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Diabetes mellitus, maternal adiposity, and insulin-dependent gestational diabetes are associated with Covid-19 in pregnancy: The INTERCOVID Study

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Diabetes mellitus, maternal adiposity, and insulin-dependent gestational diabetes are associated with Covid-19 in pregnancy: The INTERCOVID Study

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WORD COUNT: 3153 without abstract

Condensation: (20 words)

Pre-existing diabetes and overweight/obesity are risk factors for Covid-19 in pregnant women; insulin-dependent gestational diabetics are also at increased risk.

Short title: Covid-19 and gestational diabetes, diabetes, and BMI in pregnant women

AJOG at a Glance: (128 words)

A. Why was this study conducted?

- We quantified the risk of Covid-19 in pregnancy for women with gestational diabetes, pre-existing diabetes mellitus (DM) or overweight/obesity by pre- or early-pregnancy body mass index.

B. What are the key findings?

- A Covid-19 diagnosis in pregnancy was associated with pre-existing DM (RR=1.94, 95% CI=1.55, 2.42) and high body mass (≥25 kg/m^2) (RR=1.20; 95% CI=1.06, 1.37), and gestational DM (risk ratio (RR)=1.21; 95% CI: 0.99 to 1.46), specifically among those who were insulin-dependent whether they were of normal weight (RR=1.79, 95% CI: 1.06, 3.01) or overweight/obese (RR=1.77, 95% CI=1.28, 2.45).
- **C. What does this study add to what is already known?**
  Pregnant women with DM or overweight/obesity are at high risk for Covid-19. Insulin-dependent gestational DM is also associated with Covid-19 diagnosis.

ABSTRACT (405 words)

Background: Among non-pregnant individuals, diabetes mellitus (DM) and high body mass index (BMI) increase the risk of Covid-19 and its severity.

Objective: To determine whether DM and high BMI are risk factors for Covid-19 in pregnancy and whether gestational diabetes mellitus (GDM) is also associated with covid-19 diagnosis.

Study Design: INTERCOVID was a multinational study, conducted between March 2020 and February 2021 in 43 institutions from 18 countries, enrolling 2184 pregnant women ≥18 years; 2071 were included in these analyses. For each woman diagnosed with Covid-19, two non-diagnosed women delivering or initiating antenatal care at the same institution were also enrolled. Main exposures were pre-existing DM or high BMI (overweight/obesity defined as ≥25 kg/m^2), and GDM in pregnancy. Main outcome was a confirmed diagnosis of Covid-19 based on an RT-PCR test, antigen test, antibody test, radiological pulmonary findings, or ≥2 predefined Covid-19 symptoms at any time during pregnancy or delivery. Relationships of exposures and Covid-19 diagnosis were assessed using generalized linear models with a Poisson distribution and log link function, with robust standard errors to account for model misspecification. We also conducted sensitivity analyses: 1) restricted to those with an RT-PCR or antigen test in the last week of pregnancy; 2) restricted to those with an RT-PCR or antigen test during the entire pregnancy; 3) generating values for missing data using multiple imputation; and 4) analyses controlling for month of enrollment. In addition, among those who were diagnosed with Covid-19, we examined whether having GDM, DM, or high BMI, increased risk for having symptomatic vs. asymptomatic Covid-19.

Results: Covid-19 was associated with preexisting DM (RR=1.94, 95% CI=1.55, 2.42), overweight/obesity (RR=1.20; 95% CI=1.06, 1.37), and GDM (RR=1.21; 95% CI=0.99, 1.46). The GDM association was specifically among women requiring insulin, whether they were of

normal-weight (RR=1.79, 95% CI=1.06, 3.01) or overweight/obese (RR=1.77, 95% CI=1.28, 2.45). A somewhat stronger association with Covid-19 diagnosis was observed among women with pre-existing DM, whether they were of normal weight (RR=1.93, 95% CI=1.18, 3.17) or overweight/obese (RR=2.32, 95% CI=1.82, 2.97). When the sample was restricted to those with a RT-PCR or antigen test in the week before delivery or during the entire pregnancy, including missing variables using imputation, or controlling for month of enrollment, the observed associations were comparable.

Conclusion: DM and overweight/obesity are risk factors for Covid-19 diagnosis in pregnancy, and insulin-dependent GDM is also associated with the disease. It is therefore essential that those women with these co-morbidities are vaccinated.

Key words: Gestational diabetes, diabetes mellitus, body mass index, obesity, overweight, Covid-19, SARS-CoV-2, pregnancy

INTRODUCTION

Pregnant women with Covid-19 are at increased risk for severe illness compared to other pregnant and non-pregnant women.[1–4] Data from the multinational INTERCOVID study showed that neonates born to women with Covid-19 are also at increased risk of morbidity and mortality.[3] As with non-pregnant individuals, pregnant women with co-morbidities, such as diabetes mellitus (DM) and overweight/obesity, are at risk for more severe Covid-19 outcomes,[1,4–6] including mortality. In non-pregnant individuals, DM, particularly among insulin users,[7,8] and high body mass index (BMI)[9–11] not only increase risk of severe Covid-19 outcomes but SARS-CoV-2 infection itself.

As pregnant women were initially excluded from Covid-19 vaccine trials,[12] there are few data on the safety of the Covid-19 vaccines during pregnancy.[13] Concerns about safety have contributed to the lower levels of vaccine acceptance among pregnant compared to non-pregnant women.[14,15] As of 6 November 2021, only 35.3% of pregnant women in the United States are vaccinated according to the most recent CDC report, with rates as low as 20.6% among African Americans.[16] These low rates are in spite of the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine recommendation of Covid-19 vaccination for pregnant and lactating women.[17,18] Most recently, the Centers for Disease Control and Prevention (CDC) urged pregnant women to be vaccinated,[19] citing evidence from the V-safe pregnancy registry on safety of the mRNA vaccines[13] and recent data from safety monitoring systems.[20]

Herein, we explored in the INTERCOVID study the association in pregnant women between a Covid-19 diagnosis and pre-existing DM or high BMI, as well as the diagnosis of gestational diabetes mellitus (GDM). Establishing the impact of co-morbidities on the risk of infection in pregnant women can provide additional impetus for Covid-19 vaccination among those who remain hesitant.

