

SARS-CoV-2 infections among pregnant women—testing behaviour and neonatal and maternal health outcomes: a Dutch retrospective population-based cohort study

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Published in	BMJ Open
DOI	10.1136/bmjopen-2025-101803
Publication Date	2025-11
Document Version	publishersversion
Link	https://research.tilburguniversity.edu/en/publications/3a71849a-aa33-4170-9aa2-ff0ed08072ff
Citation	Klein, P P F, Crone, L & Struijs, J N 2025, 'SARS-CoV-2 infections among pregnant women—testing behaviour and neonatal and maternal health outcomes : a Dutch retrospective population-based cohort study ', BMJ Open, vol. 15, no. 11, e101803. https://doi.org/10.1136/bmjopen-2025-101803
Download Date	2026-05-17 12:46:54
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BMJ Open SARS-CoV-2 infections among pregnant women – testing behaviour and neonatal and maternal health outcomes: a Dutch retrospective population-based cohort study

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To cite: Klein PPF, Crone L, Struijs JN. SARS-CoV-2 infections among pregnant women—testing behaviour and neonatal and maternal health outcomes: a Dutch retrospective population-based cohort study. *BMJ Open* 2025;**15**:e101803. doi:10.1136/bmjopen-2025-101803

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2025-101803>).

Received 07 March 2025
Accepted 20 October 2025



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ABSTRACT

Objectives To provide population-level insights into COVID-19 testing behaviour and test results among all pregnant women in the Netherlands and to assess the effects of SARS-CoV-2 infection during pregnancy on maternal and neonatal health outcomes.

Design Retrospective population-based cohort study.

Setting Dutch registry data on maternal and neonatal health outcomes linked with COVID-19 testing and sociodemographic data for the study period 2020 and 2021.

Participants To study testing behaviour, all pregnant women who gave birth in the Netherlands during 2020 and 2021 were included (N=322 720). To study the effects of maternal infection, women who gave birth between June 2020 and September 2021 and who were tested for COVID-19 were included (N=68 059).

Primary and secondary outcome measures For testing behaviour: number of COVID-19 tests performed and COVID-19 test results. For neonatal health outcomes: preterm birth, low birth weight for gestational age (small for gestational age (SGA)), BIG2 (preterm birth and/or SGA), Apgar score at 5 min below seven (low Apgar), Apgar score at 5 min below four (very low Apgar), neonatal intensive care unit admission, congenital anomalies and mortality. For maternal health outcomes: major postpartum haemorrhage (>1000 mL), severe ruptures (third or fourth degree), type of delivery and episiotomy.

Results Compared with the reference group (women aged 30–34), women under 20 had the lowest probability of being tested (16.5% vs 31.3%; OR 0.43, 95% CI 0.38 to 0.49), but when tested, they had significantly higher odds of testing positive (19.3% vs 12.9%; OR 1.62, 95% CI 1.21 to 2.14). Women originating from ‘other African’ countries were least likely to be tested (15.1%; OR 0.37, 95% CI 0.35 to 0.39), while women whose country of origin was ‘Morocco’ were most likely to test positive when tested (33.4%; OR 3.63, 95% CI 3.35 to 3.93). While over all trimesters a SARS-CoV-2 infection during pregnancy did not show significant effects, an infection during the first trimester was associated with an increased risk of preterm birth (5.2% vs 6.4%; OR 1.25, 95% CI 1.03 to 1.52) and a low 5-min Apgar score (1.9% vs 2.9%; OR 1.50, 95% CI 1.12 to 2.02). No significant adverse maternal health effects were observed.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study was conducted on a full (pregnant) population-wide cohort and provides insights into Sars-CoV-2 testing behaviour among pregnant women and the effects of infection on birth outcomes.
- ⇒ Analyses of COVID-19 testing behaviour among different groups of pregnant women were based on data from both positive and negative test results.
- ⇒ To adjust for confounding of differences in testing behaviour, inverse probability of treatment weighting was used to analyse the effects of Sars-CoV-2 infection on birth outcomes correcting.
- ⇒ Tests conducted in hospitals and tests for which the patient did not give consent were not included; however, 87% of all positive tests performed in the Netherlands were included.

Conclusion There were significant differences in testing behaviour and the probability of testing positive for COVID-19 among pregnant women from different age groups, countries of origin and socioeconomic backgrounds. SARS-CoV-2 infection during pregnancy was not associated with significant effects on maternal health outcomes, and only limited effects on neonatal health were observed. Only infections occurring in the first trimester were linked to an increased risk of preterm births and low 5-min Apgar scores.

INTRODUCTION

The COVID-19 pandemic had a major global societal impact, with overflowing hospitals, delayed care and excess mortality.^{1–3} Although the severity and risks of a SARS-CoV-2 infection were evident from an early stage for high-risk groups, including elderly, obese and chronically ill individuals, the risks for pregnant women were less clear at that time.^{4–6}

At the start of the COVID-19 pandemic, multiple earlier cohort and case-based studies

indicated that SARS-CoV-2 infection during pregnancy negatively affected the pregnancy duration and health outcomes for both mother and child.^{4 7 8} For instance, Rajewska *et al*⁴ and Di Mascio *et al*⁹ demonstrated that children were more often born preterm or with a low birth weight, especially when the infection occurred during the third trimester of pregnancy. Other studies pointed towards an increased prevalence of stillbirths^{7 8} and caesarean deliveries¹⁰ when the mother tested positive for COVID-19 during pregnancy.

