

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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1 **Title:** Clinical risk factors of adverse outcomes among women with COVID-19 in the pregnancy
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138 **Conflicts of Interest:**

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141

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

148

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

151

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

156

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

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

163

164 Erica Lokken declares a relationship with the following entity, US NIH (paid institution) and is
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166 the study.

167

168 Karen L. Kotloff declares a relationship with the following entity, Bill and Melinda Gates
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173

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175 Foundation (payments to my institution), Yellow Chair Foundation (payments to my institution),
176 Robert Woods Johnson Foundation (payments to my institution), CDC Foundation, California
177 Health Care Foundation (payments to my institution), Tara Health Foundation (payments to my
178 institution), UCSF Women's Health Center of Excellence (payments to my institution) and
179 California Department of Health Care Services (payments made to my institution).

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181 Jose Sanin-Blair declares a relationship with the following entity, Ferring Pharmaceuticals which
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192 writing or educational events), and Sanofi Pasteur and Pfizer (Payment for expert testimony),

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210

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212 **Condensation**

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

216

217 **Short Title**

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

219

220 *AJOG at a Glance*

221 **Why was this study conducted?**

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

227

228 **What are the key findings?**

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

233

234 **What does this study add to what is already known?**

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

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240 **Abstract:**

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

244

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

247

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

250

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

256

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

263 at higher risk of ICU admission (RR 5.53, 95% CI: 2.27, 13.44), ventilation (RR 9.36, 95% CI:
264 3.87, 22.63), and pregnancy-related death (RR 14.10, 95% CI: 2.83, 70.36). Pre-pregnancy obesity
265 was also a risk factor for severe COVID-19 outcomes including ICU admission (RR 1.81, 95%
266 CI: 1.26,2.60), ventilation (RR 2.05, 95% CI: 1.20,3.51), any critical care (RR 1.89, 95% CI:
267 1.28,2.77), and pneumonia (RR 1.66, 95% CI: 1.18,2.33). Anemic pregnant women with COVID-
268 19 also had increased risk of ICU admission (RR 1.63, 95% CI: 1.25, 2.11) and death (RR 2.36,
269 95% CI: 1.15, 4.81).

270

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

277

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

280 **Introduction**

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

287
288 Initial evidence showed that SARS-CoV-2 infection during pregnancy is linked to increased
289 likelihood of adverse maternal, fetal, and neonatal outcomes ³⁻⁵. A systematic review of 42 studies
290 (N=438,548) found that pregnant women with SARS-CoV-2 infection had significantly higher
291 odds of preeclampsia, preterm birth, stillbirth, and intensive care unit (ICU) admission, compared
292 to those not infected ⁵. Although vertical transmission of COVID-19 from mother to fetus
293 reportedly occurs in a low percentage of cases, neonates can be negatively impacted by maternal
294 infection in other ways ^{6 7}. In two systematic reviews of 42 and 66 studies, neonates of mothers
295 with confirmed COVID-19 had three times higher odds of Neonatal Intensive Care Unit (NICU)
296 admission than those born to mothers not infected ^{5,6}.

297
298 Among pregnant women, multiple risk factors for severe SARS-CoV-2 infection have been
299 identified ^{3,8}. The Surveillance for Emerging Threats to Mothers and Babies Network in the United
300 States (N=7950) determined that pregnant women over 25 years of age, with pre-pregnancy
301 obesity, chronic lung disease, chronic hypertension, and pregestational diabetes mellitus had a
302 32% to 85% increased risk of moderate-to-severe COVID-19, compared to pregnant women free

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

305

306 In the general population, nutritional status has been introduced as a potential risk factor for severe
307 COVID-19. A meta-analysis of seven studies (N=9,912) found that among people with COVID-
308 19, those with anemia had 2.44 higher odds of severe illness than non-anemic people ¹⁰. A
309 scientific review found sufficient intake of micronutrients, proteins, diet fiber, short-chain fatty
310 acids, and omega-3 polyunsaturated fatty acids may act as a protective factor against severe illness
311 in COVID-19 patients ¹¹. Further research is required for pregnant women, for whom nutritional
312 guidance would be particularly useful.