MATERIALS AND METHODS

INTERCOVID was a multinational study assessing the effects of Covid-19 in pregnancy on mothers and neonates up to the time of their hospital discharge.[3,21] Briefly, 2184 pregnant women ≥18 years old, including 725 diagnosed and 1429 not diagnosed with Covid-19, were prospectively enrolled at 43 institutions in 18 countries (Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland, United Kingdom, and the United States) between 2 March 2020 and 2 February 2021 (see Supplemental Figure 1). Missing information on covariates reduced the sample size from 2184 to 2071 (approximately 5% of the total sample), which included 672 diagnosed with Covid-19 and 1399 not diagnosed.

Women received a COVID-19 diagnosis based on a positive RT-PCR or antigen test (90.3%), a positive antibody test (1.8%), radiological pulmonary findings suggestive of Covid-19 (0.6%), or ≥2 predefined Covid-19 symptoms (7.3%) at any time during pregnancy, with approximately 80% diagnosed at delivery (see Supplemental Table 1 for Covid-19 tests and Supplemental Table 2 for symptoms recorded and their frequencies).Two 'non-diagnosed' women were enrolled for each Covid-19-diagnosed woman. The non-diagnosed women had to be of similar gestation age (±2 weeks), to be receiving standard prenatal care from the same institution, and to be the patients who were provided care immediately following the diagnosed women. If a non-diagnosed woman was later diagnosed with Covid-19, she was maintained as non-diagnosed, using an "intention to treat approach".

The Oxford Tropical Research Ethics Committee and all local ethics committees approved the study. Women provided informed consent (oral or written) according to local requirements, except if a waiver/exemption of such consent was granted by a local committee.

Diagnosis of diabetes mellitus, high body mass, and gestational diabetes mellitus

Information on pre-existing diabetes mellitus, body mass, and gestational diabetes mellitus was abstracted from medical records using standardized forms. Women's height was measured in duplicate using an adult stadiometer and recorded in centimeters (cm) to 1 decimal place. Women's first trimester weight was measured; if unavailable, women were asked to approximate weight before pregnancy. Woman's prepregnancy or first trimester weight was recorded in kilograms (kg) to 1 decimal place. Body mass index (BMI) was calculated and categorized as normal weight (18.50-24.99), overweight (25.00- 29.99), and obese BMI ≥30 kg/m^2 (according to the World Health Organization definition).[22] From medical records, we also collected information on the presence or absence of GDM during the index pregnancy and whether the women had been prescribed insulin for GDM, as well as whether there was a previous diagnosis of DM. Women with pre-existing DM were considered not to have GDM (per the definition of GDM).

Data management and analysis

We used the same centrally coordinated data management system established for the INTERGROWTH-21st Project (MedSciNet, London, United Kingdom).[23] All data were entered locally into the online system with its comprehensive, built-in, quality control facility. Queries could be dispatched immediately to the study sites, which provided continuously-cleaned datasets for intermediate analysis. See https://intergrowth21.tghn.org/intercovid/intercovid-study-documents/ and previous publications for more details on study protocol and methods.[3,24]

Statistical analysis

We constructed two primary models for the analysis. The first model examined the association of Covid-19 diagnosis and GDM during the index pregnancy and pre-existing DM; women with no history of either GDM or DM served as the reference group. BMI was also included in this model. Initially, BMI was included as a 3-level variable but because there was no clear dose response in the upper two levels, the categories of overweight or obese were

collapsed to maximize sample size in that statum. Women with BMI ≥25 kg/m^2 were compared to those with BMI <25 kg/m^2 as the reference group. Covariates for the adjusted models were selected using a directed acyclic graph, and included maternal age (continuous), parity (nulliparous vs. parous), and tobacco use during pregnancy (yes vs. no).

Second, we examined the association of Covid-19 diagnosis and GDM, DM, and BMI in eight subgroups of women, including those with: a) no GDM or DM, and normal weight (reference); b) no GDM or DM, and overweight/obese; c) GDM not using insulin and normal weight; d) GDM not using insulin and overweight/obese; e) GDM using insulin and normal weight; f) GDM using insulin and overweight/obese; g) pre-existing DM and normal weight; and h) pre-existing DM and overweight/obese. Maternal age, parity, and tobacco use were also included in this model.

Relationships of exposures and Covid-19 diagnosis were assessed using generalized linear models with a Poisson distribution and log link function, with robust standard errors to account for model misspecification. Analyses were performed using Stata version 15.0.[25]

Sensitivity analyses

As women with GDM are more likely to have closer clinical surveillance during pregnancy, including for Covid-19 symptoms, we included in sensitivity analyses only those who had a RT-PCR or antigen test within the last seven days of pregnancy or on the day of delivery (n=937) (n=342 tested positive, n=595 tested negative)(Supplemental Figure 1). Due to the proximity of testing to delivery, we assumed in these cases that the diagnosis of GDM, which typically develops in the second half of pregnancy, very likely preceded the Covid-19 diagnosis. Women who tested negative for Covid-19 on a RT-PCR or antigen test but were diagnosed by other means (n=12) were excluded from the analysis.

In other sensitivity analyses, we restricted the sample to those who had received RT-PCR or antigen test at any time during pregnancy (607 who tested positive and 683 who tested negative, Supplemental Figure 1). Because the pandemic underwent fluctuations in cases in the course of the study, we also conducted sensitivity analyses controlling for month of entry into the study.

