby affecting the generalisability of the estimates. Although our sensitivity analyses aimed to tackle some of these problems, the numbers and sample sizes of the individual studies were too small to identify differences between the subgroups. The timing of assessment of the clinical manifestations of disease was generally not available. The definitions of symptoms, tests, and outcomes were heterogeneous. Furthermore, poor reporting of the criteria for caesarean section, admissions to the neonatal unit, and the causes of preterm birth, made it difficult to disentangle iatrogenic effect from the true impact of the disease. There continues to be a paucity of comparative data to assess the risk of pregnancy complications in women with and without covid-19. Studies comparing maternal and perinatal outcomes in pregnant women with covid-19 against historical cohorts of pregnant women, could be biased owing to differences in the environment in which deliveries occur. During the pandemic, healthcare systems have faced increased pressure and strain on services, with resulting effects on service delivery and quality of care.[96 97] Lockdown measures, social distancing, and changes to livelihood have led to increased depression and anxiety, and reduction in physical activity and access or attendance

Table 1 | Outcomes in pregnant and recently pregnant women with coronavirus disease 2019 (covid-19)

Outcomes	No of studies	Women (No with event/No in group (%))		Odds ratio (95% CI)	I^2 (%)
		Pregnant women with covid-19	Comparison group		
Comparison group: non-pregnant women of reproductive age with covid-19					
All cause mortality	8	103/34 047 (0.3)	3388/567 075 (0.6)	0.96 (0.79 to 1.18)	0
ICU admission	7	616/34 035 (1.8)	9568/567 073 (1.7)	2.13 (1.54 to 2.95)	71.2
Invasive ventilation	6	270/34 001 (0.8)	3280/567 043 (0.6)	2.59 (2.28 to 2.94)	0
ECMO	2	17/30 446 (0.1)	120/431 490 (0.0)	2.02 (1.22 to 3.34)	0
Oxygen through nasal cannula	2	8/48 (16.7)	49/106 (46.2)	0.21 (0.04 to 1.13)	65.7
ARDS	1	0/17 (0)	0/26 (0)	1.51 (0.03 to 79.93)	NE
Major organ failure	1	0/17 (0)	0/26 (0)	1.51 (0.03 to 79.93)	NE
Comparison group: pregnant women without covid-19					
Maternal outcomes:					
All cause mortality	8*	8/1195 (0.7)	8/3625 (0.2)	2.85 (1.08 to 7.52)	0
ICU admission	7*	64/1508 (4.2)	4/3482 (0.1)	18.58 (7.53 to 45.82)	0
Preterm birth <37 weeks	18	147/1184 (12.4)	572/7365 (7.8)	1.47 (1.14 to 1.91)	18.6
Caesarean section	21*†	669/1854 (36.1)	4221/11842 (35.6)	1.12 (0.91 to 1.38)	57.6
Perinatal outcomes:					
Stillbirth	9*	9/1039 (0.9)	26/4755 (0.5)	2.84 (1.25 to 6.45)	0
Neonatal death	8*	4/970 (0.4)	5/3316 (0.2)	2.77 (0.92 to 8.37)	0
Admission to neonatal unit	10*	329/1285 (25.6)	519/4588 (11.3)	4.89 (1.87 to 12.81)	96.2
Abnormal Apgar score at 5 minutes	6	13/662 (2.0)	46/2823 (1.6)	1.38 (0.71 to 2.70)	0
Fetal distress	2	11/77 (14.3)	13/263 (4.9)	2.37 (0.77 to 7.31)	0

ICU=intensive care unit; ECMO=extracorporeal membrane oxygenation; ARDS=acute respiratory distress syndrome; NE=not estimable.
The denominator is number of pregnancies for all outcomes.
*Includes UK Obstetric Surveillance System[44] study with historical comparative cohort (694 women).
†Includes Gulersen et al 2020[60] with historical comparative cohort (50 women).