Full population-level studies on the effects of COVID-19 across all three trimesters of pregnancy remain scarce.^{11–13} Gaining insights across all trimesters is particularly important, as infections from other infectious diseases, such as influenza and rubella, occurring during the first or second trimester of pregnancy can substantially impact maternal and neonatal health outcomes.^{14 15} The effects of SARS-CoV-2 infection on maternal and neonatal health outcomes, stratified by trimester of pregnancy, are still not well understood.

To evaluate the effects of SARS-CoV-2 infections during all trimesters of pregnancy at the population level, it is essential to know who was tested and who tested positive. To date, it remains unclear which pregnant women were tested for COVID-19 and how infections (positive test results) were distributed across subgroups of pregnant women in the Netherlands. Previous studies have indicated strong differences in incidence rates in the general population between different age groups, migration background and socioeconomic groups.^{16–18}

This study aims to provide population-level insights into COVID-19 testing behaviour and test results among all pregnant women in the Netherlands in 2020 and 2021, as well as the effects of SARS-CoV-2 infection during pregnancy in the period from June 2020 until September 2021. Accordingly, this research addresses the following questions: (1) What are the differences in COVID-19 testing behaviour and positive test rates among different groups of pregnant women in the Netherlands? (2) What are the effects of a SARS-CoV-2 infection during pregnancy on neonatal and maternal health outcomes, both in general and for each trimester?

METHODS

Study population and period

The study population comprised all women who gave birth in the Netherlands in 2020 and 2021. This population was used to answer research question 1 (the determinants for testing and testing positive). To answer research question 2, the effects of SARS-CoV-2 infection on mother and child, we constructed a subpopulation limited to the period from June 2020 to September 2021, during which all required data sources were available.

Study design and data sources

In this retrospective population-based cohort study, we used individual-level registry microdata from the

Data-InfrAstructure for ParEnts and childRen (DIAPER).¹⁹ DIAPER comprises linked data from multiple national registries, of which Perined and the System of Social Statistical Datasets (SSD) were used in this study. Linkage between registries was carried out via pseudonymised SSD personal identification numbers. Perined comprised 94.6% of all pregnancies with a gestational age of 24 weeks or older in the Netherlands during our study period and included data on maternity care usage and health outcomes of mothers and children. The SSD, provided by Statistics Netherlands, was used to determine socio-demographic characteristics of the mother, including age, country of origin, standardised household income, education level and medication usage (polypharmacy).²⁰

DIAPER data were further enriched with data from CoronIT. CoronIT comprises data on all COVID-19 tests performed and reported by Municipal Health Services (GGD) in the Netherlands between June 2020 and September 2021, including both positive and negative results. It captures 87.9% of all positive COVID-19 PCR tests conducted in the country during the study period.²¹ The remaining positive tests can be attributed to those conducted in healthcare settings, such as hospitals or nursing homes, which were not available in the CoronIT database. During the study period, all persons in the Netherlands who experienced COVID-19-like symptoms or had potential exposure to individuals with a SARS-CoV-2 infection were able to be tested free of charge.²² After the study period, data on negative test results were no longer available.

To answer research question 2, we excluded all women who received a COVID-19 vaccination before being infected with SARS-CoV-2 in order to focus solely on the effects of an infection during pregnancy. For this exclusion criterion, individual-level data on COVID-19 vaccination status were linked from the COVID-vaccination Information and Monitoring System (CIMS).²² CIMS contains all individual-level COVID-19 vaccination records in the Netherlands. Only a small number of women were excluded, as the proportion of vaccinated pregnant women was very low during the period from June 2020 to September 2021.²³

Table 1 provides an overview of all included variables, their data source and available years or months.

Study sample

The study population of pregnant women who gave birth in the Netherlands in 2020 and 2021 was derived from original raw data from Perined, which included n=372988 records. Multiple exclusion criteria were applied (online supplemental appendix A). Records that could not be linked to an SSD personal identification number were excluded (n=44774). All pregnancies for which no clear start and end date could be determined were excluded (n=1293), as well as all records of children born at a gestational age of 24 weeks or younger (n=1060). Finally, the dataset was cleaned by removing any duplicates (n=3141). This resulted in a