As noted above, missing values reduced the sample size by 113 women (n=33 for GDM diagnosis, n=88 for BMI category, n=22 for tobacco use during pregnancy, and n=7 for previous parity). In order to include these participants in sensitivity analyses, we generated values for all missing data employing multiple imputation using chained equations with 10 iterations, which brought the sample size back to 2184 women. We examined the same associations as above of Covid-19 diagnosis in relation to GDM, DM, and BMI, as well as by subgroups (e.g., by insulin use, body mass).

We recorded symptomalogy, but did not record information on severity of Covid-19. Hence, we could only consider whether GDM, DM, and BMI were more likely to be related to asymptomatic or symptomatic disease based on the women's self-report. We restricted these models to women diagnosed with Covid-19 (n=672). We examined the association of having Covid-19 symptoms vs. not having symptoms with GDM and DM (vs. women with neither medical condition), and women who were overweight/obese (vs. women of normal BMI). We repeated these analyses restricting the sample to those diagnosed by a positive RT-PCR or antigen test within the last seven days of pregnancy or on the day of delivery (n=342).

RESULTS

Women enrolled in these analyses averaged 30.2 years of age (SD=6.1) and 43.4% were nulliparous (Table 1). GDM and DM were diagnosed in 9.4% (n=194) and 2.6% (n=53) of

participants, respectively; 43.0% were overweight/obese. Overall, after adjusting for potential confounders, women with pre-existing DM had nearly double the risk of Covid-19 (RR=1.94, 95% CI=1.55, 2.42) (Table 2) and those who were overweight/obese had a 20% increase in risk (RR=1.20, 95% CI=1.06, 1.37). Women who developed GDM had a 21% increased risk of Covid-19 (RR=1.21, 95% CI=0.99, 1.46).

In Figure 1, we present the association of Covid-19 diagnosis among women in various exposure strata compared to women with a normal BMI (<25 kg/m^2) who did not have pre-existing DM or GDM. There was no association of GDM and Covid-19 diagnosis in women who were of normal weight and not using insulin (RR=0.98, 95% CI=0.64, 1.52), However, Covid-19 diagnosis was associated with being overweight/obese among women who did not have GDM (RR=1.20, 95% CI=1.04, 1.37), which was only slightly, but not significantly (p=0.44), stronger among those with GDM (no insulin) who were also overweight/obese (RR=1.34, 95% CI=1.01, 1.78). There was approximately an 80% increased risk of being diagnosed with Covid-19 among women with GDM using insulin whether they were of normal BMI (RR=1.79, 95% CI=1.06, 3.01) or overweight/obese (RR=1.77, 95% CI=1.28, 2.45). We observed the strongest association with Covid-19 diagnosis among women with pre-existing DM, which was only slightly higher (p=0.50) if they were overweight/obese (RR=2.32, 95% CI=1.82, 2.97) than if they were of normal weight (RR=1.93, 95% CI=1.18, 3.17).

In sensitivity analyses, when the sample was restricted to participants who had a Covid-19 RT-PCR or antigen test in the week before delivery, although the sample size was reduced by more than 50%, the observed associations were similar (Figure 1 and Supplemental Table 3). Results were comparable when participants were restricted to those who received RT-PCR or antigen tests at any time during pregnancy (Supplemental Table 4), when we controlled for month of enrollment (Supplemental Table 5), or when we performed multiple imputation on missing values (Supplemental Table 6).

When considering only the 672 women who were diagnosed with Covid-19 (Supplemental Table 7), neither having GDM (RR=0.96, 95% CI=0.88, 1.03) nor pre-existing DM (RR=0.97, 95% CI=0.87, 1.07) was associated with the presence of Covid-19 symptoms, suggesting that women with these conditions were not more likely to have symptomatic than asymptomatic infection. However, women who were overweight/obese were more likely to report Covid-19 symptoms than normal-weight women (RR=1.06, 95% CI=1.01, 1.11). Results were comparable when restricting the analysis to the 342 women with a positive RT-PCR or antigen test in the week before delivery.

COMMENT

a. Principal Findings: In the INTERCOVID multinational study of over 2000 pregnant women from 18 countries, pre-existing DM and higher BMI were each associated with a higher risk of being diagnosed with Covid-19, after controlling for other potential confounders. Although women with GDM overall were marginally at higher risk of Covid-19 diagnosis, we did observe a significantly higher risk of Covid-19 diagnosis associated with GDM in insulin users; the strength of the association approached that for DM, regardless of a woman's BMI. High BMI, but not GDM or DM, was related to more symptomatic disease among those with Covid-19.

b. Results in the Context of What We Know: Our results support the evidence in non-pregnant individuals, demonstrating that pre-existing DM is associated with risk of SARS-CoV-2 infection. Our findings are biologically plausible given higher rates of other types of infection, e.g. pneumonia,[26] urinary tract infections,[27] and vaginitis,[28] in individuals with DM, including during pregnancy.[29]

Acilli posed the question as to the direction of the relationship between Covid-19 and DM.[30] He concluded that although it is possible that SARS-CoV-2 can cause DM due to *in vitro* evidence demonstrating the susceptibility of β-cells to SARS-CoV-2 and that any inflammatory state can lead to insulin resistance, the more likely causal direction is that diabetes is a risk

factor for infection. Supporting this hypothesis, other researchers have shown that pancreatic islet cells express the angiotensin-converting enzyme 2 (ACE2) receptor and that SARS coronaviruses depend upon the ACE2 receptor for attachment and invasion into cells.[31] Zhao and co-workers[32] underlined the essential roles for glycosylation in mediating ACE2 receptor binding, and antigenic shielding of Sars-Cov-2 spikes. Specifically, the SARS-CoV-2 spike protein, necessary for cell adhesion and invasion, and ACE2 are glycosylated or glycated. These glycan-protein interactions in the SARS-CoV-2 spike protein – ACE2 receptor complex are important for cell invasion and infection.[32] DM is associated with increased glycation or glycosylation in a variety of cells and tissues.[33] Hill et al. also have suggested that hyperglycemia increases viral replication and suppresses the anti-viral immune response as evidenced by animal models of DM showing numerous structural changes to the lung, including increased permeability of the vasculature and break-down of the alveolar epithelium.[34,35] Similar hypotheses have been proposed for DM and GDM and Covid-19 infection during pregnancy.[36]