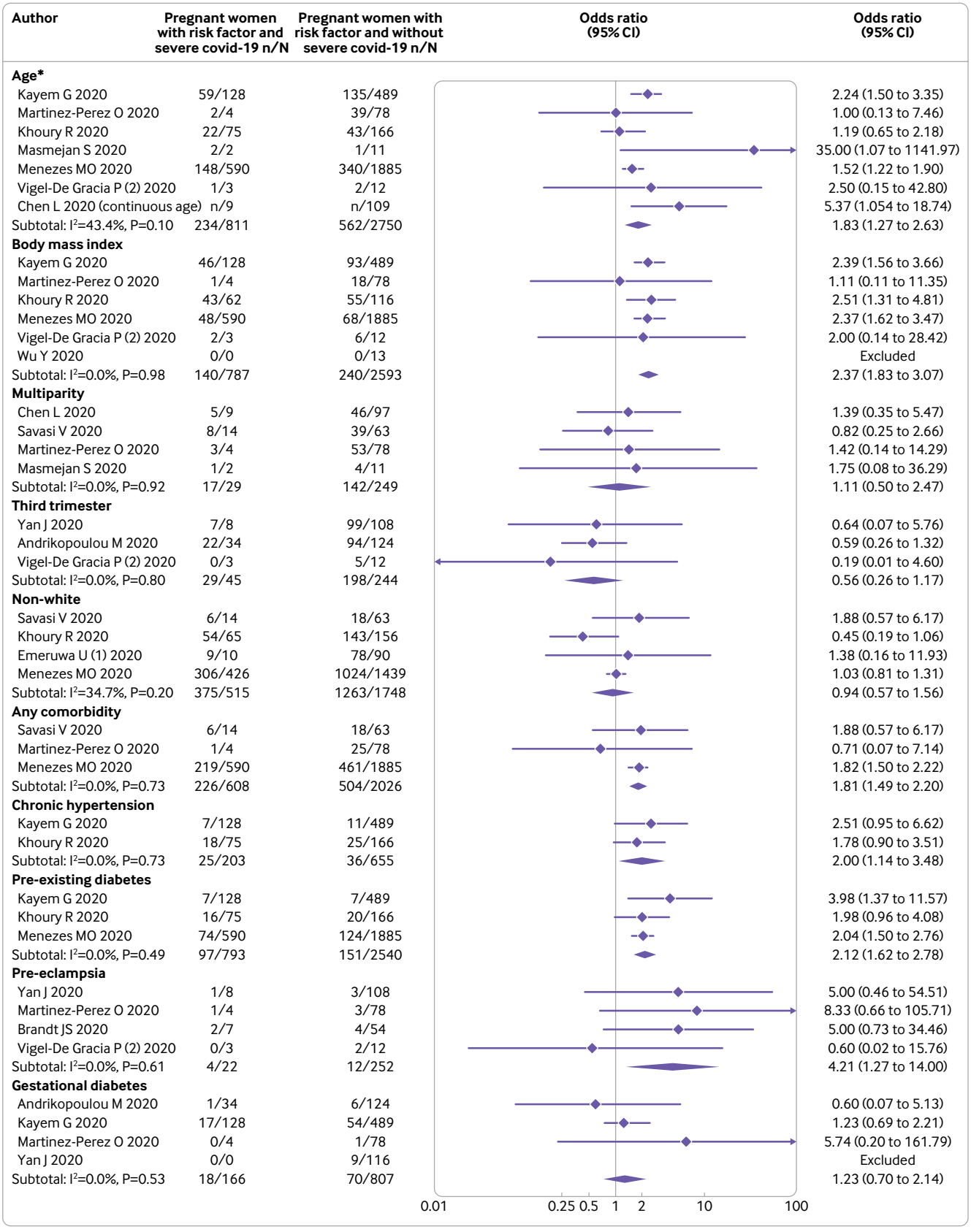

Fig 6 | Risk factors associated with severe coronavirus disease 2019 (covid-19) in pregnant and recently pregnant women. Symptom based screening: Savasi V, Kayem G; NHCC (National Health Commission China). Criteria based screening: Chen, Wu, Yan. All other studies used universal screening. Cut-off for age is 35 years or more, and for body mass index is 30 or more. *Includes one study with continuous measurement of risk factor

to healthcare facilities, which could increase the risk of maternal and perinatal complications.[98]

Not many studies reported outcomes by trimester for symptom onset, making it difficult to assess the rates of miscarriage and postpartum complications. For some outcomes, the findings were influenced by a single large study.[42] Many studies had to be excluded as we could not rule out potential overlap in the study populations.

