Mind the Gap: Socioeconomic Health Inequalities in Early Life

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Mind the Gap: Socioeconomic Health Inequalities in Early Life

Mind the Gap: Sociaal-Economische Gezondheidsverschillen Rond de Geboorte

Thesis

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HOŞGELDINIZ
WELCOME

Chapter 1

General Introduction

Early-life health, defined here as health during the perinatal period, is one of the most important determinants of health during infancy, childhood, and in later life.[1] For instance, being born too soon (known as preterm birth) or too small (operationalised as low birth weight or small for gestational age) has been linked to a higher risk of neonatal mortality and morbidity, impaired or delayed development, and chronic diseases.[2–4] Furthermore, adverse perinatal outcomes have been observed to have long-lasting consequences in terms of educational attainment and economic outcomes in adulthood.[5,6]

Adverse health outcomes are known to be unevenly distributed across the population and certain groups are known to bear a larger burden. These differences in health status between population groups are known as health inequalities, which can be observed across a range of factors, including sex, migration background, socioeconomic conditions, and religious beliefs.[7] In this dissertation I will focus on socioeconomic health inequalities, which particularly refer to health gradients related to socioeconomic status (SES). SES corresponds to a measure of economic and social position, which has been commonly defined in terms of income, occupational status, and education.[8] Even in an egalitarian country such as the Netherlands with a universal healthcare system, differences in health related to socioeconomic conditions are still present.[9] Perhaps more concerning, recent reports have found evidence in various countries, including the Netherlands, that socioeconomic health inequalities in mortality and other adult health indicators have not only remained persistent but even widened in some cases.[10,11] Consequently, the question arises as to whether inequalities may have not only increased in adult health outcomes but also in outcomes across the entire lifespan, including early-life health. Furthermore, it compels us to consider whether the widening of disparities witnessed in adult health outcomes stems from underlying early-life inequalities.

Research has shown that a mother's SES is strongly linked to the health outcomes of her child early in life.[12] However, beyond individual measures of SES, a growing body of literature has shown a consistent link between neighbourhoods' SES and perinatal health, even after accounting for individual-level characteristics and SES.[13–16] This suggests that adverse neighbourhood socioeconomic conditions can be considered independent risk factors for unfavourable health outcomes. While individual-level (or household-level) SES reflects an individual's access to material and social resources, neighbourhood SES reflects broader societal processes that impact the economic and social development of small geographical areas, which are influenced by larger-scale policies.[17] Deprived physical environments, e.g., a lack of green spaces, along with disadvantaged social environments, e.g., low social cohesion in disadvantaged SES neighbourhoods can have a detrimental impact on early-life health, highlighting the potential of neighbourhood-level interventions in reducing health inequalities.[18] However, to be able to design and evaluate such interventions, knowledge is required on the mechanisms through which neighbourhood socioeconomic conditions affect health. Unfortunately, research in this area has been limited, which hinders our ability to provide insights for public health policy aimed at reducing health inequalities.

Health inequalities can also arise from the interplay between socioeconomic circumstances and external events outside of individual’s control. For instance, disadvantaged socioeconomic conditions could amplify the adverse effect of environmental exposures such as extreme ambient temperature. These situations have the potential to exacerbate existing health inequalities and perpetuating a cycle of disadvantage. Therefore, understanding the interplay between socioeconomic circumstances and external exposures are also essential for developing public health interventions that reduce health inequalities and promote health across all population subgroups.

A key part of this dissertation concerns causal questions that explore the impact of a particular exposure on health outcomes. While randomized controlled trials (RCTs) have been the primary approach for addressing such questions, conducting RCTs in health inequalities research is often limited by practical and ethical constraints. For example, randomly assigning individuals to different socioeconomic conditions, subjecting them to extreme weather events, or exposing them to pandemic consequences is neither feasible nor ethical. Nevertheless, answering inquiries regarding the potential health effects of the exposure to extreme ambient temperatures, disadvantaged neighbourhood environments, or the aftermath of the COVID-19 pandemic remains a priority for public health policy. In such situations, researchers can only rely on the use of observational datasets, such as population and patient registries. Causal inference from observational data can be challenging due to issues such as confounding, selection bias, and reverse causality, which can lead to distorted results. Nonetheless, improvements in the collection and processing of large registries, along with recent methodological advances, have made it feasible to draw valid causal conclusions from non-randomised data, under identification assumptions defined by each method. In this dissertation, I make use of routinely collected registry data along with advanced quasi-experimental and epidemiological approaches to investigate causal relationships.

OBJECTIVES AND OUTLINE

Objectives

The overall aim of this dissertation is to explore the complex relationship between SES and early-life health by placing emphasis on neighbourhood-level socioeconomic conditions and the use of innovative approaches to investigate causal relationships from observational data.

Part 1 aims to depict inequalities in key perinatal outcomes by neighbourhood SES in the Netherlands and their evolution over time.

Part 2 investigates specific potential mechanisms underlying the relationship between neighbourhood SES and birth outcomes in the Netherlands.

Part 3 explores the role of socioeconomic conditions as moderators for the effect of in-utero exposure to external factors on early-life health.

Outline

Part 1 describes early-life health inequalities in the Netherlands by neighbourhood socioeconomic conditions and their development over time. **Chapter 2** addresses how inequalities in three different key birth outcomes have evolved over time across different strata of neighbourhood deprivation. In **Chapter 3** the focus is on longitudinal measures of neighbourhood SES and its link to inequalities in birth outcomes.

Part 2 of this dissertation examines the potential underlying mechanisms driving health inequalities in early-life. **Chapter 4** provides a didactic demonstration of causal mediation analysis in perinatal epidemiology. The real-life example in this chapter explores neighbourhood social environment as potential underlying mechanism for the relationship between neighbourhood socioeconomic conditions and birth outcomes. **Chapter 5** investigates to what extent neighbourhood crime mediates the relationship between neighbourhood SES and birth outcomes in the Netherlands.

Part 3 examines how socioeconomic conditions can modify the impact of the exposure to ecologic stressors during pregnancy on health at birth and how this interplay could result in health inequalities**. Chapter 6** investigates the effect of in-utero exposure to extreme ambient temperatures on birth outcomes in the Netherlands and whether SES might moderate this effect. In **Chapter 7** the focus is on the impact that the first COVID-19 mitigation measures implemented in the Netherlands had on the incidence of preterm birth and the heterogeneity of their effect across levels of neighbourhood SES. Last, **Chapter 8** discusses the use of natural experiments to assess the impact of public health policies and comments on the differential impact of an insurance policy expansion on birth outcomes.

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Part 1:

Trends in early-life health inequalities
in the Netherlands.


HOŞGELDINIZ

Chapter 2

Persisting inequalities in birth outcomes related to neighbourhood deprivation.

ABSTRACT

Introduction

Health inequalities can be observed in early life as unfavourable birth outcomes. Evidence indicates that neighbourhood socioeconomic circumstances influence health. However, studies looking into temporal trends in inequalities in birth outcomes including neighbourhood socioeconomic conditions are scarce. The aim of this work is to study how inequalities in three different key birth outcomes have changed over time across different strata of neighbourhood deprivation.

Methods

Nationwide time trends ecological study with area-level deprivation in quintiles as exposure. The study population consisted of registered singleton births in the Netherlands 2003-2017 between 24 and 41 weeks of gestation. Outcomes used were perinatal mortality, premature birth, and small-for-gestational-age. Absolute rates for all birth outcomes were calculated per deprivation quintile. Time trends in birth outcomes were examined using logistic regression models. To investigate relative inequalities rate ratios for all outcomes were calculated per deprivation quintile.