In the present study of Covid-19 in pregnancy, the women with DM had this condition diagnosed prior to pregnancy and thus, prior to Covid-19 diagnosis. Although the directionality of the association between Covid-19 and GDM is less clear in the larger cohort, the confirmation of results in the subgroup of women who received a Covid-19 test around the time delivery provides reassurance that GDM diagnoses preceded infection and supports the hypothesis that the hyperglycemic state decreased the immune response to infection.[26–28,37] The fact that pre-existing DM poses a higher risk than GDM, except in women who are insulin-dependent, is also biologically plausible given that women with pre-existing disease have been in this hyperglycemic state for a longer period of time. That GDM was only associated with Covid-19 diagnosis in women who were using insulin indicates that they had more severe GDM.

As in other observational epidemiologic studies, our findings could be explained by uncontrolled confounding. However, the findings persisted after we controlled for potential

confounders identified by a directed acyclic graph, and the Covid-19 non-diagnosed and diagnosed women were selected from the same hospital/country, gestation duration, and date, assuring similar clinical practices by location over the course of the Covid-19 pandemic.

c. Clinical Implications: Covid-19 during pregnancy is known to increase severe maternal morbidity and death,[2] particularly intubation and ICU admission.[3] Our data provide additional information about the increased risk of infection associated with preexisting co-morbidities such as DM and high body mass, and the association with insulin-dependent GDM. Women with these conditions should be monitored carefully for Covid-19 infection, glycemic control, and weight gain.[38] Most importantly, unvaccinated pregnant women and those considering pregnancy with these risk factors should be strongly encouraged to be vaccinated.

d. Strength and Limitations: We employed data from a large-scale multinational study that was specifically conducted to assess the symptoms and effects of Covid-19 during pregnancy on maternal and neonatal outcomes when compared with pregnant women not-diagnosed with Covid-19 and enrolled concomitantly in the same facility, same level of care, and at the same gestational age to minimize any selection bias. The study abstracted information on maternal and neonatal outcomes and used rigorous data collection procedures, employing structured forms and stringent quality control across 43 institutions to record morbidity.

The proportions of women diagnosed on the basis of Covid-19 symptoms alone and those diagnosed by RT-PCR or antigen tests changed during the course of the study in each country as laboratory testing became more available. It remains possible some of those not-diagnosed with Covid-19 may have included infected women who were asymptomatic and not identified, either because routine testing was not available or because they became infected after enrollment. This potential for misclassification would have led to more conservative estimates.

Although DM and high BMI preceded infection in all cases, GDM very likely preceded infection for roughly half of those who were diagnosed by RT-PCR or antigen tests around the time of delivery. It remains possible that women admitted to the hospital with severe complications of pregnancy, such as uncontrolled GDM or DM, were more likely to be tested for, or diagnosed with, Covid-19. However, the study design avoided such systematic bias by selecting two women immediately after a diagnosed woman at the same level of care as the reference group. In addition, when we restricted the analysis to those women who were PCR or antigen tested, the results were similar, suggesting that this bias was minimal.

In contrast to women of high BMI with Covid-19, women with GDM or DM were not more likely to have symptomatic Covid-19. Although we had information on Intensive Care Unit (ICU) hospitalization and death, we could not attribute whether Covid-19 was the cause;[3] thus, we could not conduct analyses according to the Covid-19 severity classification proposed by the National Institutes of Health, because we did not have the complete information required by these relatively recent criteria.[39]

Other limitations of this observational study are that the medical record abstractions did not indicate the criteria for GDM diagnosis, or the time during the pregnancy at which it was diagnosed. We did not interfere with the usual clinical care provided by the hospitals or clinicians provided across the 43 hospitals and clinical practices, including the protocols for prescribing insulin to women with GDM, which may have varied across these institutions[40] In addition, protocols for GDM screening may have changed over the course of the pandemic in order to prevent infection.[41–44] However, our study design, in which Covid-19 diagnosed and non-diagnosed women were matched by hospital and time, should have controlled for these changes in screening protocols.

d. Research Implications: The limitations as well as strengths of the present study noted above can inform future studies. For example, prospective multinational cohort studies in

which pregnant women are enrolled early in pregnancy, routinely and frequently tested for Covid-19 using RT-PCR, monitored carefully for onset of symptoms and severity of disease, and screened uniformly for GDM would be important to confirm our findings. In addition, future research should study the long-term sequelae of Covid-19 during pregnancy on both the woman and her child. Lastly, given the risk of Covid-19 to pregnant women, especially in those with co-morbidities, public health programs should be implemented to overcome vaccine hesitancy and barriers to access.

f. Conclusions: Our findings suggest that DM and overweight/obesity are more prevalent in women diagnosed with Covid-19 in pregnancy than in women not diagnosed with Covid-19, suggesting that these risk factors make infection more likely. Covid-19 diagnosis is also associated with GDM among those who are using insulin. This information can help guide decision-making for those women who still may be hesitant to receive Covid-19 vaccination.

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522 **Table 1.** Baseline characteristics among women in the INTERCOVID study (n=2071).