Areas of uncertainty in some of our review findings will still need to be resolved in the next updates of the living systematic review. In seeking an efficient balance between resource consumption and the value the review provides to end users, we will make

Table 2 | Maternal characteristics associated with severe coronavirus disease 2019 (covid-19) and all cause death in pregnant and recently pregnant women with a diagnosis of covid-19

Maternal risk factors and outcomes	No of studies	Total No of women	Pregnant women (No with risk factor/No in group (%))		Odds ratio (95% CI)	I^2 (%)
			With outcome	Without outcome		
Age ≥35 years:						
Severe disease	7	3561	811*	2750*	1.83 (1.27 to 2.63)	43
ICU admission	7	31710	348*	31362*	2.11 (1.69 to 2.63)	0
Invasive ventilation	3	718	18*	700*	1.72 (0.60 to 4.97)	17
Maternal death	3	31710	176*	31525*	0.91 (0.22 to 3.72)	93
Multiparity:						
Severe disease	4	278	17/159 (10.7)	12/119 (10.1)	1.11 (0.50 to 2.46)	0
ICU admission	3	815	34/501(6.8)	17/314 (5.4)	1.34 (0.72 to 2.50)	0
Invasive ventilation	1	350	1/216 (0.5)	0/134 (0)	1.87 (0.08 to 46.30)	NE
Body mass index ≥30:						
Severe disease	5	3367	787*	2580*	2.37 (1.83 to 3.07)	0
ICU admission	4	31456	339*	31117*	2.71 (1.10 to 6.63)	63
Invasive ventilation	2	485	12*	4473*	6.61 (1.98 to 22.02)	0
Maternal death	3	31085	113*	30972*	2.27 (1.20 to 4.31)	0
Non-white ethnicity:						
Severe disease	4	2263	375/1638 (22.9)	140/625 (22.4)	0.94 (0.57 to 1.57)	35
ICU admission	4	31543	306/23996 (1.3)	158/7547 (2.1)	1.66 (1.20 to 2.29)	26
Invasive ventilation	1	669	20/134 (14.9)	39/535 (7.3)	2.23 (1.25 to 3.97)	NE
Maternal death	3	31469	110/24 124 (0.5)	36/7345 (0.5)	1.61 (1.05 to 2.47)	0
Any comorbidity:						
Severe disease	3	2634	226/730 (31.0)	382/1904 (20.1)	1.81 (1.49 to 2.20)	0
ICU admission	5	31512	106/6639 (1.6)	226/24 873.9)	1.70 (1.34 to 2.15)	0
Invasive ventilation	3	715	7/71 (9.9)	11/644(1.7)	5.26 (1.76 to 15.68)	0
Maternal death	2	30639	19/6493 (0.3)	33/24 146 (0.1)	2.53 (0.78 to 8.17)	50
Chronic hypertension:						
Severe disease	2	858	25/61 (41.0)	178/797 (22.3)	2.00 (1.14 to 3.48)	0
ICU admission	5	31433	15/262 (5.7)	319/31 171 (1.0)	4.72 (2.37 to 9.41)	13
Invasive ventilation	2	484	5/24 (20.8)	7/460 (1.5)	63.82 (9.69 to 420.45)	0
Maternal death	3	31011	7/249 (2.8)	81/30762 (0.3)	4.25 (1.82 to 9.95)	0
Pre-existing diabetes:						
Severe disease	3	3333	97/248 (39.1)	696/3085 (22.6)	2.12 (1.62 to 2.78)	0
ICU admission	6	31473	36/638 (5.6)	306/30835 (1.0)	4.67 (1.94 to 11.22)	38
Invasive ventilation	2	482	2/12 (16.7)	9/470 (1.9)	18.61 (0.26 to 1324.16)	78
Maternal death	2	30723	11/620 (1.8)	41/30 103 (0.1)	14.88 (4.19 to 52.81)	53
Asthma:						
Severe disease	4	3332	39/148 (26.4)	717/3184 (22.5)	1.43 (0.85 to 2.38)	28
ICU admission	1	100	2/9 (22.2)	8/91 (8.8)	2.96 (0.53 to 16.74)	NE
Maternal death	3	889	5/39 (12.8)	63/850 (7.4)	1.68 (0.66 to 4.24)	0
Smoking:						
Severe disease	3	776	5/23 (21.7)	141/753 (18.7)	1.67 (0.64 to 4.40)	0
ICU admission	2	142	1/4 (25.0)	17/138 (12.3)	2.92 (0.35 to 24.23)	0
Maternal death	1	308	0/10 (0)	7/298 (2.3)	1.85 (0.10 to 34.60)	NE
Gestation ≥28 weeks:						
Severe disease	3	289	29/227 (12.8)	16/62 (25.8)	0.56 (0.27 to 1.17)	0
Maternal death	1	721	46/495 (9.3)	23/226 (10.2)	0.90 (0.53 to 1.53)	NE
Gestational diabetes:						
Severe disease	4	973	18/88 (20.5)	148/885 (16.7)	1.23 (0.70 to 2.14)	0
ICU admission	2	777	11/81 (13.6)	31/696 (4.5)	3.27 (1.55 to 6.89)	0
Invasive ventilation	1	350	0/32 (0)	0/318 (0)	—	NE
Pre-eclampsia:						
Severe disease	4	274	4/16 (25.0)	18/258 (7.0)	4.21 (1.27 to 14.00)	0
ICU admission	1	42	6/6 (100.0)	2/36 (5.6)	179.40 (7.69 to 4186.05)	NE