Table 1 Variables, data sources and availability of the data

Variable	Data source	Available time period
COVID-19 test outcomes		
Administered tests	CoronIT	Jun 2020–Sep 2021
Positive tests	CoronIT	Jun 2020–Sep 2021
Neonatal health outcomes		
Date of birth	Perined	2000–2021
Preterm birth (<37 weeks)	Perined	2000–2021
SGA (Hoftiezer <10)*	Perined	2000–2021
BIG2 (Hoftiezer <10 and/or pregnancy duration <37 weeks)	Perined	2000–2021
Low Apgar score (<7 after 5 min)	Perined	2000–2021
Very low Apgar score (<4 after 5 min)	Perined	2000–2021
NICU admission	Perined	2000–2021
Mortality	Perined	2000–2021
Congenital anomalies	Perined	2000–2021
Maternal health outcomes		
Type of partus	Perined	2000–2021
Mother referred to hospital	Perined	2000–2021
Episiotomy	Perined	2000–2021
Major PPH (>1000mL)	Perined	2000–2021
Severe rupture (third or fourth degree)	Perined	2000–2021
Covariates		
Age	SSD	1994–2021
Gravidity	Perined	2000–2021
Newborn's sex	Perined	2000–2021
Education level	SSD	1999–2021
Country of origin	SSD	1994–2021
Household income	SSD	2011–2021
Urbanisation degree	SSD	2000–2023
Medication usage	SSD	2006–2021
Multidimensional vulnerability†	DIAPER	2016–2021
COVID-19 vaccination status	CIMS	2021–2023

*SGA measured via Hoftiezer (ie, birth weight lower than the 10th percentile, corrected for gestational age and fetal sex.²⁹)

†Multidimensional vulnerability=a composite score of women in a vulnerable situation during pregnancy and operationalised by Molenaar *et al.*³²

CIMS, COVID-vaccination Information and Monitoring System; DIAPER, Data-InfraStructure for ParEnts and ChildRen; NICU, neonatal intensive care unit; PPH, postpartum haemorrhage; SGA, small for gestational age; SSD, Social Statistical Dataset.

study sample of n=322 720 for answering research question 1 (testing behaviour and determinants).

To answer research question 2 (the effects of a maternal SARS-CoV-2 infection), we created a subpopulation from the study sample (online supplemental appendix A, figure A2). Due to the unavailability of test data after August 31, 2021, and the resulting uncertainty regarding infection status during pregnancy, we excluded women who gave

birth after this date (n=121 517). Twin and higher-order pregnancies are a high-risk factor for adverse maternal and neonatal health outcomes compared with singleton pregnancies; therefore, non-singleton pregnancies were excluded (n=3214). To assess the effects of SARS-CoV-2 infection during pregnancy, we compared women with a positive COVID-19 test result to those who tested negative during their pregnancy. We excluded women who did not test for COVID-19 (n=110 222) and those who did not test during pregnancy (n=19 656). COVID-19 vaccinations may have a protective effect on mother and child, and for that reason, all women who received a COVID-19 vaccination before testing positive were excluded (n=52). This resulted in a subpopulation of the study sample of n=68 059.

Statistical analyses

To study testing behaviour among pregnant women (research question 1), we examined the testing rates and positive test results during pregnancy among pregnant women in 2020 and 2021. Positive test results were used to determine the SARS-CoV-2 incidence rate among pregnant women. An individual was marked as positive based on the date the positive test sample was taken. Subsequent episodes were recorded if a positive test sample was taken ≥ 90 days after the first positive test sample of the previous episode. Additional analyses on the differences in testing behaviour among women of reproductive age and pregnant women were performed; see online supplemental appendix B.

We expressed the probability of pregnant women undergoing a SARS-CoV-2 test by using ORs. The ORs for testing positive were presented for all pregnant women, as well as specifically for those who were tested for COVID-19. To gain insight into variations in tests performed and positive test results among different countries of origin and socioeconomic groups, we examined various breakdowns. These breakdowns included the mother's age at delivery, country of origin, education level, standardised household income, multidimensional vulnerability,²⁴ newborns' sex and gravidity. The subgroups that were tested most often were used as the reference groups; a ratio above one indicates higher odds of testing (positive) than the reference group and vice versa.

To study the effects of a SARS-CoV-2 infection during pregnancy on maternal and neonatal health outcomes (research question 2), we compared weighted outcomes between pregnant women who tested positive and those who tested negative for SARS-CoV-2. This was done in three steps. First, in cases of missing data, multivariate imputation by chained equations was applied to impute missing values for the covariates education and income level. For this method, the R Package 'Mice' was used.²⁵ Second, inverse probability of treatment weighting (IPTW) was applied to adjust for differences in COVID-19 testing among subgroups.²⁶ For the IPTW, the following measures were taken into account: start of pregnancy, mother's age, country of origin, education,



income, newborn's sex and gravidity. The probability of testing positive for COVID-19 during pregnancy was calculated using a propensity score based on these individual characteristics with generalized boosted models,²⁷ and weights were calculated as the inverse of the propensity score. Applying these weights to the subpopulation created a pseudo-population in which confounders were equally distributed across the positive and negative testing groups. For this, the R package 'MatchThem'²⁸ was used. Third, the ORs were computed using the weighted data to compare outcomes between pregnant women who tested positive during the pregnancy and those who tested negative. An OR greater than one indicates that the likelihood of the observed outcome is higher for women with a positive COVID-19 test than for women who tested negatively during pregnancy.

We studied the effects of a maternal infection across all three trimesters, as well as within each specific trimester. To determine in which trimester a woman was infected, the start date of pregnancy was derived from the gestational age (in days) and the date of birth. The first trimester was defined as the first 13 weeks of pregnancy, the second trimester as weeks 14–26 and the third trimester as week 27 until delivery.

