Journal Pre-proof

Clinical risk factors of adverse outcomes among women with COVID-19 in the pregnancy and postpartum period: A sequential, prospective meta-analysis

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Conflicts of Interest:

Clare Whitehead declares a relationship with the following entities, Ferring Pharmaceuticals COVID19 Investigational, Grant, NHMRC Fellowship (salary support).

Alice Panchaud declares the following research grants to institution: "H2020-Grant - Consortium member of Innovative medicine initiative call 13 topic 9 « ConcePTION », Efficacy and safety studies on Medicines EMA/2017/09/PE/11, Lot 4, WP 2 lead, Safety monitoring of COVID-19 vaccines in the EU – Reopening of competition no. 20 under a framework contract following procurement procedure EMA/2017/09/PE (Lot 3) (Euro 110'000.-), Federal Office of Public Health (207'000 CHF)"

Edward Mullins and Christoph Lees declare a relationship with the following entities National Institute for Health Research (Project grant for PAN COVID study)

Deborah Money declares a relationship with the following entities, Canadian Institutes of Health Research (payments to my institution only), Public Health Agency of Canada (payments to my institution only), BC Women's Foundation (payments to my institution only) and is a Member of the COVID-19 Immunity Task Force sponsored by the Canadian government.

Torri D. Metz declares a relationship with the following entities, Pfizer (site Principal Investigator for SARS-CoV-2 vaccination in pregnancy study, money paid to institution and member of Medical Advisory Board for SARS-CoV-2 vaccination in pregnancy study, money

paid to me), NICHD (subcommittee Chair for the NICHD Maternal-Fetal Medicine Units Network Gestational Research Assessments of COVID-19 (GRAVID) study), and Society for Maternal-Fetal Medicine (board member).

Erica Lokken declares a relationship with the following entity, US NIH (paid institution) and is an employee of AbbVie, Inc, but was employed at the University of Washington at the time of the study.

Karen L. Kotloff declares a relationship with the following entity, Bill and Melinda Gates Foundation.

Siran He declares a relationship with the following entity, Bill and Melinda Gates Foundation (payments made to my institution).

Valerie Flaherman declares a relationship with the following entities, Bill and Melinda Gates Foundation (payments to my institution), Yellow Chair Foundation (payments to my institution), Robert Woods Johnson Foundation (payments to my institution), CDC Foundation, California Health Care Foundation (payments to my institution), Tara Health Foundation (payments to my institution), UCSF Women's Health Center of Excellence (payments to my institution) and California Department of Health Care Services (payments made to my institution).

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Marta Nunes declares a relationship with the following entities: BMGF (project grant made to institution) BMGF, EDCTP, Sanofi, AstraZeneca, Pfizer (research grants made to institution), Sanofi Pasteur (Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events), and Sanofi Pasteur and Pfizer (Payment for expert testimony),

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Condensation

Individual patient data meta-analysis of >21,000 pregnancies identifies risk factors for adverse outcomes linked to COVID-19 during pregnancy, including chronic disease, co-infections, and nutritional status.

Short Title

Individual patient data meta-analysis: Risk factors among COVID-19 pregnancies

AJOG at a Glance

Why was this study conducted?

Pregnant women are at risk for severe SARS-CoV-2 complications, and those with co-morbidities might be at even higher risk for adverse outcomes. Further, some vaccines and treatment are only recommended for those at highest risk. There is no global consensus about what risk factors signify such risk. Heterogeneity in the design and analysis of published studies and limited global data further complicates definitive guidance.

What are the key findings?

We pooled individual patient data from 21 studies (33 countries, 21,977 pregnancies) and found that comorbidities, nutritional status, and older maternal age were associated with severe COVID-19-related outcomes (ICU admission, ventilation, mortality), adverse pregnancy outcomes, and fetal/neonatal morbidity and mortality.

What does this study add to what is already known?

We pooled and re-analyzed data from global collaborators. We assessed high-priority risk factors and two dozen, consistently defined maternal and newborn outcomes. Given the large sample, including data from low- and middle-income countries, we generated estimates on rare outcomes (maternal mortality, stillbirth) and risk factors (anemia, underweight, HIV) where data has been lacking.

Abstract:

Objective: This sequential, prospective meta-analysis (sPMA) sought to identify risk factors among pregnant and postpartum women with COVID-19 for adverse outcomes related to: disease severity, maternal morbidities, neonatal mortality and morbidity, adverse birth outcomes.

Data sources: We prospectively invited study investigators to join the sPMA via professional research networks beginning in March 2020.

Study eligibility criteria: Eligible studies included those recruiting at least 25 consecutive cases of COVID-19 in pregnancy within a defined catchment area.

Study appraisal and synthesis methods: We included individual patient data from 21 participating studies. Data quality was assessed, and harmonized variables for risk factors and outcomes were constructed. Duplicate cases were removed. Pooled estimates for the absolute and relative risk of adverse outcomes comparing those with and without each risk factor were generated using a two-stage meta-analysis.

Results: We collected data from 33 countries and territories, including 21,977 cases of SARS-CoV-2 infection in pregnancy or postpartum. We found that women with comorbidities (pre-existing diabetes, hypertension, cardiovascular disease) versus those without were at higher risk for COVID-19 severity and pregnancy health outcomes (fetal death, preterm birth, low birthweight). Participants with COVID-19 and HIV were 1.74 times (95% CI: 1.12, 2.71) more likely to be admitted to the ICU. Pregnant women who were underweight before pregnancy were

at higher risk of ICU admission (RR 5.53, 95% CI: 2.27, 13.44), ventilation (RR 9.36, 95% CI: 3.87, 22.63), and pregnancy-related death (RR 14.10, 95% CI: 2.83, 70.36). Pre-pregnancy obesity was also a risk factor for severe COVID-19 outcomes including ICU admission (RR 1.81, 95% CI: 1.26,2.60), ventilation (RR 2.05, 95% CI: 1.20,3.51), any critical care (RR 1.89, 95% CI: 1.28,2.77), and pneumonia (RR 1.66, 95% CI: 1.18,2.33). Anemic pregnant women with COVID-19 also had increased risk of ICU admission (RR 1.63, 95% CI: 1.25, 2.11) and death (RR 2.36, 95% CI: 1.15, 4.81).

Conclusion: We found that pregnant women with comorbidities including diabetes, hypertension, and cardiovascular disease were at increased risk for severe COVID-19-related outcomes, maternal morbidities, and adverse birth outcomes. We also identified several less commonly-known risk factors, including HIV infection, pre-pregnancy underweight, and anemia. Although pregnant women are already considered a high-risk population, special priority for prevention and treatment should be given to pregnant women with these additional risk factors.

Keywords: SARS-CoV-2, Coronavirus Disease 2019, Pregnancy, Maternal Mortality, Neonatal Mortality, Preterm Birth, Small-for-gestational Age, Pneumonia

Introduction

Since the onset of the novel coronavirus 2019 (COVID-19) pandemic, the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) classified pregnant women as a group at higher risk of severe complications from SARS-CoV-2 infection, compared to non-pregnant people [1,2]. Despite known risk, pregnant women have been widely excluded from pharmaceutical clinical trials, resulting in an under-documentation of the physiology, case count, complications, and consequences of COVID-19 in pregnancy.

Initial evidence showed that SARS-CoV-2 infection during pregnancy is linked to increased likelihood of adverse maternal, fetal, and neonatal outcomes [3–5]. A systematic review of 42 studies (N=438,548) found that pregnant women with SARS-CoV-2 infection had significantly higher odds of preeclampsia, preterm birth, stillbirth, and intensive care unit (ICU) admission, compared to those not infected [5]. Although vertical transmission of COVID-19 from mother to fetus reportedly occurs in a low percentage of cases, neonates can be negatively impacted by maternal infection in other ways [6 7]. In two systematic reviews of 42 and 66 studies, neonates of mothers with confirmed COVID-19 had three times higher odds of Neonatal Intensive Care Unit (NICU) admission than those born to mothers not infected [5,6].