ICU=intensive care unit; NE=not estimable.
*Includes one or more studies with continuous measurement of risk factor.

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decisions about the pacing of the updates of our living systematic review using a formal framework for decision making. We will use a mixed approach based on the Ottawa method to identify quantitative or qualitative signals for the need of an update,[99] and a more complex statistical prediction tool to estimate the probability that new studies identified would change the review conclusions.[100]

Comparison with existing evidence

Between the publication of the original living systematic review and this update, estimates for the prevalence of covid-19, and rates of clinical manifestations and outcomes of pregnant and recently pregnant women with covid-19 have remained similar, with improved precision in the findings. The rates for postpartum haemorrhage and admission to the neonatal unit appear to be slightly increased from the first version, while the rate of maternal pneumonia appears to be lower. High heterogeneity remains in the estimates for rates of clinical manifestations and outcomes.

We found that the same risk factors for severe covid-19 identified in the original version of the living systematic review remained associated with severe covid-19 with increased precision. Additional risk factors for severe disease, such as non-white ethnicity identified in this update, were also identified from large cohort studies such as the UK Obstetric Surveillance System and the US CDC surveillance report.[42 101] Our findings are consistent with the reports of disproportionately high rates of severe covid-19 in non-pregnant ethnic minority populations,[102] and in other areas of maternity care.[103 104] The observed disparity could be attributed to associated comorbidities, socioeconomic characteristics, and factors related to access to and quality of care in the preconception, pregnancy, and postpartum periods.[105] The multifaceted contributors to ethnic disparities need to be investigated to reduce mortality and morbidity related to both covid-19 and pregnancy.

Our review update also identified an increased risk for maternal death, need for maternal admission to the intensive care unit, and stillbirth in pregnant women with covid-19 compared to pregnant women without the disease. However, our confidence in these estimates is not high, owing to the small numbers of events in both groups. Further data are still needed to robustly assess these outcomes, along with the emerging data on increased risk of severe outcomes such as the need for ECMO.[42]

Alongside the spread of the pandemic, a shift has occurred in the types of studies published, with initial studies involving pregnant women from epidemic regions in China, followed by reports of large regional and national datasets from the US, UK, Netherlands, Spain, and, more recently, Latin American countries. The study design has also changed from initial small case series and case reports to large observational data, with recent studies also providing comparative data.