Characteristic	
Maternal age (years), Mean ± SD	30.2 ± 6.1
Parity, N (%)	
Nulliparous	898 (43.4)
Parous	1173 (56.6)
Pre-pregnancy BMI (kg/m^2), Mean ± SD	25.3 ± 5.8
Normal weight, <25 kg/m^2 , N (%)	1180 (57.0)
Overweight, 25 to <30 kg/m^2 , N (%)	535 (25.8)
Obese, ≥30 kg/m^2 , N (%)	356 (17.2)
Tobacco use during pregnancy, N (%)	
Yes	72 (3.5)
No	1999 (96.5)
Pre-existing diabetes mellitus (DM), N (%)	
Yes	53 (2.6)
No	2018 (97.4)
Pre-existing hypertension, N (%)	
Yes	56 (2.7)
No	2012 (97.3)
Gestational diabetes mellitus (GDM) during index pregnancy, N (%)	
Yes	194 (9.4)
No	1877 (90.6)
Gestational age at delivery (weeks), Mean ± SD	38.3 ± 3.3

523 BMI = body mass index

Table 2. Associations between gestational diabetes (GDM), pre-existing diabetes mellitus (DM), and body mass index, and Covid-19 diagnosis in the INTERCOVID study (n=2071).[a]

	N (column %)	Covid-19 diagnosis N (row %)	No Covid-19 diagnosis N (row %)	Unadjusted RR and 95% CI	Adjusted RR and 95% CI
Gestational Diabetes (GDM) or Diabetes Mellitus (DM)					
No GDM, no DM	1824 (88.1)	564 (30.9)	1260 (69.1)	Ref.	Ref.
GDM, no DM	194 (9.4)	75 (38.7)	119 (61.3)	1.19 (0.98, 1.44)†	1.21 (0.99, 1.46)†
Pre-existing DM	53 (2.6)	33 (62.3)	20 (37.7)	1.88 (1.51, 2.36)*	1.94 (1.55, 2.42)*
Body Mass					
Normal weight <25 kg/m^2	1180 (57.0)	344 (29.2)	836 (70.8)	Ref.	Ref.
Overweight/obese ≥25 kg/m^2	891 (43.0)	328 (36.8)	563 (63.2)	1.21 (1.06, 1.37)*	1.20 (1.06, 1.37)*

[a]Adjusted for maternal age, parity, and tobacco use during pregnancy.

†p<0.1; *p<0.05

Supplemental Table 1. Real Time Polymerase Chain Reaction, antigen tests, and antibody tests for SARS-Cov-2 used in the participating centers.

Real time PCR tests	Antibody tests
• Abbott realtime SARS-Cov-2 • Altona diagnostics RealStar SARS-CoV-2 RT-PCR • Aptima SARS-COV-2 Assay • Argene SARS-CoV-2 R-gene • BioFire® Respiratory 2.1 Panel with SARS-CoV-2 • Biozym BMS Magnetic induction cycler RT-PCR • Boshpore Novel Coronovirus (2019-NCOV) detection kit • Cepheid Xpert Xpress SARS-COV-2 • Dan Gene RT-PCR • DNA-Technology Research & Production LLC Russia SARS-CoV-2/SARS-CoV Multiplex RT-PCR • EUROIMMUN AG EURORealTime SARS-CoV-2 • GeneFinder COVID-19 Plus RealAmp Kit • Hologic SARS-CoV-2 Real-time RT-PCR assay • Liferiver SARS-CoV-2 E gene, N gene, ORF1ab gene • Roche SARS-CoV-2 RNA PCR • Sansure MA6000 • SD Biosensor Standard Q COVID-19 Antigen • Seegene Allplex 2019-nCoV Assay • Simplexa COVID-19 Direct kit • TaqPath 1-Step RT-qPCR Master Mix	• Abbott SARS-Cov-2 IgG • Canea rapid IgG and IgM antibodies serology kits • DiaSorin Liaison SARS-CoV-2 S1/S2 IgG • EUROIMMUN Anti-SARS-CoV-2 ELISA (IgG) • Healgen COVID-19 Antibody Rapid Detection Kit • Roche COVID-19 antibody test • SD Biosensor Standard Q COVID-19 IgM/IgG Duo • Shenzhen YHLO Biotech Co, Ltd SARS-CoV-2 antibodies IgM and IgG CLIA kits • Vircell ELISA SAR IgM+IgA • Vircell ELISA SARS-CoV-2 IgG • Wondfo One Step COVID-19 rapid test • Zydus Cadila IgG Kit

Supplemental Table 2. Frequency of symptoms[a] among pregnant women diagnosed with COVID-19.

Symptoms	Covid-19 'diagnosed' women (n=672) N (%)
Chest pain	19 (2.8)
Diarrhea/vomiting	48 (7.1)
Limb or joint pain	54 (8.0)
Sore throat	70 (10.4)
Flu-like symptoms	76 (11.3)
Runny nose	78 (11.6)
Breathlessness	84 (12.5)
Headache	92 (13.7)
Tiredness/lethargy	110 (16.4)
Loss of smell	116 (17.3)
Fever	88 (28.0)
Cough	232 (34.5)
One symptom	66 (9.8)
Two symptoms	125 (18.6)
Three or more symptoms	209 (31.1)
Asymptomatic	272 (40.5)

[a] Women could have more than one symptom.

Supplemental Table 3. Associations between gestational diabetes (GDM), pre-existing diabetes mellitus (DM), and body mass index, and Covid-19 diagnosis in the INTERCOVID study with a RT-PCR or antigen test in the week before or on day of delivery (N=937).[a]

	N (column%)	Covid-19 diagnosis N (row %)	No Covid-19 diagnosis N (row %)	Unadjusted RR and 95% CI	Adjusted RR and 95% CI
Gestational Diabetes (GDM) or Diabetes Mellitus (DM)					
No GDM, no DM	812 (86.7)	282 (34.7)	530 (65.3)	Ref.	Ref.
GDM, no DM	97 (10.4)	43 (44.3)	54 (55.7)	1.20 (0.94, 1.54)	1.27 (1.01, 1.61)*
Pre-existing DM	28 (3.0)	17 (60.7)	11 (39.3)	1.64 (1.19, 2.25)*	1.76 (1.29, 2.39)*
Body Mass					
Normal weight <25 kg/m^2	562 (60.0)	182 (32.4)	380 (67.6)	Ref.	Ref.
Overweight/obese ≥25 kg/m^2	375 (40.0)	160 (42.7)	215 (57.3)	1.27 (1.07, 1.51)*	1.23 (1.04, 1.45)*