Results

The prevalence of all unfavourable birth outcomes decreased over time: from 7.2 to 4.1 per 1000 births for perinatal mortality, from 61.8 to 55.6 for premature birth, and from 121.9 to 109.2 for SGA. Inequalities in all birth outcomes have decreased in absolute terms, and the decline was largest in the most deprived quintile. Time trend analyses confirmed the overall decreasing time trends for all outcomes, which were significantly steeper for the most deprived quintile. In relative terms however, inequalities remained fairly constant.

Conclusion In absolute terms, inequalities in birth outcomes by neighbourhood deprivation in the Netherlands decreased between 2003 and 2017. However, relative inequalities remained persistent.

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2.1 INTRODUCTION

The health of future generations is to a significant degree influenced by parental health around conception and maternal health during pregnancy. Foetal growth and development during pregnancy not only shape the health of the newborn in terms of unfavourable birth outcomes, such as perinatal mortality, premature birth, and small for gestational age (SGA), but also health during childhood and in later in life.[1] The global stillbirth rate was estimated in 2016 to be 1.84%, around 2.6 million stillbirths each year. For premature birth, the estimated global rate in 2014 was 10.6%, equating to an estimated 14.8 million premature births.[2] Moreover, it was estimated in 2010 that 32.4 million babies (27.5%) were born SGA worldwide.[3]

Health inequalities are observable differences in health between subgroups of a population.[4 5] These subgroups can be defined by demographic, geographic or socioeconomic factors.[6] Such health inequalities can already be observed during the earliest life stages with unfavourable birth outcomes, which are generally more prevalent among the disadvantaged groups.[7] These groups tend to cluster in deprived neighbourhoods where, next to birth outcomes, growth and development might be negatively influenced.[8]

Despite growing global prosperity, and advances in medicine and technology, health inequalities have persisted, and in many cases even widened.[9 10] Reduction of inequalities in health remains a public health policy priority. The discussion on health inequalities has, in recent years, shifted from being held only in the scientific community and policy making, to being in the general public discussion. For example, recent media coverage on faltering life expectancy in the UK raises the questions of whether and why national austerity measures might be behind a stalling in the improvements in life expectancy and higher child mortality rates; a situation where the most deprived population seems to be the most affected.[11 12] A priority in the study of health inequalities is understanding how they evolve, but current evidence mostly derives from studies with a cross-sectional design, not taking into account the dynamic nature of socioeconomic circumstances. Moreover, most studies focus on mortality and health outcomes in childhood and adulthood, [13-15] with only few paying attention to birth outcomes.[16-19] Besides, most studies consider only individual-level socioeconomic circumstances, while those studies considering neighbourhood (area level) socioeconomic conditions are scarce.

In an egalitarian country like the Netherlands, considerable geographical differences in birth outcomes are present across, between, but also within, delimited areas.[20] In addition, two consecutive perinatal health reports ranked the Netherlands poorly among European countries in terms of overall perinatal mortality,[21 22] followed by a considerable improvement in the latest report.[23] Because of these situations, the Netherlands offers a unique context for the study of trends in health inequalities in birth outcomes.[23] The aim of this work is to study how birth outcomes have evolved differentially by deprivation level in the Netherlands. Temporal trends in inequalities in three different key birth outcomes, perinatal mortality, premature birth and SGA, across different strata of neighbourhood deprivation were explored.

2.2 METHODS

Data sources

National data on all registered singleton births between 24 and 41 weeks of gestation between 2003 and 2017 were obtained from Perined in October 2018.[24] The Perined registry contains information on more than 97% of all births in the Netherlands.[24] Pregnancy, delivery, and neonatal data are routinely collected by midwives, gynaecologists and paediatricians. A detailed description of the linkage procedures can be found on the Perined website (www.perined.nl).

Outcomes

The following indicators were used to define the birth outcomes: 1) perinatal mortality, defined as intrauterine death occurring after 24 completed weeks of gestational age or neonatal death up to 7 days after birth; 2) premature birth, any birth occurring from 24 weeks of gestational age and before 37 weeks , and 3) SGA birth, birth weight below the 10^{th} centile adjusted for gestational age and sex,[25] according to national reference curves.[26]

Exposure

Deprivation indices calculated by the Netherlands Institute for Health Services Research (NIVEL), were used as area-level measure of deprivation, each area with an average of 4000 inhabitants. The deprivation index is a (lognormally) standardised population-weighted sum of the proportion of non-active persons (i.e. unemployed or not working individuals), mean individual income, mean address density, and the proportion of non-western immigrants per neighbourhood.[27] The continuous neighbourhood indices were linked to the individual pregnancies using the registered place of residence at delivery of the mother. NIVEL calculated the deprivation indices in 2003, 2008, and 2012: the 2003 deprivation index was assigned to all births occurring between 2003 and 2007, the 2008 index was assigned to any birth between 2008 and 2011, and the 2012 deprivation index was used for every birth from 2012 onwards. The deprivation index was categorised into quintiles (from Q1, least deprived, to Q5, most deprived) for each period. As result, for example, the same deprivation index in 2003 could be classified into a different quintile in 2008. By doing so, differences in the relative distribution of deprivation index between periods were taken into account.

Determinants

Degree of urbanisation was defined as the number of households per km^2 and was categorised into urban (>= 2500 households/km^2) and rural (< 2500 households/km^2). Maternal characteristics included in the analyses were: maternal age (in years), parity (primiparous versus multiparous) and maternal ethnicity (western versus non-western). In the Perined registry, maternal ethnicity is assigned by the woman's care provider, usually based on appearance, name, and information provided.[24]

Missing data

Place of residence of the mother was missing in 0.1% of pregnancies between 2003 and 2017. Also the deprivation index was not available for neighbourhoods with less than 200 inhabitants at the time of publication. Accordingly, data on neighbourhood deprivation was missing for 3.2% of the pregnancies. Data on SGA was missing in 0.09% of births due to missing information for birth weight and/or ambiguous child's sex. No data was imputed for the analyses.

Patient involvement

This research was done without patient involvement. Patients were not consulted to develop the research question, nor were they involved in identifying the study design or outcomes. We did not invite any patients to participate in the interpretation of results, nor in the writing or editing of this document. There are no plans to directly involve patients in the dissemination of research findings.

Statistical analyses

Maternal characteristics of all singleton births, as well as birth outcomes, were tabulated by deprivation index quintile and stratified by each period (e.g. 2003-2007, 2008-2011, and 2012-2017). Mean absolute perinatal mortality, premature birth and SGA rates per 1000 births were calculated per deprivation quintile per year. The absolute outcome rates were also plotted to visually asses the trends over time.

To further examine time trends in the birth outcomes, individual-level logistic regression models were fitted with the least deprived quintile as reference group. Log likelihood ratio tests indicated that natural splines did not improve model fit compared to a linear time trend. Therefore, the linear term was kept for the main analyses. Differential time trends between deprivation quintiles were accounted for by adding the interaction term year*deprivation quintile. Next to the crude models, models accounting for individual-level maternal characteristics (age, ethnicity, parity) were estimated.

Rate ratios for perinatal mortality, premature birth and SGA were calculated for each year and deprivation quintile, with the outcome rates in the least deprived quintile used as base of the ratio. The rate ratios were also plotted to visually asses the trends over time.