Among pregnant women, multiple risk factors for severe SARS-CoV-2 infection have been identified [3,8]. The Surveillance for Emerging Threats to Mothers and Babies Network in the United States (N=7950) determined that pregnant women over 25 years of age, with pre-pregnancy obesity, chronic lung disease, chronic hypertension, and pregestational diabetes mellitus had a 32% to 85% increased risk of moderate-to-severe COVID-19, compared to pregnant women free

of these conditions [9]. Pregnant women with three or more underlying health conditions had over twice the risk of moderate-to-severe COVID-19 illness than those with no comorbidities [9].

In the general population, nutritional status has been introduced as a potential risk factor for severe COVID-19. A meta-analysis of seven studies (N=9,912) found that among people with COVID-19, those with anemia had 2.44 higher odds of severe illness than non-anemic people [10]. A scientific review found sufficient intake of micronutrients, proteins, diet fiber, short-chain fatty acids, and omega-3 polyunsaturated fatty acids may act as a protective factor against severe illness in COVID-19 patients [11]. Further research is required for pregnant women, for whom nutritional guidance would be particularly useful.

There is an urgent need to pool high-quality and internationally representative data assessing the underlying risk factors and outcomes linked to COVID-19 in pregnancy. Currently, scarcity of similarly collected and analyzed data hampers our ability to make strong recommendations for the introduction and prioritization of new pharmaceutical interventions in pregnancy. The primary aim of this sequential, prospective meta-analysis (sPMA) is to accrue harmonized global data to inform policy and practice, grounded in the epidemiology of COVID-19 in the pregnancy, peripartum, and postnatal periods.

Objectives

In this analysis, we sought to identify risk factors among pregnant and postpartum women with SARS-CoV-2 infection for adverse outcomes related to: i) disease severity; ii) maternal morbidities; iii) fetal and neonatal mortality and morbidity; iv) adverse birth outcomes.

Methods

We registered the protocol for this prospective meta-analysis via PROSPERO (ID: 188955) in May 2020, and the full protocol has been published elsewhere [12]. The meta-analysis project was determined to be exempt from IRB review.

Language. Not all of those who are pregnant or give birth identify as women; throughout this document, the term 'pregnant women' should be taken to be inclusive of all persons who have the biological capability to carry a pregnancy regardless of gender identity.

Eligibility criteria. Eligible studies include registries and single- or multi-site cohort studies that recruited pregnant and recently postpartum women with confirmed or suspected COVID-19. They must have enrolled at least 25 women within a defined catchment area. We included data from those with infection onset up to 42 days after the pregnancy outcome.

Study selection. We invited principal investigators of studies of COVID-19 in pregnancy to join the sPMA via professional research networks and collaborations with key stakeholder networks.

Data extraction and IPD Integrity. Following identification of eligible studies, investigators shared individual patient data (IPD) with the technical team for review and analysis. The technical team processed data to review data quality, identify outliers, and reconstruct variables to align with harmonized definitions of outcomes as defined in our protocol. We shared results with investigators for review and approval. For study sites unable to share IPD directly, the technical

team worked with investigators to implement a common set of Stata codes to complete the same process of review, data quality checks, and harmonization.

In cases where studies collected data from overlapping catchment areas, we worked with investigators to identify and remove potential duplicates from the analysis. Because of the harmonization process and removal of overlapping data, there are some differences between our study results compared to original published studies; these differences are summarized in Table S1.

Assessment of risk of bias. We use an adapted Newcastle Ottawa Scale to review study quality and risk of bias for each participating study; criteria for determination of high or low risk for each study design element are presented in Table S2 [13].

Outcomes. We examined 24 outcomes related to: i) COVID-19 severity; ii) maternal morbidities; iii) fetal and neonatal morbidity and mortality; iv) adverse birth outcomes. Specific definitions of each outcome—as well as 4 alternative outcomes used in sensitivity analyses—are presented in Table S3. The definition of maternal, fetal, and neonatal death and adverse birth outcomes were based on WHO case definitions [14–17]. Individual study sites defined hospitalization, critical care, and maternal morbidity outcomes. For maternal morbidities, fetal and neonatal mortality, and all birth outcomes, we restricted to cases of COVID-19 with infection onset during pregnancy or within 7 days of pregnancy outcome, excluding postpartum cases with COVID-19 onset 8-42 days postpartum. Cases with unknown gestational age at onset were included in the analysis of

pregnancy-specific outcomes and are assumed to be infections during pregnancy based on study design.

Risk factors. The sPMA steering committee, based on expert opinion, identified nine high-priority maternal risk factors including comorbidities, nutritional status, age, parity, and COVID-19 symptomatic status. Comorbidities included pre-existing diabetes, hypertension, or cardiovascular disease, and HIV coinfection.

Nutrition-related risk factors included body mass index (BMI) and anemia. We relied on pre-pregnancy BMI to determine the category for each participant, and we examined two risk factors: underweight (BMI <18.5 kg/m^2) and obesity (BMI ≥30 kg/m^2). Both risk factors are compared to a reference group of participants who were normal weight or overweight pre-pregnancy (BMI 18.5-<30 kg/m^2). Anemia was diagnosed based on a hemoglobin measurement <11 g/dL at the time of COVID-19 diagnosis.

We considered two age groups as risk factors: younger maternal age (15-19 years) and older maternal age (35-45 years). Both groups are compared to a reference group of women aged 20-34 years. Lastly, we considered being symptomatic for COVID-19, as compared to those with no symptoms, as a risk factor for the outcomes of interest.

Generating study-specific estimates. We used a standard set of analysis codes to calculate study-specific estimates comparing those with and without each risk factor (proportions and relative risks with 95% confidence intervals (CI)) for each participating study. Within each study, individual

participants were excluded from the analysis if they were missing data on the risk factor of interest. Any study missing more than 25% of the data on an outcome of interest was excluded from that specific analysis.

Data synthesis. We applied a 2-stage IPD meta-analytic framework to generate pooled absolute risks and relative risks, with 95% CI for each risk factor-outcome pair when there were three or more studies with available data. We presented unadjusted estimates because the goal of this study was to present descriptive epidemiological data among a group of people (pregnant women with COVID-19 and their infants), rather than to examine a causal relationship [18], [19]. To estimate the pooled absolute risk for each adverse outcome overall and within risk factor groups, we used a logistic-normal random effects model [20]. In cases where the logistic-normal model did not converge, we employed a random effects model with the Freeman-Tukey double arcsine transformation, to ensure stable estimates and approximate asymptotic normality [21]. We used a Dersimonian and Laird random-effects meta-analysis to generate relative risks for each risk factor-outcome pair and assessed heterogeneity across studies using the I^2 statistic.

We excluded studies with zero total events from that particular analysis. In case of zero events within a risk factor subgroup, we applied a continuity correction of 0.5 when calculating pooled absolute risks. For pooled relative risks, we applied a continuity correction of the inverse number of events in the opposite group within the same study for the risk factor-outcome pair. All meta-analyses were conducted in Stata version 16.1.

Results

Study selection. We included data from 21 studies conducted across 33 countries and territories (Afghanistan, Albania, Argentina, Belgium, Brazil, Canada, Chile, China, Colombia, Democratic Republic of the Congo, Egypt, France, French Guiana, Germany, Ghana, Hong Kong (China), India, Indonesia, Ireland, Israel, Italy, Kenya, Mexico, Nigeria, Portugal, Puerto Rico (US), South Africa, Spain, Switzerland, Turkey, Uganda, United Kingdom, United States) with data from 21,977 cases of confirmed or suspected SARS-CoV-2 infections in pregnancy or the postpartum period. This iteration of the analysis included data from any study that met eligibility criteria and were able to share data by December 2021 (Figure 1). One study (Crovetto et al., 2020) included two distinct cohorts with separate recruitment strategies, which were considered separately throughout the analysis. Further, the Cancovid-Preg study (Money, 2020) follows a cohort of pregnant women with SARS-CoV-2 infection and their infants in Canada; because the study was ongoing at the time of data submission, risk factor data availability and sample size is slightly different for maternal COVID-19 severity outcomes (n=2,045) and neonatal/birth outcomes (n=2,626). Therefore, we present the outcomes from the Cancovid-Preg study as two independent subsets of the cohort in our tables (see Cancovid-Preg – Maternal Subset and Cancovid-Preg – Infant Subset).