313

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

321

322 **Objectives**

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

326

327 **Methods**

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

331

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

335

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

340

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

343

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

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

351

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

357

358 *Assessment of risk of bias.* We use an adapted Newcastle Ottawa Scale to review study quality and
359 risk of bias for each participating study; criteria for determination of high or low risk for each
360 study design element are presented in Table S2¹³.

361

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

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

373

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

378

379 Nutrition-related risk factors included body mass index (BMI) and anemia. We relied on pre-
380 pregnancy BMI to determine the category for each participant, and we examined two risk factors:
381 underweight (BMI <18.5 kg/m²) and obesity (BMI ≥ 30 kg/m²). Both risk factors are compared to
382 a reference group of participants who were normal weight or overweight pre-pregnancy (BMI
383 18.5 - <30 kg/m²). Anemia was diagnosed based on a hemoglobin measurement <11 g/dL at the
384 time of COVID-19 diagnosis.

385

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

390

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

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

397

398 *Data synthesis.* We applied a 2-stage IPD meta-analytic framework to generate pooled absolute
399 risks and relative risks, with 95% CI for each risk factor-outcome pair when there were three or
400 more studies with available data. We presented unadjusted estimates because the goal of this study
401 was to present descriptive epidemiological data among a group of people (pregnant women with
402 COVID-19 and their infants), rather than to examine a causal relationship^{18, 19}. To estimate the
403 pooled absolute risk for each adverse outcome overall and within risk factor groups, we used a
404 logistic-normal random effects model²⁰. In cases where the logistic-normal model did not
405 converge, we employed a random effects model with the Freeman-Tukey double arcsine
406 transformation, to ensure stable estimates and approximate asymptotic normality²¹. We used a
407 Dersimonian and Laird random-effects meta-analysis to generate relative risks for each risk factor-
408 outcome pair and assessed heterogeneity across studies using the I^2 statistic.

409

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

415

416 **Results**

417 *Study selection.* We included data from 21 studies conducted across 33 countries and territories
418 (Afghanistan, Albania, Argentina, Belgium, Brazil, Canada, Chile, China, Colombia, Democratic
419 Republic of the Congo, Egypt, France, French Guiana, Germany, Ghana, Hong Kong (China),
420 India, Indonesia, Ireland, Israel, Italy, Kenya, Mexico, Nigeria, Portugal, Puerto Rico (US), South
421 Africa, Spain, Switzerland, Turkey, Uganda, United Kingdom, United States) with data from
422 21,977 cases of confirmed or suspected SARS-CoV-2 infections in pregnancy or the postpartum
423 period. This iteration of the analysis included data from any study that met eligibility criteria and
424 were able to share data by December 2021 (Figure 1). One study (Crovetto et al., 2020) included
425 two distinct cohorts with separate recruitment strategies, which were considered separately
426 throughout the analysis. Further, the Cancovid-Preg study (Money, 2020) follows a cohort of
427 pregnant women with SARS-CoV-2 infection and their infants in Canada; because the study was
428 ongoing at the time of data submission, risk factor data availability and sample size is slightly
429 different for maternal COVID-19 severity outcomes (n=2,045) and neonatal/birth outcomes
430 (n=2,626). Therefore, we present the outcomes from the Cancovid-Preg study as two independent
431 subsets of the cohort in our tables (see Cancovid-Preg – Maternal Subset and Cancovid-Preg –
432 Infant Subset).

433

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

439

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

441

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

450

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

460

461 *Synthesis of results*

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

467

468 **[Figure 2. Incidence by outcome and study]**

469

470 *Comorbidities.* We found that pregnant women with COVID-19 who also had chronic illnesses,
471 including diabetes, hypertension, and cardiovascular disease, were at higher risk for most
472 outcomes related to COVID-19 severity, as well as pregnancy-related death (Table 2). Risk of
473 mortality was 3.79 times higher for pregnant women with pre-existing diabetes (95% CI: 2.61,
474 5.50; 15 studies, 15,705 pregnancies; Table S6), 2.75 times higher for those with pre-existing
475 hypertension (95% CI: 1.76, 4.28; 14 studies, 15,705 pregnancies; Table S7), and 16.76 times
476 higher for those with cardiovascular disease (95% CI: 4.42, 63.64; 11 studies, 15,368 pregnancies;
477 Table S8), compared to those without these chronic health conditions.