To assess the validity of the modelling choices for premature birth and SGA, a sensitivity analysis was performed with only data from livebirths, instead of data from all births. Subgroup analyses were done for: a) only primiparous women, to control for differences in baseline birth outcome risks versus multiparous women; b) excluding births between 24 and 26 weeks of gestation, to account for changes in active management of babies at these thresholds over the study period; c) using very small for gestational age (vSGA, birth weight below 3rd centile) as an outcome; d) adding the 95th centile as an additional cut off point within the highest level of deprivation (creating six deprivation categories Q1-Q6), as this cut-off is used by NIVEL to identify deprived neighbourhoods (those in Q6), and provide additional financial fees to midwives caring for women in those areas; and e) to examine whether neighbourhood deprivation differentials in birth outcomes varied between rural and urban areas, stratified analyses by degree of urbanisation were performed.

For all the analyses an alpha of 0.05 was used as cut off for statistical significance. All the analyses were performed using R version 3.3.3.[28]

2.3 RESULTS

Between 2003 and 2017, 2,459,346 singleton births with gestational age between 24 and 41 weeks were registered. After excluding all births with missing data on neighbourhood deprivation, 2,377,944 births were available for the analyses (Figure 1).

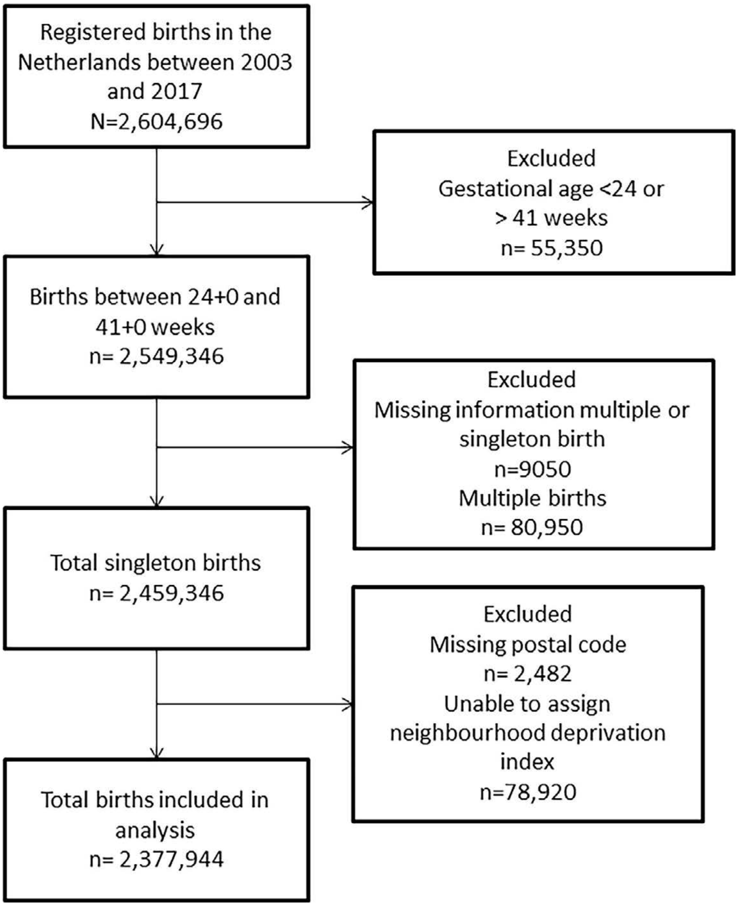

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Figure 1. Study population flow diagram.

Baseline characteristics of included births are displayed per neighbourhood deprivation quintile in Table 1. Maternal characteristics remained stable over time within each deprivation quintile. Mean maternal age was 30.5 (SD 4.9), and it was lowest in the most deprived quintile (Q5; 29.7 (SD 5.4)) and highest in the least deprived quintile (Q1; 31.1 (SD 4.6)). The percentage of primiparous women increased with each more deprived quintile (with 47.1% in Q5 compared to 41.7% in Q1). Non-western ethnicity was most prevalent in Q5 (40.6%), and decreased with lower quintiles (from 17.5% in Q4 to 5.1% in Q1). An increase in the prevalence of non-western ethnicity over time was observed. Urban areas were overrepresented within levels of deprivation, especially in Q2 to Q5.

Table 1. Population characteristics of the singleton pregnancies between 2003 and 2017 by deprivation quintile.

	Q1 (least deprived) N= 478,809	Q2 N= 474,282	Q3 N= 477,146	Q4 N= 473,164	Q5 (most deprived) N= 474,543	Total N= 2,377,944
Characteristics						
Maternal age*, mean (SD)	**31.1 (4.6)**	**30.9 (4.6)**	**30.7 (4.7)**	**30.2 (5.0)**	**29.7 (5.4)**	**30.5 (4.9)**
2003 – 2007	31.2 (4.4)	31.0 (4.5)	30.7 (4.7)	30.2 (5.0)	29.2 (5.5)	30.5 (4.9)
2008 – 2011	31.1 (4.7)	30.8 (4.7)	30.7 (4.8)	30.1 (5.1)	29.7 (5.4)	30.5 (5.0)
2012 – 2017	30.9 (4.6)	30.9 (4.6)	30.7 (4.7)	30.4 (4.9)	30.1 (5.2)	30.6 (4.8)
Primiparous*, %	**41.7**	**43.5**	**45.7**	**48.2**	**47.1**	**45.2**
2003 - 2007	41.9	43.9	46.1	49.2	47.7	45.7
2008 – 2011	41.9	43.8	46.1	49.0	47.8	45.7
2012 – 2017	41.3	42.8	45.0	46.9	46.2	44.5
Non-Western ethnicity*, %	**5.1**	**7.4**	**11.7**	**17.5**	**40.6**	**16.6**
2003 – 2007	3.4	5.3	9.6	15.4	40.8	14.5
2008 – 2011	4.7	7.4	12.3	18.3	41.7	17.0
2012 – 2017	6.9	9.4	13.2	18.7	39.8	18.1
Urban areas*, %	**19.4**	**46.9**	**67.5**	**80.4**	**89.8**	**60.7**
2003 – 2007	20.1	42.4	63.4	77.7	88.5	57.4
2008 – 2011	16.0	44.0	70.5	80.0	90.3	60.2
2012 – 2017	21.3	53.2	69.0	82.8	90.4	63.9
Perinatal outcomes						
Perinatal mortality, %	**0.52**	**0.50**	**0.51**	**0.55**	**0.65**	**0.54**
2003 – 2007	0.72	0.64	0.66	0.70	0.87	0.72
2008 – 2011	0.49	0.50	0.51	0.54	0.62	0.53
2012 – 2017	0.37	0.36	0.38	0.42	0.51	0.41
Premature birth, %	**5.53**	**5.60**	**5.83**	**6.07**	**6.41**	**5.89**
2003 – 2007	5.80	5.87	6.14	6.26	6.92	6.18
2008 – 2011	5.67	5.64	5.93	6.30	6.46	6.00
2012 – 2017	5.19	5.32	5.49	5.75	5.99	5.56
Small for gestational age*, %	**9.39**	**10.10**	**10.92**	**12.19**	**14.52**	**11.42**
2003 – 2007	10.20	10.76	11.61	13.03	15.83	12.19
2008 – 2011	9.07	9.96	10.64	12.20	14.11	11.19
2012 – 2017	8.89	9.59	10.52	11.52	13.82	10.92

Data are presented as numbers and percentages, mean and standard deviation (SD). * = variable has missing data (Maternal age: 0.06%; Parity: 0.01%; Ethnicity: 0.71%; Urban >= 2500 households/km^2. Total number of registered births per year cohort: 2003-2007 N= 791,139 (35.6%); 2008-2011 N= 648,535 (29.2%); 2012-2017 N= 938,270 (35.3%).

