

International Perinatal Outcomes in the Pandemic (iPOP) Study

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BACKGROUND: Preterm birth (PTB) is the leading cause of infant mortality worldwide, but the etiologies of preterm birth are largely unknown (1). During the COVID-19 lockdowns, unprecedented reductions in PTB rates (up to 90% in Denmark) and very low birth weight (70% in Ireland) have been reported (2, 3). It is critical to understand if this dramatic decline is a worldwide phenomenon and determine if it is offset by increases in fetal demise (4). We will seize the unique opportunity offered by the pandemic to answer these urgent questions and investigate the underlying cause(s). PTB results from inflammation that triggers premature labour. Air pollution and maternal infection in pregnancy are inflammatory stimuli and are each strongly associated with PTB. We hypothesise that reductions in air pollution and/or maternal infections in pregnancy, both of which have plummeted with pandemic-related lockdowns, have led to the extraordinary decline in PTB rates. We will leverage the current "natural experiment" to provide crucial insights into the impact of the pandemic on fetal and newborn health, and more broadly into PTB. ***Confirming the worldwide extent of this phenomenon and understanding the etiology could highlight important strategies to alleviate the burden of prematurity on healthcare and social support systems in the post-pandemic era.***

OBJECTIVE: To investigate the impact of COVID-19 lockdowns on perinatal outcomes internationally, and explore the underlying etiological factors.

- **Aim 1:** Conduct a multi-center international surveillance of preterm birth rates to determine if changes during the pandemic lockdown are ubiquitous among regions or if there are differences related to Organisation for Economic Co-operation and Development (OECD) designated countries (high, middle- and low-income countries).
- **Aim 2:** Determine if changes in PTB rate applies to spontaneous onset of preterm labour and/or medically-indicated (induced) PTB
- **Aim 3:** Determine if the change in preterm birth rates are related to pregnancies extending to full-term gestation, or if there is an increase in intrauterine fetal demise.
- **Aim 4:** Determine if the magnitude of regional reductions in PTB during lockdown are correlated with the regional magnitude of a) improvement in air quality and/or b) decline in maternal infections during the same period.

We hypothesize that spontaneous onset of preterm birth and/or pregnancy loss is reduced during pandemic lockdowns worldwide, and the magnitude of this reduction is correlated with the regional magnitude of a) improvement in air quality and b) reduction in maternal infections from pandemic-related restrictions.

APPROACH: We have assembled a collaborative international team of over 40 researchers with rapidly accessible administrative perinatal databases across 19 countries (so far). We will use the [COVID-19 Government Response Stringency Index](#) (Oxford University) to quantify the lockdown stringency and define the lockdown period for each centre. We will collect regional or institutional **aggregate data (Phase I)** from each centre over the course of the lockdown, and for the same calendar-matched period over the previous five years: rates of PTB and stillbirth (administrative perinatal data); air quality (public NASA Air Quality Database); and the COVID-19 lockdown stringency index. We will exploit variation in these factors across centres to estimate the contribution of air quality and lockdown stringency (a proxy for maternal non-COVID infections) on perinatal outcomes. We will consider OECD index and indicators of gender equality (from WHO) and COVID-19 infection rates ([Johns Hopkins database](#)) as potential

covariates or effect modifiers in this ecologic analysis. For centres where individual-level data are available, more **granular analyses (Phase II)** will be performed including covariates such as socio-economic position, race/ethnicity, access to antenatal care, comorbidities; and considering gestational age and birth weight as continuous variables. To accelerate progress and maximize feasibility, data will be analysed locally at each centre using a master protocol and meta-analysed centrally. We have successfully employed this approach in similar perinatal data linkage studies of over 7 million births from 5 countries.

Table 1 Proposed data collection for Phase I and II of the iPOP Study

Phase I: AGGREGATE Analysis (National, Regional or Hospital-level Data)	Phase II: GRANULAR Analysis (Individual-level data for each Birth/Stillbirth)
Number of Births, Preterm Births, Stillbirths	Gestational age, Birth weight, Mode of delivery For PTB: Spontaneous or Medically indicated?
Geographic location of centre	Geographic location of residence
Air pollution – NASA Air Quality Database	Local Air Pollution data
Lockdown Stringency Index – Covid-19 Government Response Tracker (Oxford University)	Local lock down parameters
COVID-19 infection rates – Johns Hopkins	COVID-19 status
Influenza infection rates - Google	Comorbidities? Smoking?
OECD Index - OECD	Socioeconomic status? Ethnicity/race
Maternity leave - OECD Gender Equality	Maternal age, parity, employment

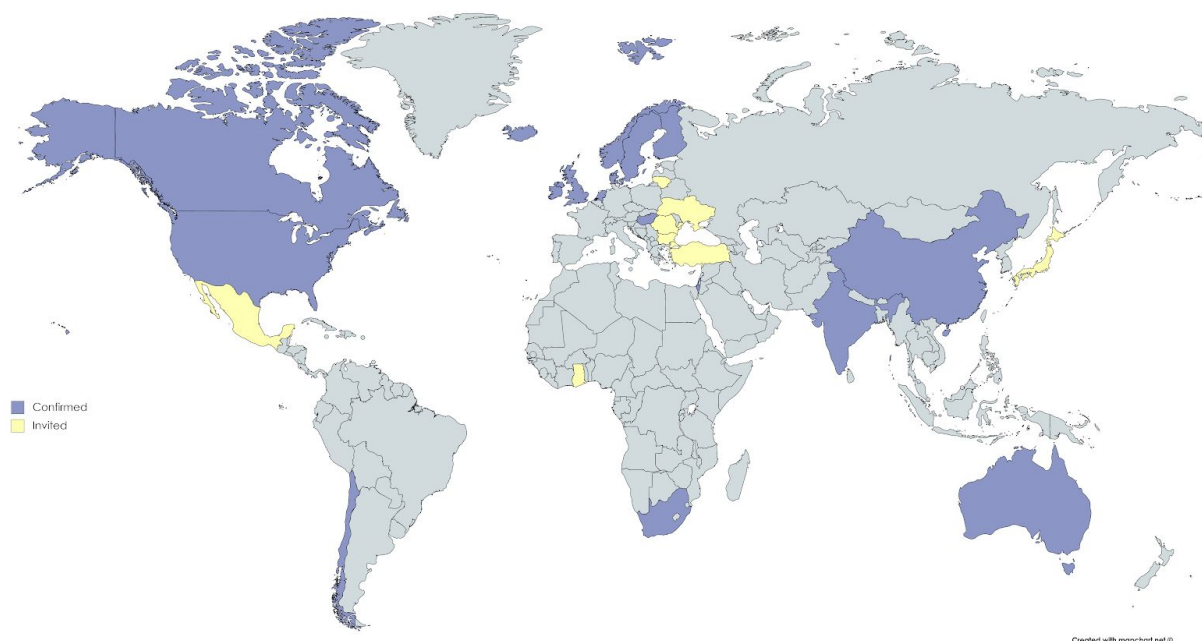


Figure 1 Map of included and confirmed countries in the iPOP study.

Link to Collaborators Directory: [iPOP Collaborators](#)

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