478

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

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

487

488 Although less data was available on HIV coinfection with COVID-19 during pregnancy, we found
489 coinfection increased the risk of severe COVID-19 disease (Table 2). Among pregnant women
490 with COVID-19, those with HIV had a 67% increased risk of being admitted to the ICU (95% CI:
491 1.06, 2.63, 3 studies, 2,150 pregnancies) and 72% increased risk of needing critical care (95% CI:
492 1.10, 2.69, 3 studies, 2,150 pregnancies). Those with both COVID-19 and HIV were more likely
493 to be delivered by cesarean delivery (RR 1.51, 95% CI: 1.00, 2.28, 3 studies, 1,688 pregnancies),
494 and babies born to those with HIV coinfection were at increased risk for perinatal death (RR 8.63,
495 95% CI: 1.40, 53.31, 3 studies, 1,727 fetuses/infants) (Table S9).

496

497 *Nutritional Status and BMI.* We found increased risk of COVID-19 severity among pregnant and
498 postpartum people who were either obese or underweight compared to those who were normal-
499 overweight prior to pregnancy (Table 3). Pregnant women with a pre-pregnancy or early
500 pregnancy BMI of 30 kg/m² or greater were at increased risk for ICU admission (RR 1.81, 95%
501 CI: 1.26, 2.60), ventilation (RR 2.05, 95% CI: 1.20, 3.51), and pneumonia (RR 1.66, 95% CI: 1.18,
502 2.33), but not for pregnancy-related death (RR 1.00, 95% CI: 0.19, 5.26) (Table S10).

503

504 Pregnant women who were underweight pre-pregnancy had more than five times increased risk
505 for ICU admission (RR 5.53, 95% CI: 2.27, 13.44, 8 studies, 1,721 pregnancies) or any critical
506 care (RR 5.71, 95% CI: 2.40, 13.59, 7 studies, 1,822 pregnancies), more than nine times increased
507 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

530 *Maternal Age.* Older maternal age (35-45 years) was associated with multiple COVID-19-
531 associated adverse outcomes compared to those aged 20-34 years (Table 4). Older maternal age
532 was associated with increased risk of ICU admission (RR 1.60, 95% CI: 1.36, 1.89, 16 studies,
533 18,758 pregnancies), ventilation (RR 2.13 95% CI: 1.68, 2.71, 16 studies, 18,407 pregnancies),
534 any critical care (RR 1.62, 95% CI: 1.38, 1.90, 15 studies, 18,452 pregnancies) (Table S13), and
535 pneumonia diagnosis (RR 1.51, 95% CI: 1.35, 1.70, 10 studies, 15,670 pregnancies). Older
536 pregnant women also had increased risk for placental abruption (RR 3.94, 95% CI: 1.40, 11.13)
537 and cesarean delivery (RR 1.21, 95% CI: 1.10, 1.32). Babies born to older pregnant women with
538 COVID-19 had higher risk of stillbirth, perinatal death, and NICU admissions, as well as higher
539 risk of being born preterm or low birthweight.

540
541 Compared to pregnant women with COVID-19 ages 20 to 34, younger pregnant women (age 15-
542 19) were at increased risk for preeclampsia or eclampsia (RR 3.27, 95% CI: 1.11, 9.64, 8 studies,
543 1,074 pregnancies) (Table S14). Babies born to younger women with COVID-19 had higher risks
544 of stillbirth, perinatal death, and neonatal death. Younger women with COVID-19 were also more
545 likely to experience adverse pregnancy outcomes, including moderate preterm birth (RR 2.90, 95%
546 CI: 1.18, 7.14, 7 studies, 1,321 infants), very low birthweight (RR 6.27, 95% CI: 1.86, 21.15, 13
547 studies, 3,203 infants), and small-for-gestational age (<3rd percentile, RR 4.33, 95% CI: 1.87,
548 10.06, 14 studies, 3,901 infants).