Trends in adverse birth outcomes in relation to area deprivation

Absolute rates

The absolute rates (per 1000 births) of each outcome over time are shown in Table 2 and Figure 2. A steady decline in the prevalence of all outcomes was observed across all levels of deprivation. The absolute decline over time was largest in the most deprived quintile (Q5) for all birth outcomes, specially between 2003 and 2008. For example, premature birth rates decreased by 6.1 per 1000 births in the least deprived quintile and by 10.5 per 1000 births in the most deprived quintile.

Table 2. Absolute rates for birth outcomes 2003-2017 per neighbourhood deprivation quintile.

Birth outcomes	2003	2008	2012	2017	Change (95% CI)*
Perinatal Mortality					
Q1 (least deprived)	7.85	5.37	4.18	3.64	-4.21(-4.21 to-4.20)
Q2	7.08	5.09	3.92	3.67	-3.41 (-3.41 to -3.40)
Q3	7.99	6.12	3.84	3.94	-4.05 (-4.05 to -4.04)
Q4	7.20	5.79	4.61	3.90	-3.30 (-3.30 to -3.29)
Q5 (most deprived)	9.71	6.65	5.92	4.39	-5.32 (-5.32 to -5.31)
Premature birth					
Q1	57.12	58.95	54.61	50.99	-6.13 (-6.13 to -6.12)
Q2	58.46	55.97	55.26	51.36	-7.10 (-7.10 to -7.09)
Q3	60.20	61.07	56.64	54.32	-5.88 (-5.88 to -5.87)
Q4	61.36	64.18	59.25	56.11	-5.25 (-5.25 to -5.24)
Q5	70.04	66.22	58.80	59.52	-10.52 (-10.52 to -10.51)
SGA					
Q1	104.54	93.56	89.73	88.92	-15.62 (-15.62 to -15.61)
Q2	111.38	97.11	97.10	94.35	-17.03 (-17.03 to -17.02)
Q3	118.27	109.31	104.23	102.95	-15.32 (-15.32 to -15.31)
Q4	133.45	121.80	116.80	112.74	-20.71 (-20.71 to -20.70)
Q5	165.50	143.18	138.06	134.22	-31.28 (-31.28 to -31.27)

Absolute rates presented per 1000 births; rate ratios calculated using least deprived quintile (Q1) as reference category; CI, 95% confidence interval; *****Change is the value of 2017 minus the value of 2003.

Time trend analyses

Time trend analyses were performed to test the observed differences in trends between quintiles, also when adjusted for maternal age, ethnicity and parity (Table 3). The coefficients for intercept and slope from the estimated models are in line with the observed patterns; significant differences between deprivation quintiles in baseline outcome rates were present, while a significant decreasing overall time trend was present across all deprivation quintiles. However, time trends across neighbourhood deprivation quintiles, assessed using the interaction term year*deprivation quintile, indicated significantly steeper decreasing trends for premature births and SGA in Q5 compared to Q1, but not for perinatal mortality. The other quintiles (Q2-Q4) did not differ significantly from Q1 regarding their time trends.

Relative rates

Rate ratios (RRs) were calculated across the observation period for each outcome using the least deprived quintile (Q1) as base. These RRs provide information on the birth outcome rates per year in Q2-Q5 relative to the birth outcome rate in Q1 in the same year. Table 4 and Figure 3 show the RRs for perinatal mortality, premature birth and SGA over time. The RRs show a social gradient similar to that seen in the absolute outcome rates, however contrary to the absolute rates, these RRs did not materially change between 2003 and 2017.

Sensitivity analyses

The findings from the sensitivity and subgroup analyses are summarised in supplementary tables a-f. Overall, findings from the subgroup analyses were in line with the findings from the main analyses. Results from subgroup analysis (e), in which an additional cut-off was introduced to delineate the 5% most deprived areas, indicated that the association between area-level deprivation and adverse birth outcomes was particularly concentrated in the most deprived areas. The trend analyses with the additional cut off showed similar results to the main analyses, indicating significantly steeper decreasing trends for premature births and SGA in Q6 compared to Q1. Analyses stratified by level of urbanisation (f) indicated that the association between neighbourhood deprivation and adverse birth outcomes was present in urbanised areas and not so much in rural areas. Furthermore, results from the time-trend analyses for urban areas also showed steeper decreasing trends for premature births and SGA in Q5 compared to Q1; however, for rural areas, no significant increasing or decreasing trends were found for any of the three birth outcomes.

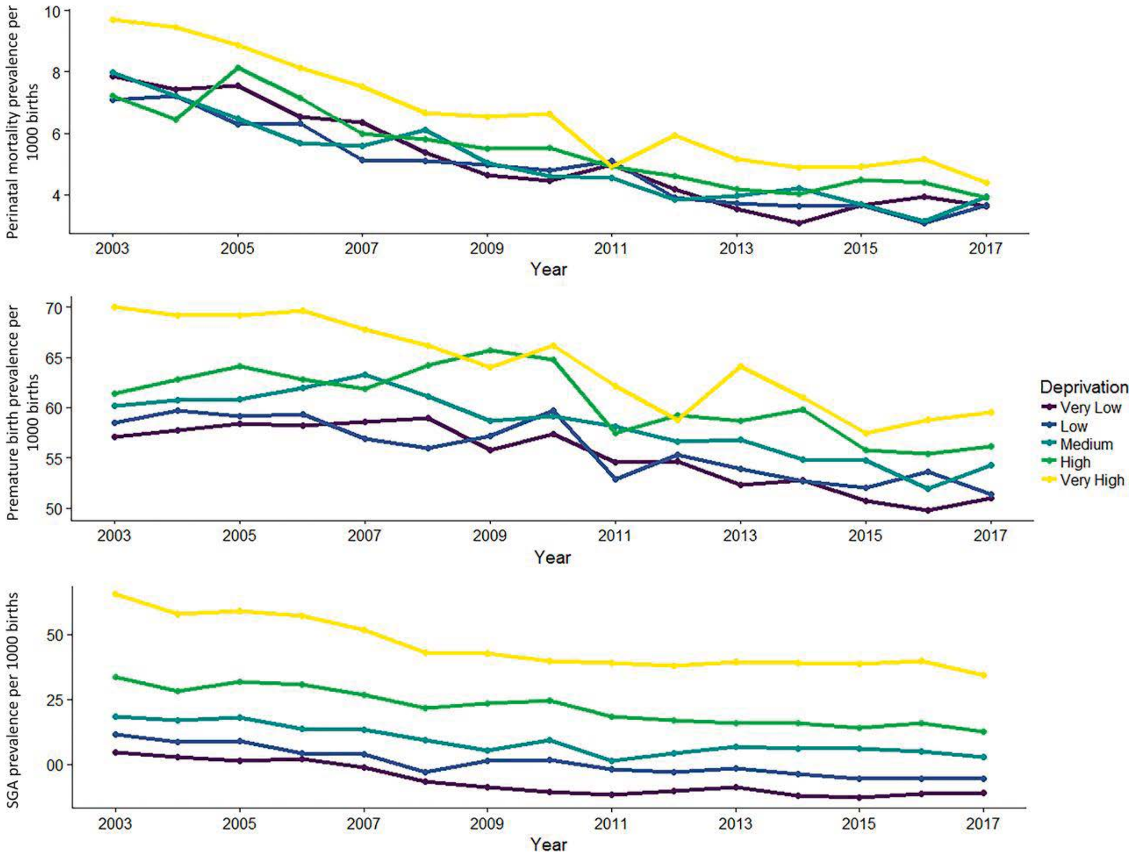

Figure 2. Prevalence (per 1000 births) of perinatal mortality, premature birth, and SGA by neighborhood deprivation quintile (2003 - 2017).

Table 3. Beta coefficients (95% CI) from logistic regressions for time trend analysis of unfavourable birth outcomes by neighbourhood deprivation quintile, The Netherlands 2003-2017.