Study characteristics. Cases occurred between January 2020 and December 2021 (Table 1). More than 11,000 cases were contributed by the Mexico National Registry (Martinez-Portilla), accounting for approximately half of the data for COVID-19 severity outcomes. The other 20 studies contributed 10,946 pregnant patients and completed follow-up through the end of pregnancy for 9,850 participants, including 9,695 live births (Table 1).

[Figure 1. PRISMA Diagram: sPMA Risk Factor Analysis]

The mean maternal age across studies was 29.4 years, ranging from 26 years in Kenya (Akelo, Tippett Barr) and India (Divakar) to 32 years in Italy (Bevilacqua, Laurita Longo). Among the 18 studies that recorded gestational age at SARS-CoV-2 infection, 11 recruited most of their participants in the third trimester; 10 of these studies included people in the postpartum period. The Nachega (multi-country Africa) and Yang (China) studies were composed entirely of patients hospitalized for COVID-19; the Knight (UK) and Poon (Hong Kong, China) studies were composed entirely (or almost entirely) of patients hospitalized for COVID-19, labor and delivery, or other causes (Table 1).

Risk of bias of included studies. Detailed risk of bias ratings for each participating study are presented in summary in Table S3 and in detail in Table S4. Studies generally had moderate- to low-risk of bias based on the adapted Newcastle Ottawa Scale criteria, with 15 of 21 studies earning at least 4 out of 5 or 4 out of 6 stars across all outcome categories where that study was included in the analysis. The most common cause for high risk of bias rating was related to representativeness of the study population; 5 of 21 studies did not collect data on the reason for screening for individual patients. Another 8 studies primarily used methods to identify cases that were deemed to be at higher risk of bias (such as testing for clinical concern based on symptoms or travel). In total, 13 of 21 studies had elevated risk of bias in this area.

Synthesis of results

Overall incidence. Overall event incidence for each site is shown in Figure 2. There is considerable heterogeneity between studies for most assessed outcomes. This is likely due to a combination of factors including varying sampling frames across studies, true differences in the incidence of outcomes in the general population, and underlying differences in the standard of care provided by health systems in each setting.

[Figure 2. Incidence by outcome and study]

Comorbidities. We found that pregnant women with COVID-19 who also had chronic illnesses, including diabetes, hypertension, and cardiovascular disease, were at higher risk for most outcomes related to COVID-19 severity, as well as pregnancy-related death (Table 2). Risk of mortality was 3.79 times higher for pregnant women with pre-existing diabetes (95% CI: 2.61, 5.50; 15 studies, 15,705 pregnancies; Table S6), 2.75 times higher for those with pre-existing hypertension (95% CI: 1.76, 4.28; 14 studies, 15,705 pregnancies; Table S7), and 16.76 times higher for those with cardiovascular disease (95% CI:4.42, 63.64; 11 studies, 15,368 pregnancies; Table S8), compared to those without these chronic health conditions.

Pregnant women with COVID-19 and one of these chronic conditions were at higher risk for maternal morbidity, including placental abruption, preeclampsia, preeclampsia or eclampsia, hypertensive disorders of pregnancy, preterm labor, and any cesarean delivery. Those with hypertension or cardiovascular disease were also at increased risk of having an intrapartum cesarean delivery. Babies born to mothers with both COVID-19 and one of these chronic conditions were at higher risk for mortality (stillbirth, perinatal death, and neonatal death), as well

as NICU admission. These infants were more likely to be born preterm, low birthweight, and small-for-gestational age.

Although less data was available on HIV coinfection with COVID-19 during pregnancy, we found coinfection increased the risk of severe COVID-19 disease (Table 2). Among pregnant women with COVID-19, those with HIV had a 67% increased risk of being admitted to the ICU (95% CI: 1.06, 2.63, 3 studies, 2,150 pregnancies) and 72% increased risk of needing critical care (95% CI: 1.10, 2.69, 3 studies, 2,150 pregnancies). Those with both COVID-19 and HIV were more likely to be delivered by cesarean delivery (RR 1.51, 95% CI: 1.00, 2.28, 3 studies, 1,688 pregnancies), and babies born to those with HIV coinfection were at increased risk for perinatal death (RR 8.63, 95% CI: 1.40, 53.31, 3 studies, 1,727 fetuses/infants) (Table S9).

Nutritional Status and BMI. We found increased risk of COVID-19 severity among pregnant and postpartum people who were either obese or underweight compared to those who were normal-overweight prior to pregnancy (Table 3). Pregnant women with a pre-pregnancy or early pregnancy BMI of 30 kg/m^2 or greater were at increased risk for ICU admission (RR 1.81, 95% CI: 1.26, 2.60), ventilation (RR 2.05, 95% CI: 1.20, 3.51), and pneumonia (RR 1.66, 95% CI: 1.18, 2.33), but not for pregnancy-related death (RR 1.00, 95% CI: 0.19, 5.26) (Table S10).

Pregnant women who were underweight pre-pregnancy had more than five times increased risk for ICU admission (RR 5.53, 95% CI: 2.27, 13.44, 8 studies, 1,721 pregnancies) or any critical care (RR 5.71, 95% CI: 2.40, 13.59, 7 studies, 1,822 pregnancies), more than nine times increased risk for ventilation (RR 9.36, 95% CI: 3.87, 22.63; 7 studies, 1,822 pregnancies), and nearly three

508 times increased risk for pneumonia (RR 2.71, 95% CI: 1.13, 6.49, 5 studies, 1,129 pregnancies) as
509 compared to pregnant women who were normal-overweight pre-pregnancy (Table S11). Although
510 based on a small sample size, underweight pregnant women with COVID-19 had a sharply
511 increased risk of pregnancy-related death (RR 14.10, 95% CI: 2.83, 70.36, 7 studies, 700
512 pregnancies).
513
514 Pre-pregnancy obesity was also associated with increased risks for maternal morbidity such as
515 preeclampsia (RR 1.60, 95% CI: 1.01, 2.54), any hypertensive disorders of pregnancy (RR 1.86,
516 95% CI:1.30, 2.67), any cesarean delivery (RR 1.23, 95% CI: 1.07, 1.41), and intrapartum cesarean
517 delivery (RR 1.28, 95% CI:1.06, 1.56) (Table 3). Alternately, pre-pregnancy underweight was
518 associated with adverse birth outcomes such as very low birthweight (RR 14.81, 95% CI: 3.25,
519 67.39), small-for-gestational age in the third percentile (RR 7.14, 95% CI: 1.98, 25.73), and
520 moderately preterm birth (RR 7.53, 95% CI: 2.33, 24.29).
521
522 Although data was limited, we found an increased risk of COVID-19 severity among pregnant
523 women with anemia at the time of COVID-19 diagnosis compared to those without anemia (Table
524 3). Those with anemia had an increased risk of ICU admission (RR 1.67, 95% CI: 1.28, 2.19, 4
525 studies, 1,089 pregnancies), ventilation (RR 1.78, 95% CI: 1.02, 3.12, 4 studies, 974 pregnancies)
526 and death (RR 2.36, 95% CI: 1.15, 4.81, 5 studies, 809 pregnancies). We also found an increased
527 risk of stillbirth for pregnant women with anemia (RR 3.75, 95% CI: 1.00, 14.11, 5 studies, 748
528 fetuses/infants) (Table S12).
529

Maternal Age. Older maternal age (35-45 years) was associated with multiple COVID-19-associated adverse outcomes compared to those aged 20-34 years (Table 4). Older maternal age was associated with increased risk of ICU admission (RR 1.60, 95% CI: 1.36, 1.89, 16 studies, 18,758 pregnancies), ventilation (RR 2.13 95% CI: 1.68, 2.71, 16 studies, 18,407 pregnancies), any critical care (RR 1.62, 95% CI: 1.38, 1.90, 15 studies, 18,452 pregnancies) (Table S13), and pneumonia diagnosis (RR 1.51, 95% CI: 1.35, 1.70, 10 studies, 15,670 pregnancies). Older pregnant women also had increased risk for placental abruption (RR 3.94, 95% CI: 1.40, 11.13) and cesarean delivery (RR 1.21, 95% CI: 1.10, 1.32). Babies born to older pregnant women with COVID-19 had higher risk of stillbirth, perinatal death, and NICU admissions, as well as higher risk of being born preterm or low birthweight.

