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Impact of national measures taken to mitigate the COVID-19 pandemic on the incidence of preterm birth in the Netherlands

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Background

The COVID-19 pandemic and the measures taken to mitigate its health impact are having an unprecedented impact on society. In the midst of this adversity there are however also opportunities. The sudden occurrence of the pandemic and the scale and immediacy of the policy responses taken provide a unique opportunity to evaluate their health impact as a 'natural experiment'.[1] Intriguingly, by applying such an approach recent reports from Denmark and Ireland independently provide evidence indicating that national COVID-19 mitigation measures were followed by substantial reductions in extremely preterm births.[2,3] Several potential underlying mechanisms have been proposed, including improvements in ambient air quality, and reductions in maternal stress and incidence of infections.[3]

Globally, over one in ten babies is born preterm, and preterm birth is the primary contributor to mortality and morbidity in early life.[4] At present, opportunities for prevention of preterm birth are limited.[5] It is therefore of pivotal importance that we further explore the possible link between national lockdown measures and the occurrence of preterm births, and if confirmed, start identifying the underlying mechanisms. This may provide novel insights into opportunities for future prevention of preterm birth.

The aforementioned Danish and Irish studies both had relatively limited sample sizes, as well as methodological limitations in the approaches used. In the current study we will use national routinely collected data to study the association between the implementation of COVID-19 mitigation measures in the Netherlands and the incidence of preterm birth. Key strengths of this study will be the large sample size and strong methodological approach, hence supporting causal inference.

Objective

Primary objective:

- Investigate whether the national implementation of COVID-19 mitigation measures in the Netherlands was associated with changes in the incidence of preterm birth.

Secondary objectives:

- Investigate whether the national implementation of COVID-19 mitigation measures in the Netherlands was associated with changes in the incidence of preterm birth within specific gestational age categories.
- Investigate whether the association between the national implementation of COVID-19 mitigation measures in the Netherlands and the incidence of preterm birth varied according to neighbourhood socio-economic status.

Methods

Study design

We will undertake a difference in regression discontinuity analysis assessing the association between the national implementation of COVID-19 mitigation measures and the incidence of preterm birth, using national routinely collected data on singleton babies having undergone neonatal blood spot screening in the Netherlands between 2010 and 2020.

Setting and participants

We will compose a national retrospective cohort of all singleton babies having undergone neonatal blood spot screening in the Netherlands between 9 October 2010 and 23 August 2020. The study period includes ten years and five months pre-implementation of the first national COVID-19 mitigation measures (9 March 2020), and five months of data post-implementation of the last comprehensive set of measures (23 March 2020) (Table 1). Data will be derived from the Praeventis database. Praeventis is a national database containing data from all babies having undergone neonatal blood spot screening. The proportion of Dutch babies undergoing neonatal blood spot screening is typically >99%, and as such may be considered to be highly representative of all births in the Netherlands. Several maternal and neonatal characteristics are recorded for each registered individual. For the purpose of this study, multiple births will be excluded due to their inherent increased risk of preterm birth. Multiple births will be identified based on having multiple records registered with identical birth dates and identical maternal name and/or address. We will furthermore exclude babies whose registered gestational age is below 24+0 weeks or above 41+6 weeks.

Table 1. Timeline of implementation of key COVID-19 mitigation measures in the Netherlands

Date	*COVID-19 mitigation measures implemented*
9 March 2020	Strong advice against handshaking, and for using paper handkerchiefs, sneezing/coughing in one's elbow, and regular handwashing
12 March 2020	Strong advice against social interaction, and visiting elderly people Events of >100 individuals are cancelled People need to work from home if possible People need to stay home if symptomatic (fever, respiratory complaints)
15 March 2020	Closing down of schools and child care facilities Closing down of hospitality industry and of non-essential services involving physical contact
23 March 2020	All events and gatherings are cancelled Social distancing is introduced (1.5-meter-rule) Issuing of fines for not complying with social distancing Municipalities may close down busy places and shops

Characteristics of the population will be cross-referenced at aggregate level against data from Perined, the national birth registry based on data from midwifery, GP, obstetric, and paediatric practices. Perined data is made available 1-2 years following initial registration. This invalidates the current primary use of Perined data to address our research question within a short time frame, hence the rationale for using data from the neonatal blood spot screening programme as an alternative. Cross-referencing of data from the current study against Perined data will only be possible for those years currently available through Perined.

Variables and data source

We will extract the following data from each individual as registered in the Praeventis database based on the neonatal blood spot screening leaflet (https://www.rivm.nl/documenten/voorbeeld-hielprikkaart): 1. date of birth; 2. gestational age (in full weeks plus days); 3. birth weight (in grams); 4. sex; and 5. post code. Post code will be used to derive: 1. province; 2. neighbourhood socioeconomic status (based on status scores of post code areas as defined by *Sociaal Cultureel Planbureau* (https://www.volksgezondheidenzorg.info/onderwerp/sociaaleconomische-status/regionaal-internationaal/regionaal#node-sociaaleconomische-status): low: <20th centile; medium: 20th-80th centile; high: >80th centile); and 3. neighbourhood urbanisation level (dichotomised, with urban areas having >2500 addresses per km^2).

Bias

Multiple births will be excluded due to their inherent increased risk of preterm birth.

There may be registration errors in the Praeventis database. To check for any potential systematic bias resulting from such errors we will, for the years in which Perined data is available, cross-reference the distribution of each variable derived from Praeventis against Perined data at aggregate level. Although we will be unable to correct registration errors, this exercise will help assess to what extent the presence of such errors might have introduced bias in our sample. It is important to note that, even if such bias would be present, it seems reasonable to assume that the nature of such bias will be fairly stable over time and as such is unlikely to affect our findings.