Variables	**Perinatal mortality**		**Premature birth**		**SGA**	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
Year†	-0.0003 (0.0003 to -0.0010)*	-0.0003 (-0.0003 to -0.0003)*	-0.0006 (-0.0008 to -0.0004)*	-0.0006 (-0.0008 to -0.0004)*	-0.0013 (-0.0015 to -0.0011)*	-0.0014 (-0.0016 to -0.0012)*
Neighbourhood deprivation quintile†						
Q1 (least deprived)	REF	REF	REF	REF	REF	REF
Q2	-0.0006 (-0.0012 to 0.0001)*	-0.0007 (-0.0013 to -0.0001)*	0.0003 (-0.0015 to 0.0021)	-0.0003 (-0.0021 to 0.0015)	0.0063 (0.0039 to 0.0087)*	0.004 (0.0016 to 0.0064)*
Q3	-0.0004 (-0.0001 to 0.0002)	-0.0006 (-0.0012 to 0.0001)*	0.0031 (0.0013 to 0.0049)*	0.0016 (-0.0002 to 0.0034)	0.0141 (0.0117 to 0.0165)*	0.0083 (0.0059 to 0.0107)*
Q4	-0.0002 (-0.0008 to 0.0004)	-0.0005 (-0.0011 to 0.0001)	0.0051 (0.0033 to 0.0069)*	0.0023 (0.0005 to 0.0041)*	0.0298 (0.0274 to 0.0322)*	0.0188 (0.0164 to 0.0212)*
Q5 (most deprived)	0.0017 (0.0011 to 0.0023)*	0.0008 (0.0002 to 0.0014)*	0.0110 (0.0092 to 0.0128)*	0.0076 (0.0058 to 0.0094)*	0.0565 (0.0541 to 0.0589)*	0.0345 (0.0320 to 0.0370)*
Interaction deprivation quintile * year†						
Q1 (least deprived)	REF	REF	REF	REF	REF	REF
Q2	0.0001 (0.0000 to 0.0002)	0.0001 (0.0000 to 0.0002)	0.0001 (-0.0001 to 0.0003)	0.0000 (-0.0002 to 0.0002)	0.0001 (-0.0002 to 0.0004)	0.0001 (-0.0002 to 0.0004)
Q3	0.0000 (-0.0001 to 0.0001)	0.0000 (-0.0001 to 0.0001)	0.0000 (-0.0002 to 0.0002)	0.0000 (-0.0002 to 0.0002)	0.0002 (-0.0001 to 0.0005)	0.0002 (-0.0001 to 0.0005)
Q4	0.0001 (0.0001 to 0.0002)*	0.0001 (0.0000 to 0.0002)	0.0001 (-0.0001 to 0.0003)	0.0001 (-0.0001 to 0.0003)	-0.0002 (-0.0005 to 0.0001)	-0.0001 (-0.0004 to 0.0002)
Q5 (most deprived)	0.0000 (-0.0001 to 0.0001)	-0.0001 (-0.0002 to 0.0000)	-0.0003 (-0.0005 to -0.0001)*	-0.0004 (-0.0006 to -0.0002)*	-0.0007 (-0.001 to -0.0004)*	-0.0004 (-0.0007 to -0.0001)*

SGA, Small for Gestational Age; CI, 95% confidence interval; *Adjusted for ethnicity, maternal age and parity; † results from models with linear trend for year; *$p < 0.05$.

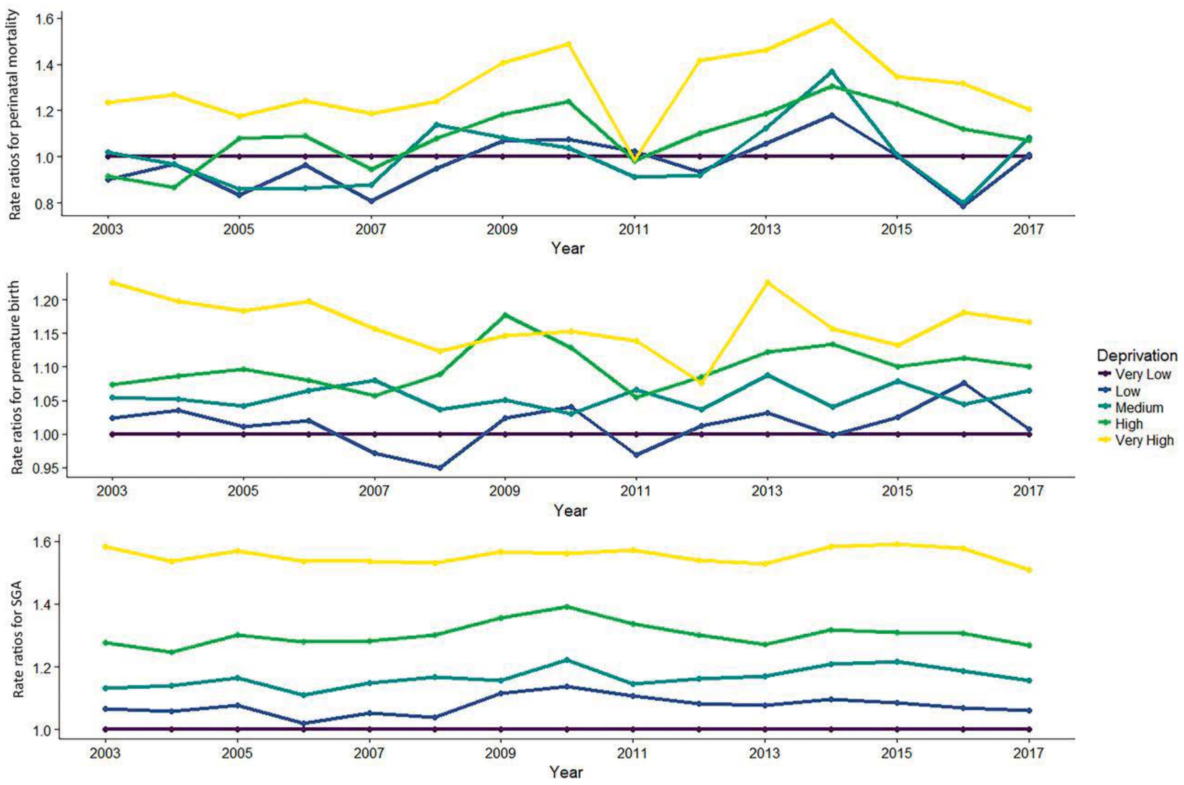

Figure 3. Rate ratios for perinatal mortality, premature birth and SGA by neighborhood deprivation quintile (least deprived quintile used as reference category) 2003 - 2017.

Table 4. Rate ratios (95% CI) for birth outcomes 2003-2017 per neighbourhood deprivation quintile.