Compared to pregnant women with COVID-19 ages 20 to 34, younger pregnant women (age 15-19) were at increased risk for preeclampsia or eclampsia (RR 3.27, 95% CI: 1.11, 9.64, 8 studies, 1,074 pregnancies) (Table S14). Babies born to younger women with COVID-19 had higher risks of stillbirth, perinatal death, and neonatal death. Younger women with COVID-19 were also more likely to experience adverse pregnancy outcomes, including moderate preterm birth (RR 2.90, 95% CI: 1.18, 7.14, 7 studies, 1,321 infants), very low birthweight (RR 6.27, 95% CI: 1.86, 21.15, 13 studies, 3,203 infants), and small-for-gestational age (<3rd percentile, RR 4.33, 95% CI: 1.87, 10.06, 14 studies, 3,901 infants).

Primiparity. Overall, we found limited differences in risks of adverse outcomes among primiparous compared to multiparous pregnant women with COVID-19 (Table 4). Primiparous women were less likely to be diagnosed with pneumonia than multiparous women (RR 0.59, 95%

CI: 0.46, 0.77, 8 studies, 4,249 pregnancies) and were more likely to experience preeclampsia or eclampsia, any hypertensive disorders of pregnancy, or intrapartum cesarean delivery, compared to multiparous women (Table S15).

Symptomatic SARS-CoV-2 Infection. We found increased risks for adverse outcomes related to COVID-19 severity among pregnant women with symptomatic infection compared to those with asymptomatic SARS-CoV-2 infection, including ICU admission, any critical care, and pneumonia (Table S16). However, most other outcomes related to maternal morbidity, fetal and neonatal mortality and morbidity, and adverse birth outcomes were similar across symptomatic and asymptomatic groups, with a few exceptions. Pregnant women with symptomatic COVID-19 were more likely to have an intrapartum cesarean delivery (RR 1.25, 95% CI: 1.05, 1.48) compared to those with asymptomatic infection (Table S17).

We also found increased risk of preterm and moderate preterm birth among symptomatic pregnant women (RR 1.30, 95% CI: 1.06, 1.60, and RR 1.65, 95% CI: 1.00, 2.73, respectively). However, when we restricted to only pregnant women with infection onset prior to 37 weeks' gestation for preterm birth and prior to 34 weeks' gestation for moderate preterm birth, we found asymptomatic pregnant women had an increased risk of preterm and moderate preterm birth (RR 0.71, 95% CI: 0.52, 0.97, and RR 0.57, 95% CI: 0.41, 0.81), compared to symptomatic pregnant women.

Comment

Principal Findings

As in the general population, we found that pregnant women with comorbidities including diabetes, hypertension, cardiovascular disease and obesity were at increased risk for severe COVID-19-related outcomes, as well as maternal morbidities, and adverse birth outcomes, compared to pregnant women without these comorbidities. Given pooled global data, we also identified several less commonly-known risk factors for pregnant women with COVID-19, including HIV coinfection, being underweight at the start of pregnancy, and anemia at the time of COVID-19 diagnosis.

Comparison with Existing Literature

We found that among pregnant women with COVID-19, those living with HIV were nearly twice as likely to be admitted to the ICU or need critical care. Women living with HIV already have greater likelihood of antenatal, delivery, and postpartum complications, including preterm birth, cesarean delivery, postpartum sepsis, venous thromboembolism, postpartum infection, and mortality [22]. Neonates born to these women are at higher risk due to prematurity, low birthweight, intrauterine growth restriction, resulting in higher rates of NICU admission, and neonatal mortality [22,23]. Factors related to HIV severity such as HIV progression, antiretroviral therapy, CD4 cell count, and viral load additionally affect the immune response to coinfection [24].

A recent systematic review of SARS-CoV-2 infection among people living with HIV in the general population found strong evidence that HIV is a risk factor for both SARS-CoV-2 infection and for mortality due to COVID-19; that review did not examine pregnant and postpartum women as a subgroup of interest [25]. Given that pregnant women are at higher risk for severe COVID-19 illness and complications from HIV, SARS-CoV-2 infection among pregnant women living with HIV

598 may face a greater burden when faced with co-infection. However, our analysis of COVID-19
599 infection among pregnant women living with HIV has several limitations. First, we do not yet have
600 sufficient data to examine either treatment status or viral load among pregnant women with HIV,
601 thus, we cannot shed light on how these factors could mediate excess risk. Furthermore, adverse
602 outcomes related to both COVID-19 severity and pregnancy outcomes can be affected by social,
603 behavioral, and structural factors prevalent in HIV-endemic regions [26].
604
605 Undernutrition in pregnant women with COVID-19 was identified as an important risk factor for
606 COVID-19 severity and adverse birth outcomes. Underweight pregnant women had elevated risks
607 for severe COVID-19 and pregnancy-related death, as well as infants being born moderately
608 preterm, very low birthweight, and small-for-gestational age. Additionally, being anemic during
609 pregnancy increased the risk for pregnancy-related death, ICU admission, and stillbirth. Although
610 the results for anemia were based on four studies, the effect estimates for severe COVID-19 are
611 consistent with those reported in a recent meta-analysis highlighting linkages between low
612 hemoglobin, and hypoxia, respiratory organ dysfunction and severe outcomes from COVID-19
613 infection in the general population [10]. In pregnant and non-pregnant women, single or multiple
614 nutritional deficiencies are known to decrease immune responses, consequently increasing the risk
615 of infection, disease severity, and morbidity and mortality [27–29]. These linkages are especially
616 important during pregnancy when the demand for macro- and micronutrients to support maternal
617 physiological functioning, placental development and fetal growth is even higher [30]. Failure to
618 meet these demands have been linked to preterm and stillbirths in both high-income [31–33] and low-
619 and middle-income countries [34]. These indicators of undernutrition are generally linked to many
620 different health conditions (*e.g.*, iron deficiency, other infections), and it is difficult to infer specific

mechanisms of action based on this analysis. Nonetheless, our findings on the association between undernutrition or anemia and preterm and stillbirths among pregnant women with COVID-19 further underscore the need for close monitoring and management of this group, including provision of additional nutritional support to prevent disease and prevent adverse birth outcomes [33,35].

We found pregnant women with any COVID-19 symptoms were at increased risk for ICU admission, ventilation, cesarean delivery, and preterm birth compared to asymptomatic pregnant women based on a large sample size of global studies; while a previous systematic review on published literature examined this question, data on symptomatic compared to asymptomatic SARS-CoV-2 infection in pregnancy were only available for a small subset of studies and participants in this review (4 studies on ICU admission with 1,178 participants; 3 studies on mechanical ventilation with 1,023 participants, 9 studies on cesarean delivery and preterm birth with 4,233 participants) [5]. Our study found that symptomatic pregnant women are more likely to give birth preterm than asymptomatic pregnant women with SARS-CoV-2 infection.

However, in a sensitivity analysis restricted only to participants infected prior to 37 weeks gestational age, we found that asymptomatic pregnant women are more likely than symptomatic pregnant women to have a preterm birth. These seemingly conflicting results may be related to features of study sampling; for example, this difference may be due to the large percentage of asymptomatic participants who are identified during screening at labor and delivery. Across the 10 studies included in the restricted analysis, 64% of babies born to asymptomatic participants

were identified at or after 37 weeks gestational age, compared to 26% of babies born to symptomatic participants.