For obvious reasons, neonatal blood spot screening is only undertaken in babies alive at the time of screening (i.e. between three and seven days after birth). Preterm babies, particularly those born extremely preterm, have a higher risk of dying in the first few days after birth than babies born at term. Hence, having babies screened as the base population for the current research project likely results in a systematic underestimation of the incidence of preterm births, particularly extremely preterm births. As the survival rates of extremely preterm babies have been fairly constant over time in the Netherlands, this is unlikely to affect our assessment of temporal changes in preterm birth incidence. Again, cross-referencing against Perined data will allow us to estimate the extent of this systematic bias.

Study size

Two earlier studies have identified a link between national implementation of COVID-19 mitigation measures and a reduction in extremely preterm births.[2,3] In the Danish study,[2] national data on post-implementation births was available for 5,162 singleton births. The Irish study was a single-centre study and had 1,381 births available for analysis.[3] The Netherlands has approximately 170,000 births annually. This translates into an anticipated ~70,000 births post-implementation, including ~4,900 preterm births, of which approximately 700 will be very preterm (i.e. <32+0 weeks) and 70 extremely preterm (i.e. <26+0 weeks). This will provide ample statistical power to identify an association between the COVID-19 mitigation measures and preterm births in the Netherlands, if present.

Statistical analysis

Characteristics of the study population will be tabulated according to the time periods from which they were derived: gestational age, birth weight, sex, province, neighbourhood socio-economic status, and neighbourhood urbanisation level. Characteristics of the study population will furthermore be tabulated against the same characteristics derived from Perined for the period in which this data is available.

The association between national implementation of the COVID-19 mitigation measures and the incidence of preterm births will be investigated using a difference in regression discontinuity approach. In our primary analyses we will consider the date that the most comprehensive set of measures was introduced (i.e. 15 March 2020) as the intervention date. We will assess four time windows before and after the intervention in separate analyses: one, two, three, and five months pre- and post-implementation. Hence, the minimum timespan surrounding the implementation of the COVID-19 mitigation measures that will be evaluated is two months (i.e. one month pre- and one month post-implementation) and the maximum will be ten months. The approach will allow for comparison of the incidence of preterm birth in the period directly preceding the implementation of the measures versus the period directly following the implementation. In the analyses we will account for seasonal variation and potential other time-variant factors affecting preterm birth incidence by comparing the period surrounding the implementation of the measures in 2020 to the exact same time periods in each of the nine years preceding the COVID-19 pandemic. By following this approach there will be no need to adjust for individual-level variables in the analysis.

In the primary analyses, the outcome of interest will be the overall incidence of preterm birth (i.e. number of babies born at a gestational age <37 weeks per 100 babies having undergone neonatal blood spot screening). In additional stratified analyses we will assess whether there were any differential changes in preterm birth incidence post-implementation of the COVID-19 mitigation measures according to the degree prematurity. For this purpose, preterm births will be stratified in the following gestational age categories: 24+0 – 25+6 weeks, 26+0 – 27+6 weeks, 28+0 – 31+6 weeks, and 32+0 – 36+6 weeks.

Substantial evidence indicates that the COVID-19 pandemic and the measures taken to mitigate its impact are differentially affecting various socio-economic groups. To assess whether there has been a variation in impact of the Dutch COVID-19 mitigation measures according to socio-economic status, we will test for potential effect modification by neighbourhood socio-economic status by including an interaction term in the analyses.

In order to assess the robustness of the findings from our primary analyses we will conduct a number of sensitivity analyses. First, we will vary the intervention date to reflect each of the dates other than 15 March 2020 on which a set of COVID-19 mitigation measures was introduced (Table 1). Second, not all mechanisms potentially underlying the link between the COVID-19 mitigation measures and preterm birth may have an immediate impact. Hence, the impact of the measures on preterm births may not be immediate. On the other hand, there may be an anticipatory effect as a part of the population may already have changed their behavior prior to formal implementation of the COVID-19 mitigation measures. To address this we will conduct two sets of sensitivity analyses introducing a period of censoring of data, thus excluding data from the first week and from the first two weeks directly prior to and directly following introduction of the measures.

Ethical considerations

According to Dutch law (*Wet medisch wetenschappelijk onderzoek met mensen*; WMO) no formal ethical review is required for the current project. Given the size of the project there will be no attempt to actively approach parents or caregivers of babies contributing data for consent.

Dissemination

Findings will be reported in a manuscript to be submitted to a peer-reviewed medical journal. Given the current interest in the findings we will consider reporting the findings through a pre-print platform (i.e. medRxiv) ahead of this process.

References

1. Been JV, Sheikh A. COVID-19 must catalyse key global natural experiments. *J Glob Health* 2020; **10**(1): 010104.
2. Hedermann G, Hedley PL, Baekvad-Hansen M, et al. Changes in premature birth rates during the Danish nationwide COVID-19 lockdown: a nationwide register-based prevalence proportion study. *medRxiv* 2020: 2020.05.22.20109793.
3. Philip RK, Purtill H, Reidy E, et al. Reduction in preterm births during the COVID-19 lockdown in Ireland: a natural experiment allowing analysis of data from the prior two decades. *medRxiv* 2020: 2020.06.03.20121442.
4. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019; **7**(1): e37-e46.
5. Matei A, Saccone G, Vogel JP, Armson AB. Primary and secondary prevention of preterm birth: a review of systematic reviews and ongoing randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol* 2019; **236**: 224-39.