The following neonatal and maternal health outcomes were taken into account. For neonatal health outcomes: preterm birth, low birth weight for gestational age (small for gestational age (SGA²⁹)), BIG2 (preterm birth and/or SGA), Apgar score at 5 min below seven (low Apgar), Apgar score at 5 min below four (very low Apgar), neonatal intensive care unit (NICU) admission, congenital anomalies and mortality (see [table 1](#)). For maternal health outcomes: major postpartum haemorrhage (>1000 mL), severe ruptures (third or fourth degree), type of delivery and episiotomy.

Software

All analyses in this study were performed using the statistical software R V.4.2.2, Rstudio and Python 3.12.1.^{30 31}

Patient and public involvement

The study did not incorporate patient or public input in its design or execution.

RESULTS

Descriptive statistics

The study population consisted of 322 720 pregnant women ([table 2](#)) and was used to address research question 1 (the determinants of testing and testing positive). The mean maternal age at delivery was 31 years. Most women had the Netherlands as their country of origin (n=217 171; 67.4%) and were highly educated (n=1 35 937, 47.4%). The group of women who gave birth between June 2020 and September 2021 (n=201 088) was highly comparable to the full study population (see online supplemental appendix C, table A2 for more details). The subpopulation used to answer research question 2 (the

Table 2 Descriptive statistics

Description	Women giving birth in 2020 and 2021 (%) (research question 1)	Women giving birth between June 2020 and September 2021 who tested for COVID-19 (%) (research question 2)
N	322 720	68 059
Age mean (SD)	31.2 (4.6)	31.5 (4.3)
Age categories		
19 years and younger	2006 (0.6)	260 (0.4)
20–24 years old	22 279 (6.9)	3504 (5.1)
25–29 years old	90 567 (28.1)	17 836 (26.2)
30–34 years old	133 012 (41.3)	30 327 (44.6)
35–39 years old	62 293 (19.3)	13 890 (20.4)
40 years and older	12 232 (3.8)	2242 (3.3)
Country of origin		
Netherlands	217 171 (67.4)	51 273 (75.3)
Europe (excl. Netherlands)	28 076 (8.7)	4595 (6.8)
Turkey	11 305 (3.5)	2048 (3.0)
Morocco	13 714 (4.3)	2279 (3.3)
Suriname	13 714 (4.3)	1426 (2.1)
Dutch Caribbean	4511 (1.4)	672 (1.0)
Indonesia	4648 (1.4)	1093 (1.6)
Other Africa	10 205 (3.2)	1079 (1.6)
Other Asia	18 411 (5.7)	2316 (3.4)
Others Americas and Oceania	6202 (1.9)	1278 (1.9)
Education		
Low	32 342 (11.3)	4562 (7.1)
Medium	118 548 (41.3)	23 999 (37.5)
High	135 937 (47.4)	35 511 (55.4)
Income quintiles		
0%–20% (lowest)	43 567 (13.7)	5292 (7.8)
20%–40%	35 514 (11.2)	6244 (9.2)
40%–60%	56 536 (17.8)	12 556 (18.5)
60%–80%	82 469 (25.9)	19 739 (29.1)
80%–100% (highest)	100 339 (31.5)	24 012 (35.4)
Multidimensional vulnerability*		
Yes	23 755 (7.4)	3965 (5.8)
Polypharmacy†		
Yes	42 524 (13.2)	9470 (13.9)
Newborn's sex		
Girl	157 152 (48.7)	33 152 (48.7)
Gravida		

Continued

Table 2 Continued

Description	Women giving birth in 2020 and 2021 (%) (research question 1)	Women giving birth between June 2020 and September 2021 who tested for COVID-19 (%) (research question 2)
Primigravida	113 121 (35.1)	21 336 (31.3)
Gravida 2	101 389 (31.4)	23 590 (34.7)
Gravida 3	57 048 (17.7)	13 057 (19.2)
Gravida 3	51 107 (15.8)	10 069 (14.8)
Positive tests	13 228 (4.1)	9 723 (14.3)

*Multidimensional vulnerability=a composite score of women in a vulnerable situation during pregnancy.³²
 †Polypharmacy=the use of 5 or more Anatomical Therapeutic Chemical 4 (ATC4) medication groups per year. The sum of a variable can differ from the total (N) due to missing values, see online supplemental appendix C.

effects of an infection on mother and child) consisted of 68 059 women. This subpopulation, comprising COVID-19-tested women, contained relatively fewer women under the age of 30 (7.5% vs 5.5%), more women with a country of origin other than the Netherlands (67.4% vs 75.3%), a higher proportion of highly educated women (47.4% vs 55.4%) and fewer women in a multidimensional vulnerable situation (7.4% vs 5.8%). Within this subpopulation, 14.3% of women tested positive for COVID-19. Pregnant women were tested slightly less often than women of reproductive age (online supplemental appendix B).

Differences in testing (positive)

To address research question one—the differences in COVID-19 testing behaviour and positive test rates among different groups of pregnant women in the Netherlands—we analysed the odds of being tested and testing positive within specific subgroups (table 3), see online supplemental appendix D for absolute numbers and percentages of (positive) tests. Variations were observed in the odds of being tested during pregnancy (column 1), the odds of receiving a positive test result during pregnancy (column 2) and the odds of testing positive among those tested during pregnancy (column 3), across specific subgroups, each compared with the subgroup with the highest testing frequency (the reference group).