Strengths and limitations. IPD meta-analyses are considered the gold-standard method for generating aggregate estimates. Here, we standardized data quality assessment and harmonized definitions of risk factors and outcomes. This is especially valuable for outcomes such as stillbirth, preterm birth, and perinatal mortality, which have varying definitions globally. We included data from 33 countries and territories, including many low- and middle-income countries, whereas the bulk of the published literature on COVID-19 in pregnancy comes from middle- or high-income countries. Therefore, by pooling global data we were able to investigate risk factors such as HIV status, undernutrition, and anemia, which are more common in low-income countries, but for which individual studies may not have adequate power to draw meaningful conclusions. We were also able to identify risks linked to rare outcomes such as pregnancy-related death and stillbirth.

Our study had several limitations. First, the studies contributing to the IPD meta-analysis recruited participants differently, varying from hospital-based surveillance to universal screening during antenatal care. Further, representativeness of the sample was deemed to be at elevated risk of bias for the majority of studies due to limited information about identification and screening at the individual patient level or the use of identification strategies that are only somewhat representative of the population of interest. Some studies only recruited women admitted to the hospital with COVID-19 infection, while others included both symptomatic and asymptomatic women who tested positive for the infection. Given the heterogeneity of the sampling frames between studies, it is not possible to draw inferences about the absolute risk of adverse outcomes. The heterogeneity

in baseline rates of adverse outcomes globally further complicates interpretation of the absolute risks. However, the relative risks comparing those with and without the risk factors of interest generally appear consistent between sites and heterogeneity is relatively low for pooled estimates. Additionally, although this analysis pooled a large, global sample of pregnant and postpartum women with COVID-19, half of the overall sample for critical care outcomes (ICU admission, ventilation, any critical care, pneumonia, and mortality) was derived from the Mexican National Registry, which collected no information on maternal morbidity, birth or neonatal outcomes. This analysis also did not examine risk factors related to social determinants of health, which may exacerbate the biological risk factors identified in this analysis.

We identified risk factors for adverse maternal morbidities, fetal, and neonatal outcomes among pregnant women with COVID-19, and these are generally consistent with risk factors for adverse pregnancy outcomes including pre-existing diabetes or hypertension [36–38], cardiovascular disease [39], obesity [38,40], underweight [40,41], anemia [42,43], and HIV infection [22,23]. Because the studies in this IPD meta-analysis only included individuals with SARS-CoV-2 infection, we were unable to evaluate whether the presence of infection confers additional risk beyond the risk due to risk factors without the presence of COVID-19 infection. Similarly, we identified risk factors for adverse COVID-19 related outcomes, and these are generally consistent with risk factors identified in the general non-pregnant population. Nonetheless, this study provides high-quality evidence that pregnant women with these risk factors are also at risk for adverse outcomes from COVID-19 illness.

Conclusions and Implications

Although pregnant women are already considered a high-risk population by the WHO and should be given equitable access to safe and effective preventives and therapeutics, special priority should be given to pregnant women with additional risk factors, including chronic and infectious comorbidities, nutritional status, and maternal age. This data strongly supports the need for access to vaccines and treatments for SARS-CoV-2 infection for pregnant women, prioritizing those with risk factors for severe illness and adverse birth outcomes.

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Table 1. Description of studies contributing to the individual patient data meta-analysis

					Gestational Age at Infection							
Study PI	**Countries**	**Total pregnancies**	**Livebirths**	**Mean age (SD)**	**1st Tri**	**2nd Tri**	**3rd Tri**	**Postpartum**	**Unknown**	**Hospitalized (%)**	**Admitted to ICU (%)**	**Data collected through**
Martinez-Portilla, 2021	Mexico	11,031	n/a	28.5 (6.0)	n/a	n/a	n/a	n/a	100%	20%	2%	March 2021
Favre, Panchaud, 2021	14 countries [1]	2,391	1,830	31.3 (5.4)	10%	20%	37%	5%	29%	22% [2]	4%	December 2021
Money, 2020 - Maternal Subset [3]	Canada	2,045	--	31.2 (5.4)	7%	28%	49%	0%	16%	n/a	2%	September 2021
Money, 2020 - Infant Subset [3]	Canada [4]	--	2,626	--	2%	7%	19%	0%	72%	n/a	n/a	September 2021
Carrillo, 2021	Chile	1,347	1,113	29 (6.2)	1%	12%	64%	4%	19%	16%	6%	November 2020
Knight, 2021	United Kingdom	1,243	1,034	31.0 (6.0)	3%	12%	75%	4%	7%	100% [5]	6%	October 2020
Bracero, Valencia, Delgado-Lopez, 2021	Puerto Rico (USA)	938	744	26.6 (5.6)	11%	20%	38%	1%	30%	n/a	*n/a*	October 2021
Sakowicz, 2020	USA (Chicago)	503	509	30.8 (5.8)	5%	21%	73%	0%	1%	n/a	1%	February 2021
Sanin, Mesa, Tolosa, 2021	Colombia	409	188	n/a	4%	9%	32%	3%	52%	68%	22%	March 2021
Nachega, 2021	DRC, Ghana, Kenya, Nigeria, South Africa, Uganda	349	136	30.7 (5.8)	6% [6]	18% [6]	64% [6]	0% [6]	12% [6]	100%	19%	December 2020
Waldorf, Lokken, 2021	USA (Washington State)	240	156	28.6 (5.8)	16%	28%	56%	0%	0%	10%	3%	September 2020
Divakar, 2021	India (Karnataka State)	214	216	26.4 (4.2)	0%	2%	82%	15%	0%	n/a	n/a	December 2020
Gil, Fernandez Buhigas, 2021	Spain (Madrid)	212	168	32.6 (5.9)	29%	37%	33%	0%	1%	4%	0%	May 2021

Crovetto, 2020, Cohort II	Spain (Barcelona)	176	178	32.0 (6.2)	n/a	n/a	14.% [7]	1% [7]	86% [7]	16%	1%	May 2020
Crovetto, 2020, Cohort I	Spain (Barcelona)	173	154	32.7 (5.4)	n/a	n/a	n/a	n/a	100% [7]	0%	0%	March-May 2020, with follow-up through labor and delivery
Bevilacqua, Laurita Longo, 2020	Italy (Rome)	163	156	32.3 (5.4)	6%	5%	88%	0%	2%	7%	1%	March 2021
Nunes, 2021	South Africa	139	137	31.8 (6.6)	2%	22%	71%	0%	5%	15%	n/a	September 2020
Akelo, Tippett Barr, 2021	Kenya	125	94	26.3 (5.2)	1%	12%	31%	27%	29%	9%	n/a	August 2021
Yang, Juan, 2020	China	116	100	30.8 (3.8)	3%	6%	82%	9%	1%	100%	8%	March 2020
Kalafat, 2020	Turkey	77	72	28.0 (5.9)	n/a	n/a	n/a	n/a	100%	75%	1%	June 2020
Brandt, 2020	USA (New Brunswick)	61	60	30.3 (6.4)	0%	5%	90%	5%	0%	7%	2%	June 2020
Poon, 2021	Hong Kong	25	24	33.7 (5.4)	4%	28%	64%	0%	4%	92%	4%	June 2021

1 Note: The COVI-Preg study estimates in this analysis are drawn from facilities in 14 countries: Afghanistan (1%), Albania (<1%), Argentina (2%), Belgium (1%), Brazil (7%), Egypt (<1%), France (22%), French Guyana (3%), Germany (1%), Indonesia (1%), Ireland (2%), Israel (9%), Portugal (5%), and Switzerland (45%). Facilities participating in the COVI-Preg study with the potential to record overlapping cases with other sites participating in the current analysis were excluded, including facilities in Chile, China, Colombia, Italy, Spain (Barcelona), Mexico, Canada, United Kingdom, and the USA.

2 Hospitalization data was missing in the COVI-Preg study for 194 participants (8% of the sample). ICU admission data is only available from those with a recorded hospital admission.

3 The Cancovid-Preg study follows a cohort of pregnant women with SARS-CoV-2 infection and their infants; because the study was ongoing at the time of data submission, risk factor data availability and sample size is slightly different for maternal COVID-19 severity outcomes and neonatal/birth outcomes. We present the data as two subsets of the same cohort for this ongoing study. In the "Maternal Subset", we present data on pregnant women with COVID-19, including outcomes on ICU admission, ventilation, and critical care (n=2,045). In the "Infant Subset", we present data on live births to pregnant women with COVID-19, including outcomes on preterm birth (n=2,626).