549
550 *Primiparity.* Overall, we found limited differences in risks of adverse outcomes among
551 primiparous compared to multiparous pregnant women with COVID-19 (Table 4). Primiparous
552 women were less likely to be diagnosed with pneumonia than multiparous women (RR 0.59, 95%

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

556

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

565

566 We also found increased risk of preterm and moderate preterm birth among symptomatic pregnant
567 women (RR 1.30, 95% CI: 1.06, 1.60, and RR 1.65, 95% CI: 1.00, 2.73, respectively). However,
568 when we restricted to only pregnant women with infection onset prior to 37 weeks' gestation for
569 preterm birth and prior to 34 weeks' gestation for moderate preterm birth, we found asymptomatic
570 pregnant women had an increased risk of preterm and moderate preterm birth (RR 0.71, 95% CI:
571 0.52, 0.97, and RR 0.57, 95% CI: 0.41, 0.81), compared to symptomatic pregnant women.

572

573 **Comment**

574 *Principal Findings*

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

582

583 *Comparison with Existing Literature*

584 We found that among pregnant women with COVID-19, those living with HIV were nearly twice
585 as likely to be admitted to the ICU or need critical care. Women living with HIV already have
586 greater likelihood of antenatal, delivery, and postpartum complications, including preterm birth,
587 cesarean delivery, postpartum sepsis, venous thromboembolism, postpartum infection, and
588 mortality²². Neonates born to these women are at higher risk due to prematurity, low birthweight,
589 intrauterine growth restriction, resulting in higher rates of NICU admission, and neonatal mortality
590 ^{22,23}. Factors related to HIV severity such as HIV progression, antiretroviral therapy, CD4 cell
591 count, and viral load additionally affect the immune response to coinfection²⁴.

592

593 A recent systematic review of SARS-CoV-2 infection among people living with HIV in the general
594 population found strong evidence that HIV is a risk factor for both SARS-CoV-2 infection and for
595 mortality due to COVID-19; that review did not examine pregnant and postpartum women as a
596 subgroup of interest²⁵. Given that pregnant women are at higher risk for severe COVID-19 illness
597 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

621 mechanisms of action based on this analysis. Nonetheless, our findings on the association between
622 undernutrition or anemia and preterm and stillbirths among pregnant women with COVID-19
623 further underscore the need for close monitoring and management of this group, including
624 provision of additional nutritional support to prevent disease and prevent adverse birth outcomes
625 ^{33,35}.

626
627 We found pregnant women with any COVID-19 symptoms were at increased risk for ICU
628 admission, ventilation, cesarean delivery, and preterm birth compared to asymptomatic pregnant
629 women based on a large sample size of global studies; while a previous systematic review on
630 published literature examined this question, data on symptomatic compared to asymptomatic
631 SARS-CoV-2 infection in pregnancy were only available for a small subset of studies and
632 participants in this review (4 studies on ICU admission with 1,178 participants; 3 studies on
633 mechanical ventilation with 1,023 participants, 9 studies on cesarean delivery and preterm birth
634 with 4,233 participants) ⁵. Our study found that symptomatic pregnant women are more likely to
635 give birth preterm than asymptomatic pregnant women with SARS-CoV-2 infection.