Pregnant women aged 20–24 years were less likely to be tested compared with the reference group of women aged 30–34 years, who were tested most frequently (21.5% vs 31.3%; OR 0.60, 95% CI 0.58 to 0.62). During pregnancy, 20–24-year-olds were more likely to have a positive test result than those aged 30–34 years, regardless of whether they were tested (4.3% vs 4.0%; OR 1.08, 95% CI 1.01

to 1.16). Among women who were tested during their pregnancy, those aged 20–24 years were most likely to test positive (20.3% vs 12.9%; OR 1.71, 95% CI 1.59 to 1.85).

Pregnant women aged 19 or younger were least likely to be tested for COVID-19 (16.5%; OR 0.43, CI 95% 0.38–0.49) compared with pregnant women aged 30–34 years old (31.3%; reference group). Women aged 25–29 had the highest odds of testing positive for COVID-19 during pregnancy (4.5%; OR 1.12, 95% CI 1.08 to 1.17). When considering the country of origin, significant differences were observed between the subgroups. Women from ‘other African’ countries were least likely to be tested compared with those from ‘the Netherlands’ (15.1% vs 32.3%; OR 0.37, 95% CI 0.35 to 0.39). Women originating from ‘Morocco’ had the highest odds of testing positive during pregnancy (7.4%; OR 1.95, 95% CI 1.82 to 2.08), and when solely focusing on the women who were tested during pregnancy, they were also most likely to test positive (33.4%; OR 3.63, 95% CI 3.35 to 3.93).

Pregnant women with a lower education level were less likely to be tested (19.2%; OR 0.42, 95% CI 0.41 to 0.44) compared with highly educated women (35.8%; reference group), but they were more likely to test positive when tested (19.5% vs 11.1%; OR 1.94, 95% CI 1.81 to 2.08). Women belonging to the 20% lowest household income group were least likely to be tested compared with the 60%–80% household income group (16.9% vs 33.0%; OR 0.41, 95% CI 0.40 to 0.42). When tested, women in the lowest 20% household income group were more likely to test positive (21.6%; OR 1.75, 95% CI 1.64 to 1.87), whereas women in the highest 20% income group were the least likely to test positive (11.4%; OR 0.82, 95% CI 0.78 to 0.86).

Neonatal and maternity outcomes

To address research question 2 (the effects of SARS-CoV-2 infection during pregnancy on neonatal and maternal health outcomes), we analysed the effects of a SARS-CoV-2 infection across all trimesters and repeated the analyses for each specific trimester.

When considering SARS-CoV-2 infections during pregnancy, regardless of trimester, no significant effects were observed on the studied neonatal or maternal health outcomes (figure 1A; see online supplemental appendix E,F for more details). However, when focusing on the effects of infection during the first trimester, we observed an increased risk of preterm birth (5.2% vs 6.4%; OR 1.25, 95% CI 1.03 to 1.52) and an increased risk on a low 5-min Apgar score (1.9% vs 2.9%; OR 1.50, 95% CI 1.12 to 2.02) (figure 1B). In contrast, no significant effects on neonatal and maternal health outcomes were observed when infection occurred in the second or third trimester.

DISCUSSION

The aim of this research was twofold. The first aim was to provide insights into the COVID-19 testing behaviour and test results among pregnant women in the Netherlands.

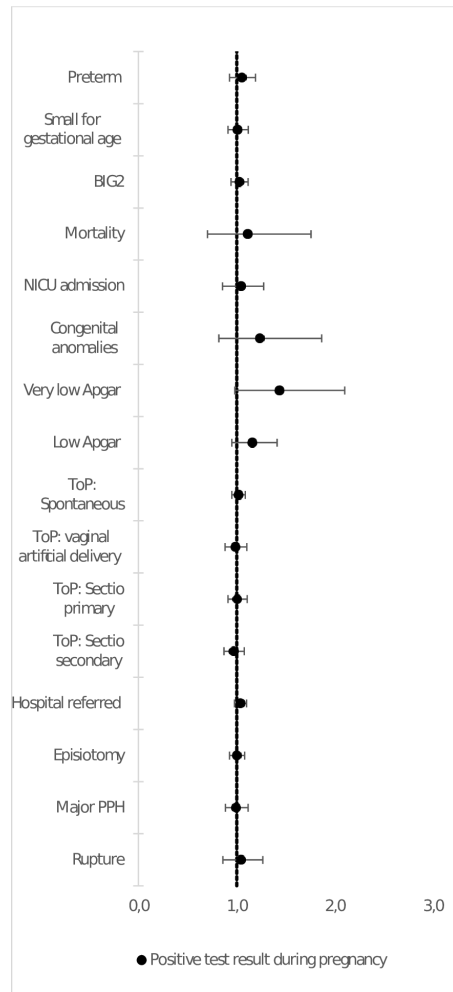
**Table 3** ORs for pregnant women to test for COVID-19 and test positive for COVID-19, for country of origin and socioeconomical groups (n=322 720)