[a]Adjusted for maternal age, parity, and tobacco use during pregnancy.
[†]p<0.1; *p<0.05

Supplemental Table 4. Associations between gestational diabetes (GDM), pre-existing diabetes mellitus (DM), and body mass index, and Covid-19 diagnosis in the INTERCOVID study with a RT-PCR or antigen test at any time in the pregnancy (N=1290).[a]

	N (%)	Crude RR and 95% CI	Adjusted RR and 95% CI
Model 1			
Gestational Diabetes (GDM) or Diabetes Mellitus (DM)			
No GDM, no DM	1123 (87.1)	Ref	Ref.
GDM, no DM	123 (9.5)	1.13 (0.95, 1.35)	1.18 (0.99, 1.40)†
Pre-existing DM	44 (3.4)	1.52 (1.27, 1.83)*	1.60 (1.33, 1.91)*
Body Mass			
Normal weight <25 kg/m^2	750 (58.1)	Ref.	Ref.
Overweight/obese ≥25 kg/m^2	540 (41.9)	1.27 (1.13, 1.43)*	1.24 (1.11, 1.40)*
Model 2			
No GDM or DM, normal weight	696 (54.0)	Ref.	Ref.
No GDM or DM, overweight/obese	427 (33.1)	1.26 (1.11, 1.43)*	1.23 (1.09, 1.40)*
GDM without insulin, normal weight	34 (2.6)	0.93 (0.60, 1.44)	0.96 (0.63, 1.45)
GDM without insulin, overweight/obese	58 (4.5)	1.30 (1.01, 1.68)*	1.33 (1.04, 1.72)*
GDM with insulin, normal weight	9 (0.7)	1.62 (1.01, 2.60)*	1.73 (1.13, 2.64)*
GDM with insulin, overweight/obese	22 (1.7)	1.88 (1.47, 2.40)*	1.91 (1.52, 2.41)*
Pre-existing DM, normal weight	11 (0.9)	1.55 (0.98, 2.44)†	1.63 (1.05, 2.53)*
Pre-existing DM, overweight/obese	33 (2.6)	1.92 (1.57, 2.34)*	1.97 (1.62, 2.38)*

[a]Adjusted for maternal age, parity, and tobacco use during pregnancy.

†p<0.1; *p<0.05

Supplemental Table 5. Associations between gestational diabetes (GDM), pre-existing diabetes mellitus (DM), and body mass index, and Covid-19 diagnosis in the INTERCOVID study (n=2071), with additional adjustment for month of enrollment.[a]

	N (%)	Adjusted RR and 95% CI
Model 1		
Gestational Diabetes (GDM) or Diabetes Mellitus (DM)		
No GDM, no DM	1824 (88.1)	Ref.
GDM, no DM	194 (9.4)	1.23 (1.01, 1.49)*
Pre-existing DM	53 (2.6)	1.93 (1.54, 2.42)*
Body Mass		
Normal weight <25 kg/m^2	1180 (57.0)	Ref.
Overweight/obese ≥25 kg/m^2	891 (43.0)	1.21 (1.07, 1.38)*
Model 2		
No GDM or DM, normal weight	1099 (53.1)	Ref.
No GDM or DM, overweight/obese	725 (35.0)	1.20 (1.05, 1.38)*
GDM without insulin, normal weight	54 (2.6)	1.01 (0.65, 1.55)
GDM without insulin, overweight/obese	87 (4.2)	1.37 (1.03, 1.83)*
GDM with insulin, normal weight	14 (0.7)	1.81 (1.07, 3.08)*
GDM with insulin, overweight/obese	39 (1.9)	1.81 (1.31, 2.51)*
Pre-existing DM, normal weight	13 (0.6)	1.94 (1.18. 3.18)*
Pre-existing DM, overweight/obese	40 (1.9)	2.33 (1.82, 3.00)*

[a]Adjusted for maternal age, parity, tobacco use during pregnancy, and month of enrollment.

†p<0.1; *p<0.05

Supplemental Table 6. Associations between gestational diabetes (GDM), pre-existing diabetes mellitus (DM), and body mass index, and Covid-19 diagnosis in the INTERCOVID study using multiple imputation of missing values (n=2184).[a]

	N (%)	Crude RR and 95% CI	Adjusted RR and 95% CI
Model 1			
Gestational Diabetes (GDM) or Diabetes Mellitus (DM)			
No GDM, no DM	1824 (88.1)	Ref	Ref.
GDM, no DM	194 (9.4)	1.16 (0.96, 1.40)	1.18 (0.97, 1.42)†
Pre-existing DM	53 (2.6)	1.84 (1.47, 2.30)*	1.89 (1.52, 2.36)*
Body Mass			
Normal weight <25 kg/m^2	1180 (57.0)	Ref.	Ref.
Overweight/obese ≥25 kg/m^2	891 (43.0)	1.19 (1.05, 1.35)*	1.19 (1.05, 1.34)*
Model 2			
No GDM or DM, normal weight	1099 (53.1)	Ref.	Ref.
No GDM or DM, overweight/obese	725 (35.0)	1.18 (1.04, 1.35)*	1.18 (1.03, 1.35)*
GDM without insulin, normal weight	54 (2.6)	0.94 (0.61, 1.46)	0.96 (0.62, 1.48)
GDM without insulin, overweight/obese	87 (4.2)	1.27 (0.95, 1.68)	1.29 (0.97, 1.71)†
GDM with insulin, normal weight	14 (0.7)	1.68 (0.99, 2.87)†	1.74 (1.03, 2.92)*
GDM with insulin, overweight/obese	39 (1.9)	1.73 (1.26, 2.38)*	1.72 (1.25, 2.37)*
Pre-existing DM, normal weight	13 (0.6)	1.81 (1.09, 3.02)*	1.87 (1.14, 3.08)*
Pre-existing DM, overweight/obese	40 (1.9)	2.19 (1.71, 2.80)*	2.24 (1.76, 2.87)*

[a]Adjusted for maternal age, parity, and tobacco use during pregnancy.