636
637 However, in a sensitivity analysis restricted only to participants infected prior to 37 weeks
638 gestational age, we found that asymptomatic pregnant women are more likely than symptomatic
639 pregnant women to have a preterm birth. These seemingly conflicting results may be related to
640 features of study sampling; for example, this difference may be due to the large percentage of
641 asymptomatic participants who are identified during screening at labor and delivery. Across the
642 10 studies included in the restricted analysis, 64% of babies born to asymptomatic participants

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

645

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

656

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

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

675

676 We identified risk factors for adverse maternal morbidities, fetal, and neonatal outcomes among
677 pregnant women with COVID-19, and these are generally consistent with risk factors for adverse
678 pregnancy outcomes including pre-existing diabetes or hypertension³⁶⁻³⁸, cardiovascular disease
679³⁹, obesity^{38,40}, underweight^{40,41}, anemia^{42,43}, and HIV infection^{22,23}. Because the studies in this
680 IPD meta-analysis only included individuals with SARS-CoV-2 infection, we were unable to
681 evaluate whether the presence of infection confers additional risk beyond the risk due to risk
682 factors without the presence of COVID-19 infection. Similarly, we identified risk factors for
683 adverse COVID-19 related outcomes, and these are generally consistent with risk factors identified
684 in the general non-pregnant population. Nonetheless, this study provides high-quality evidence
685 that pregnant women with these risk factors are also at risk for adverse outcomes from COVID-19
686 illness.

687

688 **Conclusions and Implications**

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

695

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

Study PI	Countries	Total pregnancies	Livebirths	Mean age (SD)	Gestational Age at Infection					Hospitalized (%)	Admitted to ICU (%)	Data collected through
					1st Tri	2nd Tri	3rd Tri	Postpartum	Unknown			
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
Nachegea, 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, Tippet 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.

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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	1 6	2.55 (1.97, 3.31)	1 4	2.10 (1.63, 2.70)	12	2.98 (1.83, 4.85)	3	1.67 (1.06, 2.63)
Ventilation	1 4	5.88 (2.77, 12.48)	1 3	4.87 (2.93, 8.09)	12	6.11 (2.85, 13.08)	3	1.01 (0.30, 3.32)
Critical Care	1 4	3.03 (1.86, 4.92)	1 2	2.42 (1.73, 3.39)	11	2.82 (1.78, 4.48)	3	1.72 (1.10, 2.69)
Pneumonia	1 0	2.02 (1.65, 2.47)	1 8	2.13 (1.74, 2.61)	8	1.18 (0.65, 2.16)	1	--
Pregnancy-related death	1 5	3.79 (2.61, 5.50)	1 4	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	1 0	2.98 (1.61, 5.51)	1 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	1 2	1.40 (1.13, 1.74)	1 1	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	1 6	6.53 (2.13, 20.05)	1 5	3.43 (1.41, 8.37)	12	9.10 (2.24, 36.92)	4	2.97 (0.35, 25.26)

Perinatal death	1 2	7.71 (2.12, 28.03)	1 1	4.94 (2.07, 11.81)	10	8.47 (2.70, 26.53)	3	8.63 (1.40, 53.31)
Early neonatal death	1 2	6.97 (1.07, 45.27)	1 1	11.74 (3.23, 42.70)	10	12.58 (2.69, 58.80)	3	--
Neonatal death ³	1 3	6.85 (1.22, 38.49)	1 2	8.10 (2.71, 24.25)	10	13.04 (3.18, 53.43)	4	--
NICU Admission at Birth	1 8	1.83 (1.15, 2.93)	1 6	2.28 (1.26, 4.13)	5	2.02 (0.65, 6.30)	1	--
Adverse Birth Outcomes								
Very low birthweight (<1500g)	1 3	5.28 (2.62, 10.63)	1 2	6.30 (3.16, 12.55)	10	8.35 (3.64, 19.19)	4	2.41 (0.80, 7.20)
Low birthweight (<2500g)	1 3	1.80 (1.21, 2.69)	1 2	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)	1 4	4.11 (1.53, 11.06)	1 3	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)	1 4	1.62 (0.81, 3.21)	1 3	1.91 (1.29, 2.84)	11	1.84 (1.11, 3.03)	4	1.57 (0.93, 2.63)
Moderate preterm birth (<34w)	1 4	3.23 (2.09, 5.01)	1 3	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	1 8	2.03 (1.24, 3.31)	1 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)	1 5	2.25 (1.77, 2.86)	1 4	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	1 8	1.40 (0.97, 2.01)	1 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 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.