Description	OR being tested during pregnancy (95% CI)	OR positive test result during pregnancy (95% CI)	OR positive test result when tested during pregnancy (95% CI)
Age categories			
19 years and younger	0.43 (0.38 to 0.49)***	0.78 (0.60 to 1.01)	1.62 (1.21 to 2.14)***
20–24 years	0.60 (0.58 to 0.62)***	1.08 (1.01 to 1.16)*	1.71 (1.59 to 1.85)***
25–29 years	0.81 (0.80 to 0.83)***	1.12 (1.08 to 1.17)***	1.35 (1.30 to 1.42)***
30–34 years†	1.00	1.00	1.00
35–39 years	0.98 (0.96 to 1.00)	0.92 (0.87 to 0.97)***	0.93 (0.88 to 0.98)***
40 years and older	0.76 (0.72 to 0.79)***	0.88 (0.79 to 0.97)***	1.09 (0.98 to 1.21)
Country of origin			
Netherlands†	1.00	1.00	1.00
Europe (excl. Netherlands)	0.62 (0.60 to 0.64)***	0.78 (0.73 to 0.84)***	1.13 (1.05 to 1.22)***
Turkey	0.68 (0.65 to 0.71)***	1.88 (1.74 to 2.03)***	2.99 (2.74 to 3.26)***
Morocco	0.59 (0.57 to 0.62)***	1.95 (1.82 to 2.08)***	3.63 (3.35 to 3.93)***
Suriname	0.67 (0.63 to 0.70)***	1.29 (1.16 to 1.43)***	1.89 (1.69 to 2.11)***
Dutch Caribbean	0.55 (0.51 to 0.59)***	1.15 (0.99 to 1.32)	1.98 (1.68 to 2.32)***
Indonesia	0.98 (0.92 to 1.04)	0.83 (0.70 to 0.98)*	0.83 (0.70 to 0.99)*
Other Africa	0.37 (0.35 to 0.39)***	0.84 (0.75 to 0.93)***	2.02 (1.78 to 2.29)***
Other Asia	0.47 (0.45 to 0.48)***	0.94 (0.86 to 1.01)	1.84 (1.68 to 2.01)***
Others Americas and Oceania	0.82 (0.78 to 0.87)***	0.93 (0.81 to 1.07)	1.08 (0.94 to 1.25)
Education			
Lower	0.42 (0.41 to 0.44)***	0.94 (0.88 to 1.00)	1.94 (1.81 to 2.08)***
Medium	0.69 (0.68 to 0.70)***	1.19 (1.15 to 1.24)***	1.63 (1.57 to 1.70)***
High†	1.00	1.00	1.00
Income quintiles			
0%–20% lowest	0.41 (0.40 to 0.42)***	0.80 (0.76 to 0.85)***	1.75 (1.64 to 1.87)***
20%–40%	0.65 (0.63 to 0.67)***	0.98 (0.92 to 1.04)	1.40 (1.31 to 1.50)***
40%–60%	0.88 (0.86 to 0.90)***	1.03 (0.98 to 1.08)	1.15 (1.09 to 1.21)***
60%–80%†	1.00	1.00	1.00
80%–100% highest	0.98 (0.97 to 1.00)	0.83 (0.79 to 0.87)***	0.82 (0.78 to 0.86)***
Multidimensional Vulnerability			
No†	1.00	1.00	1.00
Yes	0.69 (0.67 to 0.72)***	0.93 (0.86 to 0.99)*	1.26 (1.17 to 1.36)***
Newborn's sex			
Boy	1.00 (0.99 to 1.01)	1.02 (0.99 to 1.06)	1.03 (0.99 to 1.07)
Girl†	1.00	1.00	1.00
Gravida			
Primigravida	0.77 (0.75 to 0.78)***	0.97 (0.93 to 1.01)	1.20 (1.15 to 1.26)***
Gravida 2†	1.00	1.00	1.00
Gravida 3	0.97 (0.95 to 1.00)*	1.05 (0.99 to 1.10)	1.07 (1.02 to 1.13)***
Gravida>3	0.80 (0.78 to 0.82)***	1.07 (1.01 to 1.13)*	1.29 (1.22 to 1.37)***

*p<0.05, **p<0.01, ***p<0.001.

†Reference group.

A Effects of SARS-CoV-2 infection during pregnancy overall



B Effects of SARS-CoV-2 infection during the first, second and third trimester of pregnancy