Birth outcomes	2003	2008	2012	2017	Change (95% CI)*
Perinatal Mortality					
Q1 (least deprived)	REF	REF	REF	REF	REF
Q2	0.91 (0.87 to 0.93)	0.95 (0.90 to 0.98)	0.94 (0.89 to 0.97)	1.01 (0.96 to 1.05)	0.10 (0.09 to 0.10)
Q3	1.02 (0.98 to 1.05)	1.15 (1.09 to 1.18)	0.92 (0.88 to 0.95)	1.09 (1.03 to 1.12)	0.07 (0.06 to 0.07)
Q4	0.92 (0.88 to 0.95)	1.08 (1.03 to 1.12)	1.11 (1.06 to 1.14)	1.08 (1.03 to 1.11)	0.16 (0.15 to 0.17)
Q5 (most deprived)	1.24 (1.19 to 1.27)	1.24 (1.19 to 1.28)	1.42 (1.36 to 1.46)	1.21 (1.15 to 1.25)	-0.03 (-0.03 to -0.05)
Premature birth					
Q1	REF	REF	REF	REF	REF
Q2	1.02 (1.01 to 1.03)	0.94 (0.93 to 0.96)	1.01 (0.99 to 1.02)	1.01 (0.99 to 1.02)	-0.01 (-0.01 to -0.01)
Q3	1.05 (1.04 to 1.06)	1.03 (1.02 to 1.05)	1.03 (1.02 to 1.05)	1.06 (1.05 to 1.07)	0.01 (0.01 to 0.01)
Q4	1.07 (1.06 to 1.08)	1.08 (1.07 to 1.1)	1.08 (1.07 to 1.09)	1.10 (1.08 to 1.11)	0.04 (0.03 to 0.04)
Q5	1.22 (1.21 to 1.24)	1.12 (1.10 to 1.13)	1.07 (1.06 to 1.09)	1.16 (1.15 to 1.18)	-0.06 (-0.06 to -0.05)
SGA					
Q1	REF	REF	REF	REF	REF
Q2	1.06 (1.05 to 1.07)	1.03 (1.02 to 1.04)	1.08 (1.07 to 1.09)	1.07 (1.05 to 1.07)	0.01 (0.01 to 0.01)
Q3	1.13 (1.12 to 1.14)	1.16 (1.15 to 1.18)	1.16 (1.15 to 1.17)	1.15 (1.14 to 1.16)	0.02 (0.01 to 0.02)
Q4	1.27 (1.26 to 1.28)	1.30 (1.28 to 1.31)	1.30 (1.28 to 1.31)	1.26 (1.25 to 1.27)	-0.01 (-0.01 to -0.01)
Q5	1.58 (1.56 to 1.59)	1.53 (1.51 to 1.54)	1.53 (1.52 to 1.55)	1.51 (1.49 to 1.52)	-0.07 (-0.07 to -0.06)

Absolute rates presented per 1000 births; rate ratios calculated using least deprived quintile (Q1) as reference category; CI, 95% confidence interval; *Change is the value of 2017 minus the value of 2003.

2.4 DISCUSSION

In the Netherlands, between 2003 and 2017, the prevalence of perinatal mortality, premature birth and SGA consistently decreased over time in all area deprivation quintiles, being the most deprived areas the ones showing the largest improvements. Although absolute inequalities in these outcomes decreased over time, relative inequalities in birth outcomes by neighbourhood deprivation level remained fairly constant.

A major strength of this study is its longitudinal approach, which allows observing time trend differences in birth outcomes. Another strength is the amount of data available for the analyses; the dataset was drawn from a national-level registry over a long period 2003-2017, covering more than 97% of all births in the Netherlands, resulting in over 2.3 million records available for analysis. The dynamic nature of neighbourhood deprivation was taken into account, since the index was updated over the study period. This is important as most previous studies only used a single cross-sectional measure of neighbourhood deprivation for the entire period.[29 30] Our finding of declining absolute but persisting relative inequalities confirmed that considering absolute and relative measures of health inequalities is necessary and provides complimentary information. A limitation is that not all births in the dataset could be linked to a deprivation index, mainly due to the deprivation index not being available for areas with less than 200 inhabitants or a missing place of residence of the mother, but the impact is likely small since only 3.2% of all births had a relevant data item missing.

A decrease in the overall prevalence of unfavourable birth outcomes in the Netherlands is consistent with the findings of European reports.[23 32] The overall decreasing trend and the reduction of absolute inequalities could partly be explained by changes in the organisation of preconceptional, antenatal and postnatal care and public health actions.[33] Apart from strategies to improve birth outcomes in the general population, policies targeting the most deprived sectors of the population were also made available in this period. Also, multiple intervention programs to improve perinatal health were launched with a general focus on vulnerable populations.[34 35] As found in previous studies,[36] maternal smoking is an important contributor to inequalities in birth outcomes. It is possible that the reduction in absolute inequalities may in part have been affected by changes in tobacco control policies and decreasing smoking rates.[37]

Studies looking into trends in health inequalities in birth outcomes using area-level deprivation are rather rare.[17 19] The results from the present study are in line with previous studies in the field of health inequalities, while adding to the literature in multiple ways. In the current study, the absolute rates and rate ratios showed a social gradient, where the largest inequalities were observed between the most and the least deprived quintiles. Furthermore, the social gradient in relative terms, remained persistent over the study period. These results are similar to what was found by Gray et al. in Scotland,[17] however, their study focused on premature birth, in contrast, the present study also includes perinatal mortality and SGA as outcomes.

As in the study by Luo et al.,[19] conducted in the Canadian province of British Columbia, the largest inequalities in the present study were observed in urbanised neighbourhoods, however, this paper has the added value of using a nationwide population database. An explanation for these results could be that residents of deprived neighbourhoods in urbanised areas have higher exposure to social and environmental risk factors for unfavourable birth outcomes, such as air pollution, ambient noise, higher temperatures, and stress.[38] Alternatively, stronger inequalities in urbanised areas may be found due to the calculation method of the NIVEL deprivation index. The index includes address density, where higher density values have a higher contribution to the index and vice versa.[27 39] This feature might make the index less sensitive to displaying disadvantage in low urbanised areas as the variation in address density is likely lower in rural areas and its contribution to inequalities smaller. Additionally, some authors have argued that existing deprivation indexes mostly take into account characteristics of urban settings that may be less relevant in capturing rural deprivation.[40 41] A particular difference, and asset, of the present study compared to previous research, is the context of overall substantial improvement in birth outcomes in the Netherlands during the study period. The results of this study are remarkable as they show that even in a context of such large overall improvements, where these have permeated in absolute terms across all deprivation levels, relative inequalities have still remained persistent over time.

The present study aimed to describe trends in health inequalities in birth outcomes in the Netherlands to provide insight and aid in the formulation of hypotheses for future, potentially, research on the underlying mechanisms, instead of focusing on finding causal associations. Further research is necessary to explore the underlying mechanisms for the likely causal effects of neighbourhood deprivation on birth outcomes.

The main findings indicate that there is still work to be done to reduce inequalities in birth outcomes between more and less deprived neighbourhoods in the Netherlands. Apart from the general importance of promoting health across all age groups, the reduction of inequalities in birth outcomes is especially important because of evidence linking early life conditions to long-term health and social functioning. Long term health outcomes could be jeopardised not only by unfavourable birth outcomes, but also due to the additional effect of growing up in a disadvantaged neighbourhood. Moreover the association between neighbourhood deprivation and birth outcomes could be an important channel explaining how poor health and social performance prevails across generations.[42]

In conclusion, while absolute inequalities in adverse birth outcomes in the Netherlands have been narrowing over time, relative inequalities remained persistent over the observed period. These findings provide support for continuing public health actions to reduce these inequalities, and advancing research efforts to explore the underlying mechanisms of neighbourhood effects on health outcomes.

ONLINE SUPPLEMENTARY FILES

The supplementary files referred to in this Chapter are available online at https://github.com/LizBurgosOchoa/Mind_the_Gap_SF/blob/main/Supplementary_files_Chapter2.pdf

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HOŞGELDINIZ

Chapter 3

Association between neighbourhood socioeconomic trajectories and preterm birth and small-for-gestational-age in the Netherlands: a nationwide population-based study.

ABSTRACT

Background

Adverse birth outcomes have serious health consequences, not only during infancy but throughout the entire life course. Most evidence linking neighbourhood socioeconomic status (SES) to birth outcomes is based on cross-sectional SES measures, which do not reflect neighbourhoods' dynamic nature. We described the association between neighbourhood SES trajectories and adverse birth outcomes, i.e. preterm birth and being small-for-gestational-age (SGA) for births occurred between 2003 and 2017.