4 Data from Cancovid-Preg represents all provinces, with missing data randomly distributed across provinces except for the risk factor "pre-existing hypertension", which is unavailable for the full cohort from Ontario.

5 Note that for the UKOSS study, 100% of patients are hospitalized. However, the reason for hospitalization may not be COVID-19 and some participants presented at the hospital for an unrelated reason and were found to have an incidental COVID-19 infection.

6 For the AFREHealth study, gestational age at COVID-19 onset was not recorded. Here, we present trimester of hospital admission as a proxy. N= 41 were missing trimester of hospital admission (12%). However, the study is not included in the risk factor analysis for gestational age at onset.

7 Antibody testing at ANC (Cohort I) and at labor and delivery (Cohort II) was the primary method of diagnosis, thus gestational age at COVID-19 onset is unknown for almost all observations.

Table 2. Relative risk and 95% CI comparing women with each risk factor to women without risk factor - comorbidites

Outcome	Diabetes		Hypertension		CVD		HIV Coinfection	
	N	Pooled RR (95% CI)	N	Pooled RR (95% CI)	N	Pooled RR (95% CI)	N	Pooled RR (95% CI)
COVID-19 Severity & Mortality								
ICU admission	16	**2.55 (1.97, 3.31)**	14	**2.10 (1.63, 2.70)**	12	**2.98 (1.83, 4.85)**	3	**1.67 (1.06, 2.63)**
Ventilation	14	**5.88 (2.77, 12.48)**	13	**4.87 (2.93, 8.09)**	12	**6.11 (2.85, 13.08)**	3	1.01 (0.30, 3.32)
Critical Care	14	**3.03 (1.86, 4.92)**	12	**2.42 (1.73, 3.39)**	11	**2.82 (1.78, 4.48)**	3	**1.72 (1.10, 2.69)**
Pneumonia	10	**2.02 (1.65, 2.47)**	8	**2.13 (1.74, 2.61)**	8	1.18 (0.65, 2.16)	1	--
Pregnancy-related death	15	**3.79 (2.61, 5.50)**	14	**2.75 (1.76, 4.28)**	11	**16.76 (4.42, 63.64)**	4	2.70 (0.58, 12.47)
Maternal Morbidity								
Haemorrhage	7	1.89 (0.96, 3.70)	7	1.33 (0.60, 2.94)	5	2.42 (0.29, 20.01)	3	1.06 (0.57, 1.99)
Placental Abruption	6	**7.25 (2.47, 21.25)**	6	**6.68 (2.35, 18.98)**	3	**9.99 (1.70, 58.58)**	2	--
Preeclampsia	10	**2.98 (1.61, 5.51)**	9	**5.80 (4.11, 8.19)**	8	**4.78 (2.24, 10.22)**	2	--
Preeclampsia or Eclampsia	7	**4.32 (1.58, 11.84)**	6	**4.09 (2.08, 8.07)**	6	**6.38 (2.80, 14.58)**	2	--
Hypertensive Disorders of Pregnancy (Any)	9	**2.73 (1.62, 4.58)**	8	**3.16 (2.24, 4.47)**	8	**4.29 (2.17, 8.48)**	2	--
Hypertensive Disorders of Pregnancy (At/After Covid-19)	2	--	2	--	1	--	0	--
Preterm labor	8	**3.54 (1.89, 6.61)**	7	**3.93 (1.44, 10.75)**	8	**3.94 (1.39, 11.19)**	2	--
Preterm labor with onset before 37w GA [1]	6	**2.48 (1.24, 4.98)**	5	2.16 (0.73, 6.40)	5	2.40 (0.31, 18.46)	2	--
Cesarean Delivery	12	**1.40 (1.13, 1.74)**	11	**1.31 (1.09, 1.57)**	10	**1.44 (1.08, 1.92)**	3	**1.51 (1.00, 2.28)**
Intrapartum Cesarean Delivery	9	1.30 (0.90, 1.87)	8	**1.58 (1.23, 2.04)**	9	**1.59 (1.03, 2.48)**	3	1.47 (0.91, 2.37)
Fetal & Neonatal Mortality and Morbidity								
Stillbirth [2]	16	**6.53 (2.13, 20.05)**	15	**3.43 (1.41, 8.37)**	12	**9.10 (2.24, 36.92)**	4	2.97 (0.35, 25.26)

Perinatal death	12	**7.71 (2.12, 28.03)**	11	**4.94 (2.07, 11.81)**	10	**8.47 (2.70, 26.53)**	3	**8.63 (1.40, 53.31)**
Early neonatal death	12	**6.97 (1.07, 45.27)**	11	**11.74 (3.23, 42.70)**	10	**12.58 (2.69, 58.80)**	3	--
Neonatal death [3]	13	**6.85 (1.22, 38.49)**	12	**8.10 (2.71, 24.25)**	10	**13.04 (3.18, 53.43)**	4	--
NICU Admission at Birth	8	**1.83 (1.15, 2.93)**	6	**2.28 (1.26, 4.13)**	5	2.02 (0.65, 6.30)	1	--
Adverse Birth Outcomes								
Very low birthweight (<1500g)	13	**5.28 (2.62, 10.63)**	12	**6.30 (3.16, 12.55)**	10	**8.35 (3.64, 19.19)**	4	2.41 (0.80, 7.20)
Low birthweight (<2500g)	13	**1.80 (1.21, 2.69)**	12	**1.87 (1.39, 2.50)**	10	**2.01 (1.19, 3.39)**	4	1.38 (0.93, 2.04)
Small for gestational age (3rd)	14	**4.11 (1.53, 11.06)**	13	**3.34 (1.86, 6.00)**	11	**3.14 (1.58, 6.23)**	4	**2.14 (1.02, 4.48)**
Small for gestational age (10th)	14	1.62 (0.81, 3.21)	13	**1.91 (1.29, 2.84)**	11	**1.84 (1.11, 3.03)**	4	1.57 (0.93, 2.63)
Moderate preterm birth (<34w)	14	**3.23 (2.09, 5.01)**	13	**3.55 (2.48, 5.08)**	11	**3.04 (1.57, 5.91)**	4	1.78 (0.67, 4.74)
Moderate preterm birth (<34w) with onset before 34w GA [1]	8	**2.03 (1.24, 3.31)**	7	**2.23 (1.46, 3.41)**	5	2.27 (0.93, 5.50)	3	2.18 (0.93, 5.07)
Preterm birth (<37 wks)	15	**2.25 (1.77, 2.86)**	14	**2.22 (1.72, 2.86)**	12	**1.90 (1.41, 2.56)**	4	1.22 (0.83, 1.81)
Preterm birth (<37 wks) with onset before 37w GA [1]	8	1.40 (0.97, 2.01)	7	**1.61 (1.21, 2.12)**	6	1.25 (0.63, 2.49)	3	1.40 (0.81, 2.41)

Notes: Relative risks are calculated by pooling unadjusted relative risks from all participating studies with at least 1 adverse event for the given outcome using a DerSimonian-Laird random effects model meta-analysis. For any study with zero events in one arm (Risk Group or Reference Group), we used a continuity correction of the inverse of the number of events in the oppposite group within the same study.

1 These outcomes (preterm labor, moderate preterm birth before 34 weeks gestation, and preterm birth before 37 weeks' gestation) were included in the sensitivity analyses where we restrict confirmed COVID-19 cases to those with confirmed COVID-19 onset prior to 37 weeks' gestation (or 34 weeks for very moderate preterm birth). The full comparison group is used for each of the sensitivity analyses.

2 The outcome presented here is stillbirths occurring at or after 28 weeks gestational age per the WHO definition.

3 The outcome "neonatal death" is reported by 15 participating studies. However, most studies were not designed to follow-up neonates until 28 days after birth. Therefore, counts of neonatal death are underestimated.