†p<0.1; *p<0.05

Supplemental Table 7. Associations between gestational diabetes (GDM), pre-existing diabetes mellitus (DM), and body mass index and Covid-19 symptoms among all those diagnosed with Covid-19 (N=672), and among those diagnosed with a positive RT-PCR or antigen test in the week before or on day of delivery (N=342).[a]

	Covid-19 without symptoms N (%)	Covid-19 with symptoms N (%)	RR and 95% CI[a]
All women with Covid-19			
Gestational Diabetes (GDM) or Diabetes Mellitus (DM)			
No GDM, no DM	226 (40.1)	338 (59.9)	Ref.
GDM, no DM	32 (42.7)	43 (57.3)	0.96 (0.88, 1.03)
Pre-existing DM	14 (42.4)	19 (57.6)	0.97 (0.87, 1.07)
Body Mass			
Normal weight <25 kg/m^2	152 (44.2)	192 (55.8)	Ref.
Overweight/obese ≥25 kg/m^2	120 (36.6)	208 (63.4)	1.06 (1.01, 1.11)*
Women with positive RT-PCR or antigen test in week before or on day of delivery			
Gestational Diabetes (GDM) or Diabetes Mellitus (DM)			
No GDM, no DM	164 (58.2)	118 (41.8)	Ref.
GDM, no DM	25 (58.1)	18 (41.9)	0.97 (0.87, 1.09)
Pre-existing DM	9 (52.9)	8 (47.1)	1.02 (0.87, 1.20)
Body Mass			
Normal weight <25 kg/m^2	114 (62.6)	68 (37.4)	Ref.
Overweight/obese ≥25 kg/m^2	84 (52.5)	76 (47.5)	1.08 (1.00, 1.09)*

[a]Adjusted for maternal age, parity, and tobacco use during pregnancy.
†p<0.1; *p<0.05

Supplemental Figure 1. Enrollment flow chart for the INTERCOVID study.