Methods

We linked individual-level data from the Dutch perinatal registry to the Netherlands Institute for Social Research neighbourhood SES scores. Based on changes in their SES across four years, neighbourhoods were categorised into seven trajectories. To investigate the association between neighbourhood SES trajectories and birth outcomes we used adjusted multilevel logistic regression models .

Findings

Data on 2 334 036 singleton births were available for analysis. Women living in stable low-SES neighbourhoods had higher odds of preterm birth (OR[95%CI]= 1.12[1.07-1.17]) and SGA (OR[95%CI]= 1.19[1.15-1.23]), compared to those in the most advantaged areas. Higher odds of preterm birth (OR[95%CI]= 1.12[1.05-1.20]) and SGA (OR[95%CI]=1.12[1.06-1.18]) were observed for those living in areas declining to low SES. Women living in a neighbourhood where SES improved from low to medium showed higher odds of preterm birth (OR[95%CI]= 1.09[1.02-1.18]), but not of SGA (OR[95%CI]= 1.04[0.98-1.10]).

Interpretation

In the Netherlands, disadvantaged neighbourhood SES trajectories were associated with higher odds of adverse birth outcomes. Longitudinal neighbourhood SES measures should also be taken into account when selecting a target population for public health interventions.

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3.1 INTRODUCTION

Adverse birth outcomes, defined as preterm birth and small for gestational age (SGA), have serious health consequences, not only during infancy but throughout the entire life course.[1] Being born preterm or SGA increases the risk for early-life mortality, and subsequent lifelong morbidity.[2,3] Evidence from population-based studies has consistently linked low neighbourhood socioeconomic status (SES) with adverse birth outcomes, even after adjustment for individual characteristics.[4,5] As such, adverse birth outcomes could be considered the earliest manifestations of socioeconomic inequalities. The majority of the current literature is based on cross-sectional measures of neighbourhood SES.[6] Cross-sectional measures fail to reflect that neighbourhoods are not static but dynamic entities that can experience improvement or deterioration as the result of economic, social and migration processes.[7,8]

Longitudinal approaches to investigating the link between neighbourhood conditions on health outcomes are scarce. The best available evidence comes from social experiments, e.g., Moving to Opportunity (MTO), a program that randomised disadvantaged families in the US to receive vouchers for residential mobility. People who moved to low poverty neighbourhoods within MTO experienced improvements in various health outcomes.[9] However, studies like MTO investigated only the effects of improving neighbourhood SES, while it is also relevant to look at the consequences of negative changes. From a policy and public health perspective, it is essential to explore changes in neighbourhoods' SES themselves, as the majority of the population does not move, or when they do, it is generally to similar areas.[10]

Few studies have investigated the association between the change in neighbourhood socioeconomic characteristics and birth outcomes.[6,7,11] These available studies are based on single US states and count with relatively limited sample sizes. Their findings may not apply to European countries due to demographic, social, economic, and health care differences.[10] Most of these studies place their focus on long-term neighbourhood change (e.g. across 40 years). However, exploring the link between short-term changes and health is also relevant. One of the main mechanisms through which changes in neighbourhood SES may affect health outcomes is stress.[6,7] It has been argued that neighbourhood residents are probably accustomed to a certain amount of perks and problems within their neighbourhood, and it might be the rapid changes that result in health impact.[12] Short-term changes in neighbourhood SES have been associated with changes in risks factors for adverse birth outcomes, e.g. unhealthy food environment,[13] and poor mental health.[14] Only one previous work, conducted in New York City, has explored the association between short-term changes in neighbourhood SES and birth outcomes.[11] However, this study only focused on gentrifying neighbourhoods rather than the full spectrum of SES trajectories.

The Netherlands offers an ideal setting for the study of short-term changes in neighbourhood conditions and their association with birth outcomes. Previous research has shown that a fifth of the Dutch neighbourhoods experienced decline or improvement in four years.[15,16] The purpose of the study is to describe the relationship between short-term neighbourhood SES trajectories and birth outcomes in the Netherlands. Based on the available literature, we hypothesise that neighbourhoods with persistently low SES, or those that decline to low SES, will show the poorest outcomes.[6,7,11,17]

3.2 METHODS

Study design and participants

In this retrospective population-based cohort study, we linked individual-level birth records to routinely collected neighbourhood-level data, population register data, and income and tax records. The cohort comprised singleton births with gestational ages between 24+0 and 41+6 weeks registered in the Netherlands between 1 January 2003 and 31 December 2017. Birth records before 2003 were not included in the analysis as information on household income is only available from 2003 onwards.

We obtained the birth records from the Netherlands Perinatal Registry (Perined). Perined comprises routinely collected data on maternal characteristics, pregnancy, delivery, and birth outcomes, covering 97% of all births in the Netherlands.[18] The data is subject to strict quality and consistency checks to ensure that only valid values of the perinatal variables are kept in the final dataset.[19] Perined also provides the four-digit postcode of the mothers' residence.

CBS performed the individual-level linkage of Perined records to the national population registry held at CBS. As a result of this linkage, CBS assigns each mother and child a unique identification number (RIN number). This identifier is a meaningless and dimensionless number that identifies a natural person.[20] Every individual in the Netherlands has a unique RIN number that is used by CBS to link a wide variety of administrative records and surveys. Given that each mother and child have unique identifiers, siblings born from the same mother are identifiable. Instances, where the linkage algorithm did not link a registered birth to a RIN number could be because the mother was not registered in the population records (non-residents), the child was stillborn, or due to linkage error (false-matches and missed-matches). Given that stillbirths were non-linkable, records available for analysis consisted of live births only. From the available Perined birth records, 3% could not be linked to CBS data.

CBS population and income and tax records include sociodemographic information of the country's residents. This information is routinely collected from different sources, e.g., municipality records and the Dutch Tax and Customs Authority. CBS data registries are subject to strict quality checks and follow several procedures to ensure the validity of the data.[21]

Data variables and measurement

The following definitions were used for the birth outcomes: 1) preterm birth, any livebirth occurring from 24+0 weeks of gestational age and before 37+0 weeks, and 2) SGA birth, birth weight below the 10^{th} centile adjusted for gestational age and sex, according to national reference curves.[22] Gestational age is estimated by using information on the last menstrual cycle and foetal scans.[23] Births with gestational age <24+0 were not included in the analysis as Dutch national multidisciplinary guidelines advise against active management of babies born at gestational ages of less than 24 weeks and 0 days.[24,25] Furthermore, birthweight <400g was considered implausible and treated as missing, as European and national guidelines advise against the active management of babies with birthweight below this threshold.[25]Based on previous studies, birthweight was also considered implausible and set as missing if >6500g.[26,27]

We used the household income corresponding to the child's year of birth to measure of individual-level SES. Researchers have recommended using household income to better measure women's SES over other individual-level measures for health inequalities research.[28] Moreover, health inequalities research has shown that household income performs as good as other individual-level SES indicators (e.g. education or composite measures) in capturing health variation.[29] Information on household-equivalised disposable income was obtained from CBS income and tax records. This measure accounts for the household size and composition using the modified Organisation for Economic Co-operation and Development (OECD) equivalence scale.[30] Data on mother's education was not included in the main analysis (but in a sensitivity analysis) as information on this variable was missing for a considerable part of the dataset (i.e., 19.6%). [31]

We obtained maternal migration background (ethnicity and generation) information, and residential history from CBS records. Ethnicity was assigned based on the mother's country of birth. CBS categorises this variable based on the largest ethnic groups present in the Netherlands: Dutch background, Turkish, Moroccan, Surinamese, Antillean, others western, others non-western.[32] A woman would have a western migration background if she or at least one of the parents was born in Europe, North America or Oceania.[32] Information on whether the mother was a first-generation or second-generation migrant was also obtained from CBS records.