Table 3. Relative risk and 95% CI comparing women with each risk factor to women without risk factor - nutrition-related factors

Outcome	Obese		Underweight		Anemia	
	N	Pooled RR (95% CI)	N	Pooled RR (95% CI)	N	Pooled RR (95% CI)
COVID-19 Severity & Mortality						
ICU admission	8	**1.81 (1.26, 2.60)**	8	**5.53 (2.27, 13.44)**	4	**1.67 (1.28, 2.19)**
Ventilation	7	**2.05 (1.20, 3.51)**	7	**9.36 (3.87, 22.63)**	4	**1.78 (1.02, 3.12)**
Critical Care	7	**1.89 (1.28, 2.77)**	7	**5.71 (2.40, 13.59)**	3	--
Pneumonia	5	**1.66 (1.18, 2.33)**	5	**2.71 (1.13, 6.49)**	2	--
Pregnancy-related death	7	1.00 (0.19, 5.26)	7	**14.10 (2.83, 70.36)**	5	**2.36 (1.15, 4.81)**
Maternal Morbidity						
Haemorrhage	4	1.43 (0.85, 2.41)	4	6.00 (0.89, 40.41)	2	--
Placental Abruption	2	--	2	--	2	--
Preeclampsia	4	**1.60 (1.01, 2.54)**	4	2.18 (0.63, 7.53)	3	--
Preeclampsia or Eclampsia	3	2.16 (0.68, 6.82)	3	3.08 (0.64, 14.81)	3	--
Hypertensive Disorders of Pregnancy (Any)	5	**1.86 (1.30, 2.67)**	5	1.93 (0.59, 6.26)	3	0.87 (0.52, 1.46)
Hypertensive Disorders of Pregnancy (At/After Covid-19)	1	--	1	**--**	1	--
Preterm labor	6	0.91 (0.57, 1.46)	6	3.76 (0.95, 14.82)	2	--
Preterm labor with onset before 37w GA [1]	4	0.84 (0.51, 1.39)	3	0.62 (0.02, 18.50)	2	--
Cesarean Delivery	7	**1.23 (1.07, 1.41)**	7	1.15 (0.54, 2.45)	4	0.75 (0.47, 1.19)
Intrapartum Cesarean Delivery	6	**1.28 (1.06, 1.56)**	6	1.42 (0.26, 7.78)	3	0.67 (0.28, 1.62)
Fetal & Neonatal Mortality and Morbidity						
Stillbirth [2]	8	1.89 (0.31, 11.60)	8	--	5	**3.75 (1.00, 14.11)**
Perinatal death	6	3.17 (0.43, 23.21)	6	--	3	--
Early neonatal death	6	--	6	--	3	--
Neonatal death [3]	6	--	6	--	4	2.98 (0.49, 18.13)
NICU Admission at Birth	4	1.42 (0.82, 2.47)	4	2.21 (0.26, 18.78)	2	--
Adverse Birth Outcomes						
Very low birthweight (<1500g)	6	1.70 (0.76, 3.79)	6	**14.81 (3.25, 67.39)**	4	1.64 (0.47, 5.73)
Low birthweight (<2500g)	6	0.97 (0.68, 1.37)	6	1.98 (0.74, 5.26)	4	0.99 (0.60, 1.62)
Small for gestational age (3rd)	6	0.68 (0.24, 1.95)	6	**7.14 (1.98, 25.73)**	4	1.11 (0.56, 2.21)
Small for gestational age (10th)	6	0.75 (0.41, 1.37)	6	2.46 (0.90, 6.70)	4	0.99 (0.64, 1.53)

Moderate preterm birth (<34w)	6	**1.75 (1.06, 2.89)**	6	**7.53 (2.33, 24.29)**	4	0.91 (0.51, 1.61)
Moderate preterm birth (<34w) with onset before 34w GA [1]	3	1.46 (0.89, 2.40)	2	--	2	--
Preterm birth (<37 wks)	7	**1.38 (1.10, 1.73)**	7	1.58 (0.59, 4.26)	4	0.94 (0.67, 1.32)
Preterm birth (<37 wks) with onset before 37w GA [1]	3	1.17 (0.90, 1.51)	2	--	3	0.92 (0.62, 1.37)

Notes: Relative risks are calculated by pooling unadjusted relative risks from all participating studies with at least 1 adverse event for the given outcome using a DerSimonian-Laird random effects model meta-analysis. For any study with zero events in one arm (Risk Group or Reference Group), we used a continuity correction of the inverse of the number of events in the oppposite group within the same study.

1 These outcomes (preterm labor, moderate preterm birth before 34 weeks gestation, and preterm birth before 37 weeks' gestation) were included in the sensitivity analyses where we restrict confirmed COVID-19 cases to those with confirmed COVID-19 onset prior to 37 weeks' gestation (or 34 weeks for very moderate preterm birth). The full comparison group is used for each of the sensitivity analyses.

2 The outcome presented here is stillbirths occurring at or after 28 weeks gestational age per the WHO definition.

3 The outcome "neonatal death" is reported by 15 participating studies. However, most studies were not designed to follow-up neonates until 28 days after birth. Therefore, counts of neonatal death are underestimated.

Table 4. Relative risk and 95% CI comparing women with each risk factor to women without risk factor - maternal age and primiparity

Outcome	Age 15-19		Age 35-45		Primiparity	
	N	Pooled RR (95% CI)	N	Pooled RR (95% CI)	N	Pooled RR (95% CI)
COVID-19 Severity & Mortality						
ICU admission	12	1.42 (0.53, 3.77)	16	**1.60 (1.36, 1.89)**	14	0.90 (0.71, 1.13)
Ventilation	12	2.59 (0.79, 8.51)	16	**2.13 (1.68, 2.71)**	12	0.67 (0.39, 1.16)
Critical Care	11	1.24 (0.48, 3.17)	15	**1.62 (1.38, 1.90)**	12	0.82 (0.62, 1.08)
Pneumonia	9	0.82 (0.62, 1.08)	10	**1.51 (1.35, 1.70)**	8	**0.59 (0.46, 0.77)**
Pregnancy-related death	13	0.73 (0.27, 1.94)	16	1.62 (0.81, 3.24)	14	0.75 (0.45, 1.25)
Maternal Morbidity						
Haemorrhage	6	1.93 (0.94, 3.98)	6	1.17 (0.82, 1.68)	7	1.26 (0.90, 1.77)
Placental Abruption	5	--	6	**3.94 (1.40, 11.13)**	6	0.64 (0.19, 2.09)
Preeclampsia	10	2.03 (0.89, 4.61)	13	1.12 (0.73, 1.74)	11	**2.10 (1.45, 3.03)**
Preeclampsia or Eclampsia	8	**3.27 (1.11, 9.64)**	9	0.93 (0.63, 1.37)	8	**1.75 (1.22, 2.53)**
Hypertensive Disorders of Pregnancy (Any)	10	2.06 (0.77, 5.55)	12	1.17 (0.93, 1.49)	10	**1.56 (1.13, 2.15)**
Hypertensive Disorders of Pregnancy (At/After Covid-19)	2	--	3	1.91 (0.45, 8.16)	3	1.39 (0.54, 3.57)
Preterm labor	8	2.48 (0.53, 11.60)	10	1.39 (0.96, 2.02)	8	0.86 (0.51, 1.43)
Preterm labor with onset before 37w GA [1]	5	1.62 (0.42, 6.22)	8	1.28 (0.87, 1.87)	6	0.88 (0.51, 1.51)
Cesarean Delivery	10	0.86 (0.65, 1.13)	13	**1.21 (1.10, 1.32)**	12	1.00 (0.90, 1.11)
Intrapartum Cesarean Delivery	9	0.90 (0.63, 1.31)	10	1.03 (0.89, 1.20)	8	**1.35 (1.14, 1.60)**
Fetal & Neonatal Mortality and Morbidity						
Stillbirth [2]	15	**4.59 (1.69, 12.45)**	18	1.75 (0.92, 3.33)	17	1.34 (0.62, 2.90)
Perinatal death	11	**4.80 (1.28, 17.99)**	14	1.53 (0.82, 2.83)	12	1.78 (0.89, 3.54)
Early neonatal death	11	**5.94 (1.02, 34.56)**	14	1.80 (0.51, 6.33)	12	1.60 (0.45, 5.62)
Neonatal death [3]	12	**9.38 (2.21, 39.89)**	15	1.96 (0.65, 5.87)	13	1.25 (0.43, 3.60)
NICU Admission at Birth	6	1.59 (0.48, 5.23)	9	**1.35 (1.12, 1.63)**	8	1.03 (0.85, 1.25)
Adverse Birth Outcomes						
Very low birthweight (<1500g)	13	**6.27 (1.86, 21.15)**	16	1.39 (0.89, 2.16)	14	1.03 (0.61, 1.73)
Low birthweight (<2500g)	13	0.96 (0.54, 1.73)	16	**1.24 (1.04, 1.47)**	14	**1.27 (1.04, 1.54)**
Small for gestational age (3rd)	14	**4.33 (1.87, 10.06)**	17	**1.46 (1.01, 2.12)**	15	**2.11 (1.42, 3.11)**
Small for gestational age (10th)	14	1.40 (0.83, 2.36)	17	0.98 (0.79, 1.21)	15	**1.74 (1.41, 2.15)**