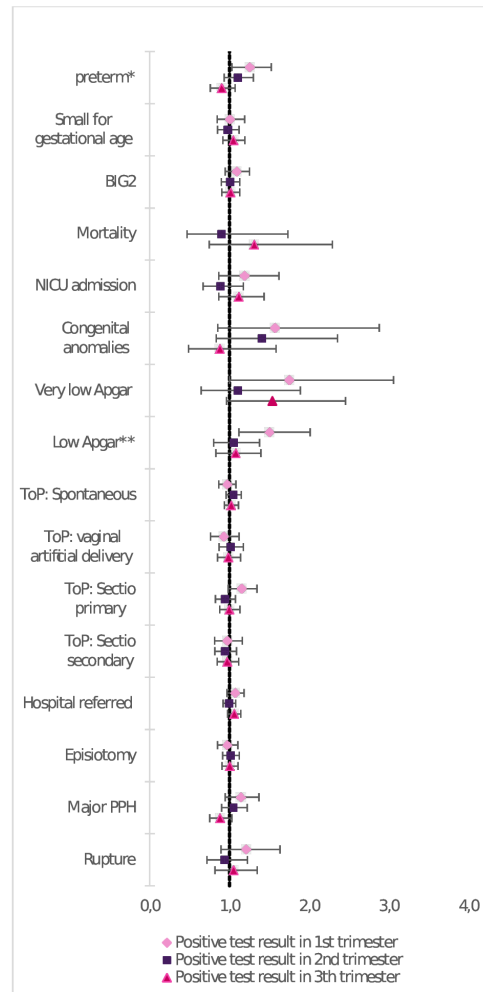


Figure 1 ORs (95% CI) neonatal and maternal outcomes when infected with SARS-CoV-2 during pregnancy. BIG2, SGA or preterm birth; major PPH, postpartum haemorrhage (>1000 mL); NICU, neonatal intensive care unit; SGA, small for gestational age (Hoftiezer²⁹); ToP, type of partus. *p<0.05, **p<0.01, ***p<0.001.

This was achieved by determining the odds of having a COVID-19 test conducted during pregnancy and the odds of receiving a positive test result across different age, country of origin and socioeconomic groups of pregnant women. After adjusting for these differences in testing behaviour, we addressed the second aim: to provide insight into the effects of a SARS-CoV-2 infection during pregnancy on neonatal and maternal health outcomes, both across all trimesters and within each individual trimester.

COVID-19 test behaviour and positive test rates varied considerably between distinct groups of pregnant women. Major differences in the probability of testing were seen within subgroups defined by age, country of origin, education and income. Women aged 30–34 years were tested most frequently, while those younger than 30 and those over 40 were tested significantly less often. Women of a ‘Moroccan’ or ‘Turkish’ origin tested less frequently compared with women of ‘Dutch’ origin, but when tested, they had three times higher odds of receiving a

positive result. This suggests a marked disparity in both willingness and ability to test and positive test rates among groups with different countries of origin. Similar patterns were observed among different income and education groups, with those in the lower income and education groups being tested less frequently but having higher odds of testing positive when they had been tested.

Our findings regarding differences in positive test rates among various groups of pregnant women are in line with those observed among different countries of origin and socioeconomic groups in the general population.^{16–18} The same characteristics of women who were tested less frequently are also typically associated with higher risks of adverse maternal and neonatal outcomes.^{32 33} Our results indicate that the women with these maternal high-risk characteristics were less likely to access COVID-19 testing facilities during the pandemic, but when they did get tested, they had higher odds of testing positive.

To overcome uncertainty regarding willingness versus necessity to test, we chose to focus on individuals who



were tested at least once during their pregnancy when answering research question 2 (the effects of an infection on mother and child). The odds that a pregnant woman tests positive are determined for all pregnant women, regardless of whether they have been tested or not. To determine the odds that a tested pregnant woman has a positive result, only women who have actually been tested are considered. The study shows that these odds differ. The observed positive test rates are influenced by the number of tests conducted. If the willingness to test in certain groups is very low, the observed incidence rates might be underestimated. On the other hand, it is possible that the actual natural incidence in that group is lower, thereby reducing the necessity to test.

Our results demonstrate that a SARS-CoV-2 infection during the first trimester is associated with an increased risk for the newborn to have a low 5-min Apgar score and an increased risk of preterm birth. No other significant effects on maternal and neonatal health outcomes were observed regardless of the stage of pregnancy at the time of infection. These adverse outcomes—a low 5-min Apgar score and preterm birth—are associated with long-term neurologic disabilities, lower cognitive function in early adulthood and increased infectious morbidity.^{34 35} Given these health risks associated with an infection during the first trimester, it may be useful to actively seek ways to mitigate these risks during this phase of the pregnancy.

Our finding of an increased risk of a preterm birth when infected with a SARS-CoV-2 infection during pregnancy aligns with findings from a French population-level study.¹² Unlike other full population studies, such as Anselem *et al*¹² and Skhvtaridze *et al*,¹³ we did not observe significant effects on the number of caesarean deliveries among women infected during pregnancy.

While multiple case and cohort studies (eg, DiMascio *et al*⁹ and Rajewska *et al*⁴) predominantly indicate an effect on preterm birth when infection occurs during the third trimester, we only found an effect when an infection occurred during the first trimester. This difference may be due to the lack of positive tests identified within hospitals in our study, unlike in these case studies. It is likely that a large proportion of the most severe COVID-19 cases towards the end of pregnancy are hospital-diagnosed; by missing these test results in our data, we may have missed some COVID-19-related preterm births. However, with our access to nationwide COVID-19 registry data, we gained a more comprehensive understanding of infections occurring during the first trimester. Our finding of higher odds of preterm birth aligns with research by Waldorf and McAdams,¹⁴ which underscores the risks of preterm births associated with infections during the first trimester.