The prevalence of covid-19 varied widely between studies, particularly when sampling was done based on symptoms or history of contact, highlighting the variations in criteria for testing. The current update includes 50 new studies from 11 additional countries on the prevalence of covid-19 in pregnancy. Despite the addition of five times more studies between the original version of our living systematic review and this update, from diverse populations globally, the prevalence of covid-19 in pregnant and recently pregnant women remains unchanged. Unlike the general population who are mostly tested for SARS-CoV-2 on the basis of symptoms or contact history, universal screening of all pregnant women attending the hospital for any reason could contribute to the consistency in the findings. However, the true prevalence of covid-19 in pregnancy is likely to be lower than the current estimate if all pregnant women, including those not attending the hospital are included.

In the recent cohort study of all individuals admitted with covid-19 in the UK, the cluster of respiratory symptoms of cough, fever, and breathlessness were observed in more than two thirds of individuals,[106] similar to reported rates in the US and China.[107-109] But in our review, fewer pregnant and recently pregnant women with covid-19 manifested these symptoms than the non-pregnant population, indicating possible high rates of asymptomatic presentation in this population. This is likely because of the strategy of universal screening for covid-19 in pregnancy and the low thresholds for testing in pregnant women than in non-pregnant women. Despite the potential higher possibility of universal screening to detect pregnant women with mild disease, we observed an increase in admissions to the intensive care unit and need for invasive ventilation compared with non-pregnant women of reproductive age with covid-19. The findings were mainly influenced by the recently updated large Centers for Disease Control and Prevention report from the US,[42] and a report from the Mexican General Directorate of Epidemiology registry.[41]

By accessing the unpublished data from our collaborators, we were able to include both women with and without symptoms from the US CDC surveillance data, in addition to the women with symptoms only who were included in the published report.[42] Pregnancy status was not ascertained in a large proportion of women of reproductive age in the CDC report, which could affect the estimates. Furthermore, the outcomes for which the data were missing from the report were considered to be absent, potentially leading to bias. The report from the Mexican General Directorate of Epidemiology registry, available only as a preprint, included only women with symptoms who might be at high risk of complications. We recommend that studies comparing covid-19 related outcomes in pregnant versus non-pregnant women report the relevant estimates for both women with and without symptoms to avoid overestimation of the risk of complications due to selective reporting. The pooled estimates for severe covid-19 and admission to an intensive care

unit were, however, still relatively high in the non-comparative data, indicative of a potential high risk in pregnancy. This is supported by the recent analysis in a Swedish study suggesting a high risk of admission to an intensive care unit and invasive ventilation in pregnant women compared to non-pregnant women.[110]

Similar to the general population, high body mass index and pre-existing comorbidity seemed to be risk factors for severity of covid-19 in pregnancy, including admission to an intensive care unit and invasive ventilation.[106] Complications related to covid-19 did not seem to be increased in women presenting in the third trimester versus earlier in pregnancy or in multiparous versus primiparous women—but existing sample sizes are not large. Both chronic hypertension and pre-existing diabetes were associated with maternal death in pregnant women with covid-19, which are known risk factors in the general population. But it is not known if covid-19 was the direct cause of death for these women, and the numbers of studies are small. We observed an increase in rates of preterm birth in pregnant women with covid-19 compared with pregnant women without the disease. These preterm births could have been medically indicated, as the overall rates of spontaneous preterm births in pregnant women with covid-19 was broadly similar to those observed in the pre-pandemic period. Although about 50% of pregnant women underwent caesarean section in the non-comparative studies, we did not find a statistically significant difference in comparative studies of pregnant women with and without covid-19. The precision of the estimates is expected to improve with the publication of more data in the future. The overall rates of stillbirths and neonatal deaths do not seem to be higher than the background rates. The indications for admissions to the neonatal unit, observed in about a third of neonates delivered to mothers with covid-19, have not been reported. Local policies on observation and quarantine of infants with exposure to SARS-CoV-2 might have influenced these rates.