Moderate preterm birth (<34w)	14	**3.06 (1.48, 6.35)**	17	**1.51 (1.19, 1.93)**	15	1.10 (0.84, 1.44)
Moderate preterm birth (<34w) with onset before 34w GA [1]	7	**2.90 (1.18, 7.14)**	10	**1.43 (1.07, 1.90)**	8	1.07 (0.74, 1.53)
Preterm birth (<37 wks)	14	1.22 (0.84, 1.78)	18	**1.40 (1.19, 1.64)**	15	1.02 (0.87, 1.19)
Preterm birth (<37 wks) with onset before 37w GA [1]	7	1.06 (0.68, 1.67)	11	**1.27 (1.07, 1.50)**	9	1.02 (0.83, 1.26)

Notes: Relative risks are calculated by pooling unadjusted relative risks from all participating studies with at least 1 adverse event for the given outcome using a DerSimonian-Laird random effects model meta-analysis. For any study with zero events in one arm (Risk Group or Reference Group), we used a continuity correction of the inverse of the number of events in the opposite group within the same study.

1 These outcomes (preterm labor, moderate preterm birth before 34 weeks gestation, and preterm birth before 37 weeks' gestation) were included in the sensitivity analyses where we restrict confirmed COVID-19 cases to those with confirmed COVID-19 onset prior to 37 weeks' gestation (or 34 weeks for very moderate preterm birth). The full comparison group is used for each of the sensitivity analyses.

2 The outcome presented here is stillbirths occurring at or after 28 weeks gestational age per the WHO definition.

3 The outcome "neonatal death" is reported by 15 participating studies. However, most studies were not designed to follow-up neonates until 28 days after birth. Therefore, counts of neonatal death are underestimated.

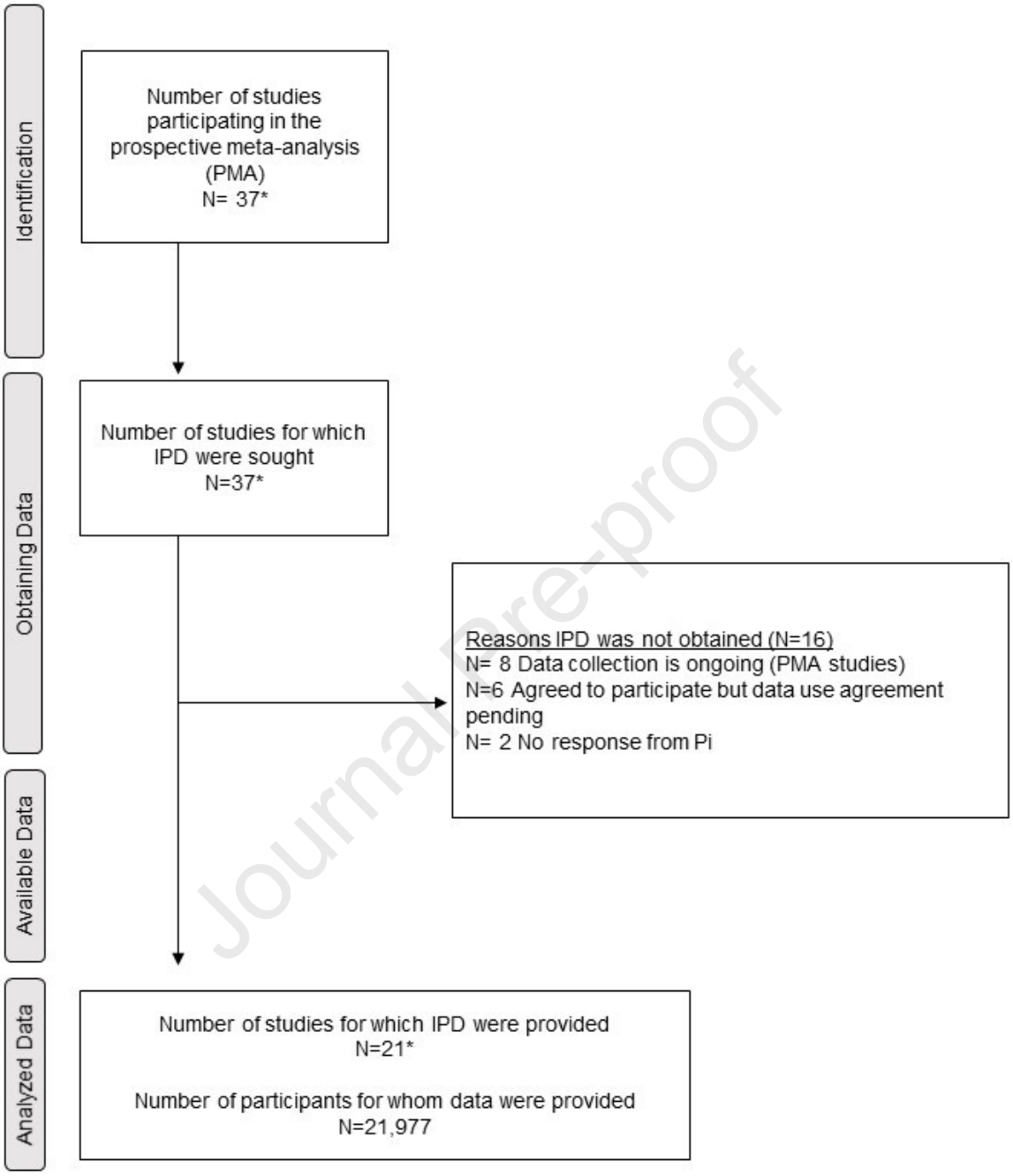
Figure Legends

Figure 1. PRISMA diagram for risk factor analysis study

The PRISMA flow diagram outlines the identification and recruitment of studies and final inclusion of individual patient data for this study.

Figure 2. Incidence of outcomes by study

This figure presents the incidence and 95% confidence intervals of selected adverse outcomes across the 21 participating studies, including: A) ICU admission, B) ventilation, C) pregnancy-related death, D) preeclampsia, E) cesarean delivery, F) stillbirth, G) neonatal death, H) low birthweight, and I) preterm birth. Studies are grouped by World Bank income group levels: lower-middle income countries are shown in red; upper-middle income countries are shown in green; those from high income countries are shown in blue. Two studies (shown in purple) are multi-country studies that contain countries from multiple income groups. The complete list of countries for each of these multi-country studies is presented in Table 1.



**Crovetto 2020 was published as a single study, but included 2 distinct cohorts. We analyze theses as two separate studies in the IPD meta-analysis. The Cancovid-Preg study (Money, 2020) is drawn from a cohort of pregnant women with COVID-19 and their infants in Canada; because the study was ongoing at the time of data submission, data availability and sample size is slightly different for maternal COVID-19 severity outcomes and neonatal/birth outcomes. We therefore examine two independent subsets of data from this cohort: "Maternal Subset" and "Infant Subset."*