Strengths and limitations

A major strength of this study is that we were able to investigate the effects of SARS-CoV-2 infection during pregnancy at a nationwide level, including all pregnant

women in the Netherlands. Furthermore, our data included information on both positive and negative tests, allowing us to analyse testing behaviour among different groups of pregnant women. Additionally, this enabled us to adjust for confounding in test behaviour among groups of women.

Nevertheless, this study also had limitations. To start, we did not have access to the results of all COVID-19 tests performed in the Netherlands. Self-tests and tests conducted in medical settings, such as hospitals and nursing homes, were not included. As we relied on registered positive COVID-19 tests to determine whether a woman was infected with SARS-CoV-2, some infections may have been missed. By missing medical test result data, we potentially underestimated the effects in the most severe cases. However, 87.9% of all positive PCR tests performed in the Netherlands were included in our dataset,²¹ allowing us to provide insights into the majority of COVID-19 cases among pregnant women in the Netherlands. Individuals being tested for COVID-19 had to give informed consent to share their data for research purposes. It is unclear how consent rates varied across different subgroups in the population. This consent requirement meant that not all test results could be included in our dataset.

Another limitation was that testing was not mandatory. Some subgroups were tested less frequently compared with others. This could result in an underestimation of the SARS-CoV-2 incidence in the Dutch pregnant population. To mitigate potential biases in our results regarding the effects of infection during pregnancy, due to variances in test behaviour across pregnant women, we applied the statistical method of IPTW. This method was used to focus solely on the effects of a SARS-CoV-2 infection, disregarding other influences on neonatal and maternal health outcomes as much as possible.

Finally, due to the timeframe of this study, we were not able to examine differences in the effects of infection during pregnancy between the types of SARS-CoV-2 viruses, especially the Omicron variant and its different subtypes. During the COVID-19 pandemic, various SARS-CoV-2 variants were present, each with different pathogenic and replication characteristics.³⁶ Differences in severity and risk have been observed, with the Omicron variant being the most infectious, while health outcomes appear less severe than with earlier variants.^{37 38} In our study period, we predominantly examined the Original, Alpha (B.1.1.7) and Delta (B.1.617.2) variants, which were dominant during the study period (June 2020 until September 2021; see online supplemental appendix G). This was an appropriate study period to solely investigate the effects of a SARS-CoV-2 infection, as the vaccination rate among pregnant women was still very low. Therefore, there was minimal risk of bias due to immunity acquired through vaccination, since only a small number of pregnant women had been vaccinated at that time;²³ those who had been vaccinated were excluded from our analysis. Future research is needed to investigate the effects

of infection during pregnancy from SARS-CoV-2 variants that circulated in the Netherlands after September 2021. Especially when studying the Omicron-dominant period, consideration should be given to the interaction with vaccination, as a larger proportion of pregnant women were vaccinated during that period.²³

Future research

In this study, we focused on the effects of a SARS-CoV-2 infection during pregnancy and demonstrated that only infection during the first trimester was associated with adverse birth outcomes. Future research should be conducted to explore the effectiveness of COVID-19 vaccination in preventing infection and its effects on neonatal and maternal health outcomes in the Dutch setting. This future research should not solely focus on the effectiveness and effects of a COVID-19 vaccination during pregnancy, but especially also on vaccination prior to pregnancy. This approach would provide insight into the impact of having antibodies in the first trimester on neonatal health outcomes—a period when, according to our study, the fetus could benefit most.

Furthermore, as evident from this research, COVID-19 testing did not reach all groups equally. Individuals with lower levels of education and income and those of non-Dutch origin were less likely to be tested. Both future research and policy makers should focus on ways to enhance equity in access to preventive care services, such as disease testing, for pregnant women. Such research should investigate the underlying mechanisms that make certain groups harder to reach and identify effective methods to reduce this equity gap. This would help to ensure that these groups will have the same opportunities to be tested in the event of a future pandemic and improve understanding of key factors influencing individuals' decisions to test or not to test.

CONCLUSION

To conclude, this study has shown that substantial differences exist in testing behaviour and in the probability of testing positive for COVID-19 among different age groups, countries of origin and socioeconomic groups.

Overall, SARS-CoV-2 infection during pregnancy did not show significant effects on neonatal and maternal health outcomes. However, when focusing on infections occurring in the first trimester of pregnancy, an increased risk of preterm birth and low 5-min Apgar score was observed.

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Acknowledgements We would like to thank our reviewers and advisors within and outside the RIVM.

Contributors PPFK and LC did the data analysis. All authors contributed to the study conception, design and interpretation of results. PPK, LC and JNS drafted the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. PPFK is the guarantor. ChatRIVM, a secured version of ChatGPT, was used for proofreading.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval According to Dutch law, formal approval was not required as this study relied on secondary anonymised data collection in the context of performing statutory tasks. Statistics Netherlands functioned as a trusted third party, enabling the linkage between the datasets, while ensuring the privacy of the involved participants, according to Dutch law (Statistics Netherlands Act 2003). This was confirmed by the RIVM Clinical Expertise Center, reference number VPZ-565.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Access to the data from Perined, Statistics Netherlands, CoronIT and CIMS can be requested from the relevant parties.

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