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 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.

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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.

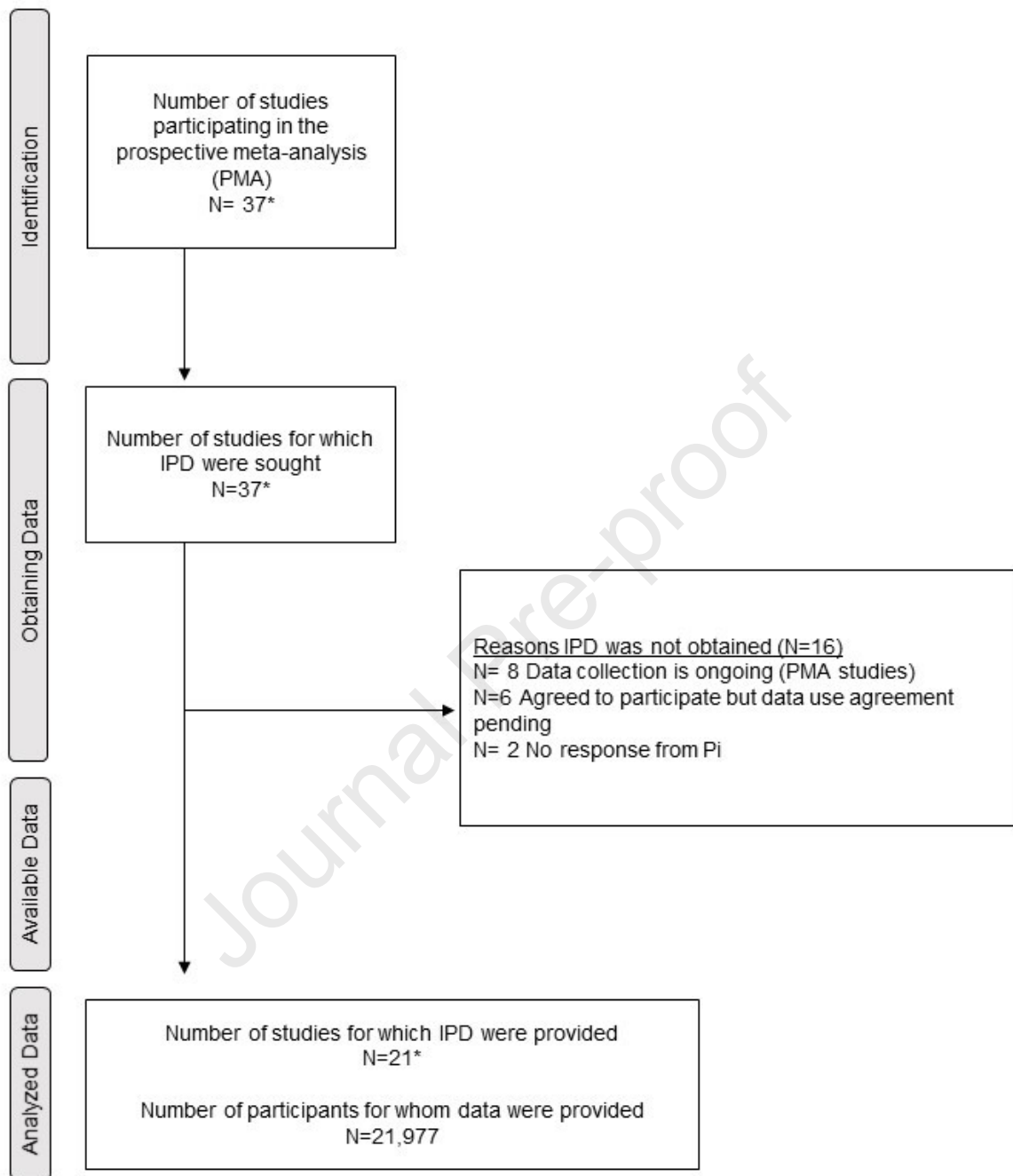
Figure Legends

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 these 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."