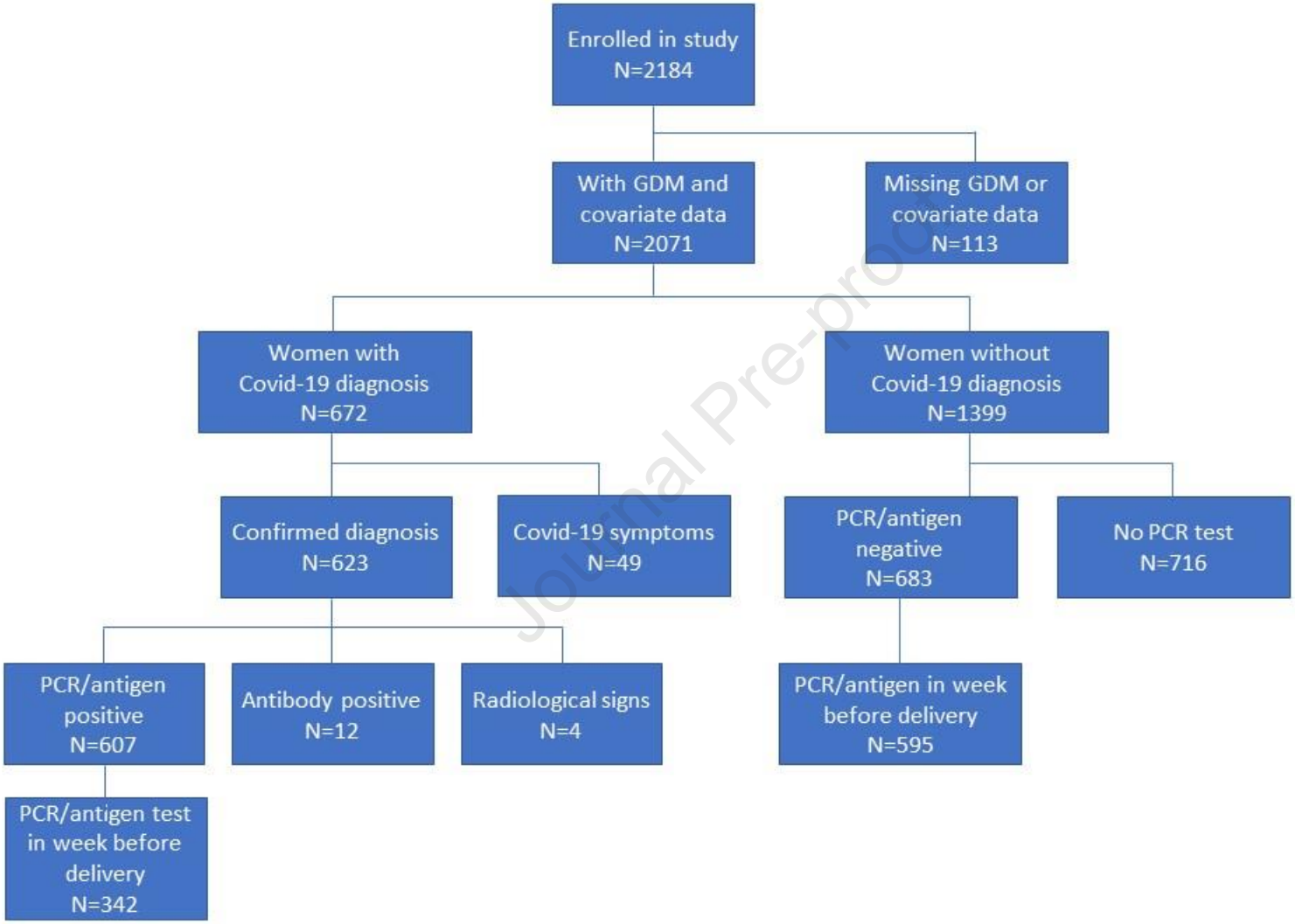
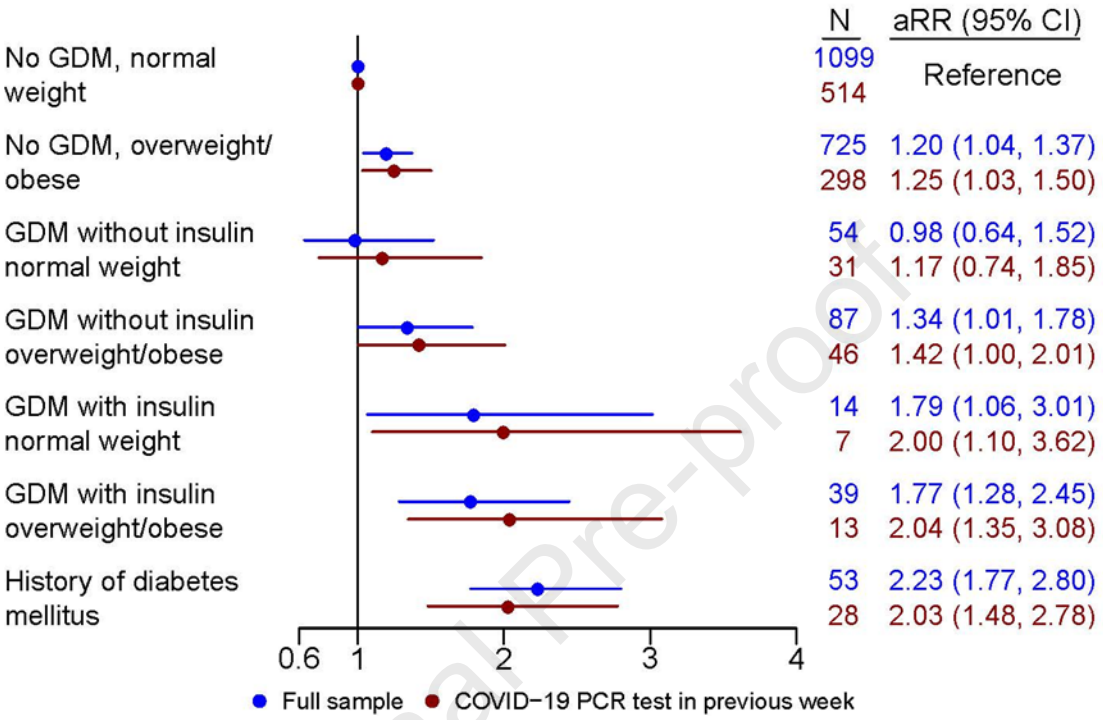
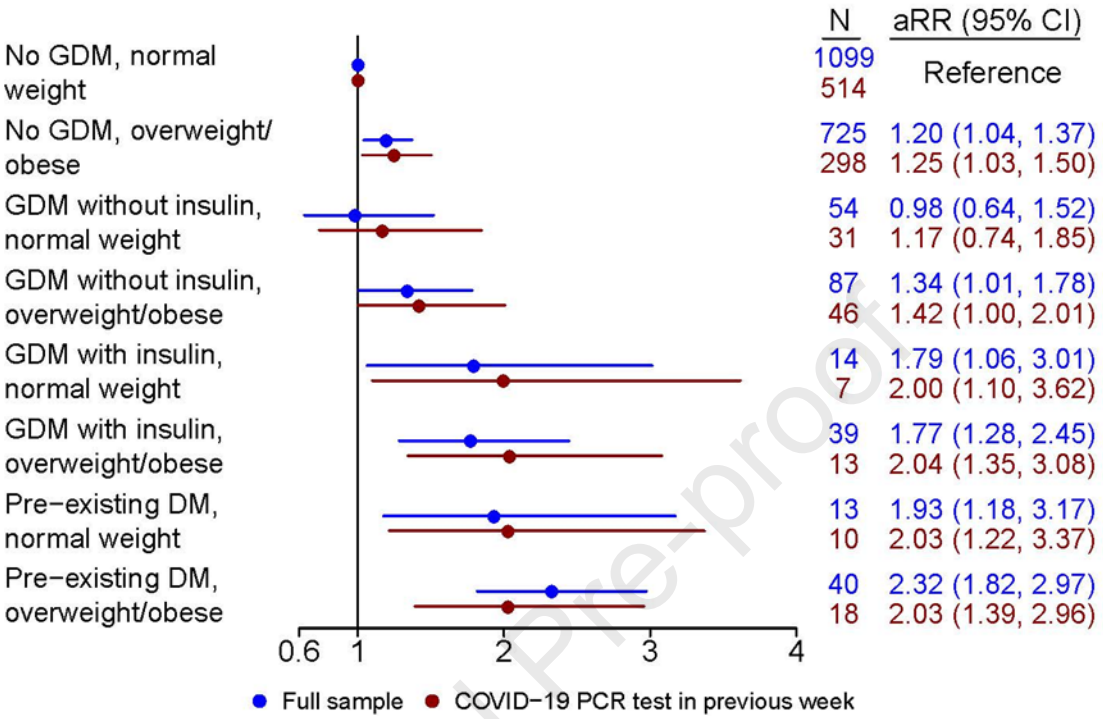


Figure 1. Risk of Covid-19 diagnosis according to gestational diabetes (GDM), insulin use, body mass index, and pre-pregnancy history of diabetes mellitus (DM), for participants in the INTERCOVID study, in the full population (n=2071) and the subset of women with a RT-PCR test in the week before or on day of delivery (N=937).[a]



[a]Adjusted for maternal age, previous parity, and tobacco use during pregnancy.

Figure 1. Risk of Covid-19 diagnosis according to gestational diabetes (GDM), insulin use, body mass index, and pre-existing diabetes mellitus (DM), for participants in the INTERCOVID study, in the full population (n=2071) and the subset of women with a RT-PCR or antigen test in the week before or on day of delivery (N=937).[a]



[a]Adjusted for maternal age, parity, and tobacco use during pregnancy.