Relevance for clinical practice and research

Based on existing data, healthcare professionals should be aware that pregnant and recently pregnant women with covid-19 might manifest fewer symptoms than the general population, with the overall pattern similar to that of the general population. Pregnant women should be informed of the increase in severity of covid-19 including admission to intensive care units, need for ECMO and invasive ventilation compared with non-pregnant women, and encouraged to undertake safety measures to reduce the risk of infection. Pregnant women with pre-existing comorbidities will need to be considered as a high risk group for covid-19, along with those who are obese and of older maternal age. Healthcare professionals need to be aware of the increased risk of severe covid-19 in pregnant and recently pregnant women of non-white ethnic origin, to plan close monitoring and have a low threshold for escalation of care. Clinicians will need to balance the need for regular multidisciplinary antenatal care to manage women with pre-existing comorbidities against unnecessary exposure to the virus, through virtual clinic appointments when possible. Pregnant women with covid-19 before term gestation might need to be managed in a unit with facilities to care for preterm neonates.

Further data are still needed to assess robustly if pregnancy related maternal and neonatal complications are increased in women with covid-19 compared to pregnant women without the disease. Similarly, the association between pregnancy specific risk factors such as pre-eclampsia and gestational diabetes on covid-19 related outcomes needs further evaluation. Pre-eclampsia was reported to be associated with severe covid-19 in small studies, but this requires further assessment as the clinical and laboratory presentation of severe pre-eclampsia could mimic worsening covid-19.[111] Robust collection of maternal data by trimester of exposure, including the periconception period, is required to determine the effects of covid-19 on early pregnancy outcomes, fetal growth, and risk of miscarriage or stillbirth. We need detailed reporting of outcomes by ethnicity to quantify the risk of severe covid-19 in women from different ethnicities. Qualitative studies on behaviour and attitude to the pandemic can disentangle the relative importance of factors behind the ethnic disparities observed in the severity of covid-19.

Systematic reviews are considered to be the highest quality evidence informing guidelines, and poor quality reviews will have a direct impact on clinical care. Despite the urgent need for evidence on the impact of covid-19 in pregnant women, systematic reviews and meta-analyses still need to adhere to the reporting guidelines on search criteria, quality assessment, and analysis. This is particularly important as large numbers of non-peer reviewed scientific papers and reports are currently available in the public domain in multiple versions. Primary studies need to explicitly state if duplicate data have been included to avoid double counting of participants in evidence synthesis. Individual participant data meta-analysis of the emerging cohorts is critical to assess both differential presentation and outcomes by underlying risk factors, and to determine the differential effects of interventions to reduce the rates of complications. With the establishment of several national and global prospective cohorts, we expect the sample size of our meta-analysis to increase further in the coming months. Our living systematic review and meta-analysis with its regular search and analyses updates is ideally placed to assess the impact of new findings on the rapidly growing evidence base.

AUTHOR AFFILIATIONS

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK

[2]WHO Collaborating Centre for Global Women's Health, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

[3]Clinical Biostatistics Unit, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain

[4]CIBER Epidemiology and Public Health (CIBERESP), Madrid, Spain
[5]UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland
[6]Birmingham Medical School, University of Birmingham, Birmingham, UK
[7]Division of Birth Cohort Study, Guangzhou Women and Children's Medical Centre, Guangzhou Medical University, Guangzhou, China
[8]Department of Woman and Child Health Care, Guangzhou Women and Children's Medical Centre, Guangzhou Medical University, Guangzhou, China
[9]Department of Obstetrics and Gynaecology, Guangzhou Women and Children's Medical Centre, Guangzhou Medical University, Guangzhou, China
[10]Netherlands Satellite of the Cochrane Gynaecology and Fertility Group, Amsterdam University Medical Centre, Amsterdam, Netherlands
[11]Department of Obstetrics and Gynaecology, Amsterdam University Medical Centre, Amsterdam, Netherlands
[12]Blizard Institute, Queen Mary University of London, London, UK
[13]Barts Health NHS Trust, London, UK
[14]St George's, University of London, London, UK
[15]Sexual and Reproductive Health care, Catalan Health Service, Barcelona, Catalonia, Spain
[16]Elizabeth Glaser Paediatric AIDS Foundation, Washington, DC, USA
[17]Women's Health Research Unit, Queen Mary University of London, London, UK
[18]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

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The corresponding author (ST) affirms 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 have been disclosed.

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Supplementary information: Appendices 1-9