We used the Netherlands Institute for Social Research (SCP) Status Scores to measure neighbourhood socioeconomic status.[33] The SCP Status Scores are a relative measure of neighbourhood SES calculated for areas corresponding to four-digit postcodes, with an average of 4 000 inhabitants,[34] and a median size of 5.3 km^2. The SCP Status Scores are based on postcode-level data collected yearly by CBS, which is calculated by aggregating the information of all residents from each four-digit postcode.[35] The SCP status scores summarise information from four indicators: 1) average neighbourhood income, 2) percentage of inhabitants with a low income, 3) percentage of inhabitants without a paid job, and 4) percentage of inhabitants with a low education level. The SCP Status Scores have been previously used in health inequalities research in the Netherlands.[36–38] The SCP provides updated Status Scores every four years. For this work, we used the SCP Status Scores corresponding to the years 1998, 2002, 2006, 2010, and 2014.

The exposure of interest was neighbourhood SES trajectory. To construct the SES trajectories, we first created cross-sectional measures of neighbourhood SES by categorising the SCP Status Scores into Low (lowest quintile), Medium (second to fourth quintiles), and High (highest quintile). Then, by comparing two consecutive cross-sectional SES measures (e.g. 2006 vs 2002), the neighbourhoods were categorised into seven SES trajectories: 1) Stable High, 2) Stable Medium, 3) Stable Low, 4) Improving to High, 5) Improving to Medium, 6) Declining to Medium, and 7) Declining to Low. Categories portraying a drastic change in neighbourhood SES, i.e., Improving Low to High and Declining High to Low were also considered. However, such steep changes are rare in the Netherlands,[15] and across the period 2003-2017, only <0.3% of the births could be assigned to any of these trajectories. These cases were thus included in the trajectories Improving to High and Declining to Low, respectively.

Birth records were grouped into four mutually exclusive periods (table 1). The exposure (neighbourhood SES trajectory) was assigned to the births that occurred within each period, as stated in table 1. For example, for each neighbourhood, the trajectory resulting from comparing 2006 versus 2002 cross-sectional SES measures was used as exposure for births occurring in the period 2006-2009. The corresponding neighbourhood SES trajectory was assigned to each birth using maternal four-digit postcode registered at delivery.

Table 1. Exposure assignment to birth records.

Exposure (neighbourhood SES trajectory)	Birth period
2002 vs 1998	1) 2003-2005
2006 vs 2002	2) 2006-2009
2010 vs 2006	3) 2010-2013
2014 vs 2010	4) 2014-2017

**First birth time period includes only 3 years instead of 4 (as later periods). Birth records before 2003 were not included in the analysis as information on household income is only available from 2003.*

Due to privacy considerations, SCP does not calculate status scores for areas with less than 100 households.[18] Therefore, neighbourhood trajectories could not be assigned to births from mothers living in such areas or birth records without a postcode available. As a result, neighbourhood SES trajectory was missing for 1.5% of the records. Due to the low proportion of missing data, no data was imputed for the analyses.

Statistical analysis

To assess the relationships between neighbourhood SES trajectories and adverse birth outcomes, we used two-levels (level 1, births; level 2, neighbourhoods) logistic random-intercepts regression models with pooled cross-sections. The pooled cross-sections technique combines elements from time series and cross-sectional data to analyse datasets that consist of several cross-sections from the same population collected at different time points (e.g. years or periods) but where the observations do not refer to the same units.[39,40] The percentage of variation between neighbourhoods in preterm birth and SGA prevalence (intra-class correlation, ICC) was around 2% and statistically significant, supporting the decision to use multilevel models.[41] The Stable High SES trajectory, reflecting the most advantaged neighbourhoods, was used as reference.

We adjusted the models for the following individual-level characteristics: maternal ethnicity, migration generation, maternal age at delivery in categories (≤19, 20-34, ≥35 years), equivalised household income in categories (quintiles), and parity registered at (antenatal) intake (primiparous vs multiparous). Maternal lifestyle factors (e.g. smoking, drug and alcohol use, BMI), aside from suffering from severe underreporting,[44] have been suggested as mediators for the relationship between neighbourhood SES and health outcomes.[45–48] To avoid bias due to over-adjustment,[49,50] these variables were not included in the main models. At the neighbourhood level, we did not adjust for physical (e.g. pollution and greenness[51,52]) and social factors (e.g. social cohesion and crime[52,53]) as they have also been found to mediate the exposure-outcome relationship. Variables registering maternal comorbidities (e.g. pre-existent diabetes and hypertension) were not included in the main models as they are likely to suffer underreporting in the Perined dataset[18]

Dummy variables for all but one time period were included in the models to account (and test) for changes in the outcomes across different periods.[40] Next, interaction terms between each time-period dummy variable and neighbourhood SES trajectories were added to account for changes over time in the relationship between exposure and outcomes.[40]

We conducted a set of sensitivity analyses to assess the robustness of our findings: 1) Models were additionally adjusted for the duration of residence in the neighbourhood at the time of delivery (in years). 2) We excluded births in 2006, 2010 and 2014 to assess whether our results were driven by cases born in the first years of the periods. 3) We conducted two analyses to assess the impact of women moving to a different neighbourhood during, or before, their pregnancy on the results: a) including only women who had been living in the neighbourhood for at least one year at the time of delivery, and b) restricting the analysis to women who have resided in the same residential address throughout the entire four years period corresponding to the assigned exposure (see Table 1). 4) We assessed the robustness of our results to the adjustment for the mother's educational level (low, medium, high). 5) We also assessed the robustness of our results to the adjustment for a) maternal comorbidities (pre-existing diabetes and hypertension), and b) unhealthy lifestyle factors, i.e., smoking, alcohol consumption, and drug use (binary variables). The attenuation of the estimates after adjusting for lifestyle factors may be a sign of mediation. 6) Restricted the analysis to only spontaneous births. 7) Excluded observations with implausible birthweight given gestational age values, i.e., birthweight was assumed missing if it was recorded as >1500g and gestational age <29 weeks. For gestational age 29 to 33 weeks birthweight was assumed missing if it was recorded as >2800 g.[54] 8) We fitted joint regression models for correlated binary outcomes to account for any potential interdependence between the outcomes. We followed the procedure developed by Ghebremichael,[55] which was applied to a multilevel scenario by Di Fang et al.[56] 9) We conducted a siblings-comparison analysis (within-family or family fixed-effects analysis) to reduce unobserved confounding at mother's level. The siblings-comparison analysis controls by design for all time-constant (shared by the siblings) observed and unobserved confounders including the mother's ability, genetics, ethnicity, etc. The siblings-comparison model was additionally adjusted for time-variant covariates, i.e., maternal age, household income, and parity.

For all analyses, a p value of less than 0.05 was used to indicate statistical significance. All analyses were performed using R version 3.6.3.[57]

Ethical considerations

According to Dutch law (WMO) no formal ethical review was required. According to standard procedures and under strict conditions that were fulfilled, CBS anonymised the data before making it available to the researchers.[26] Perined provided approval (19.13) for this research project.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3.3 RESULTS

Between 2003 and 2017, 2 629 207 births were registered in the Netherlands, of which 2 538 897 (~97%) could be linked by CBS. After removing multiple births, births with gestational age below 24+0 weeks or above 41+6 weeks, and births with missing data on covariates, 2 334 036 births were available for the analysis (figure 1).

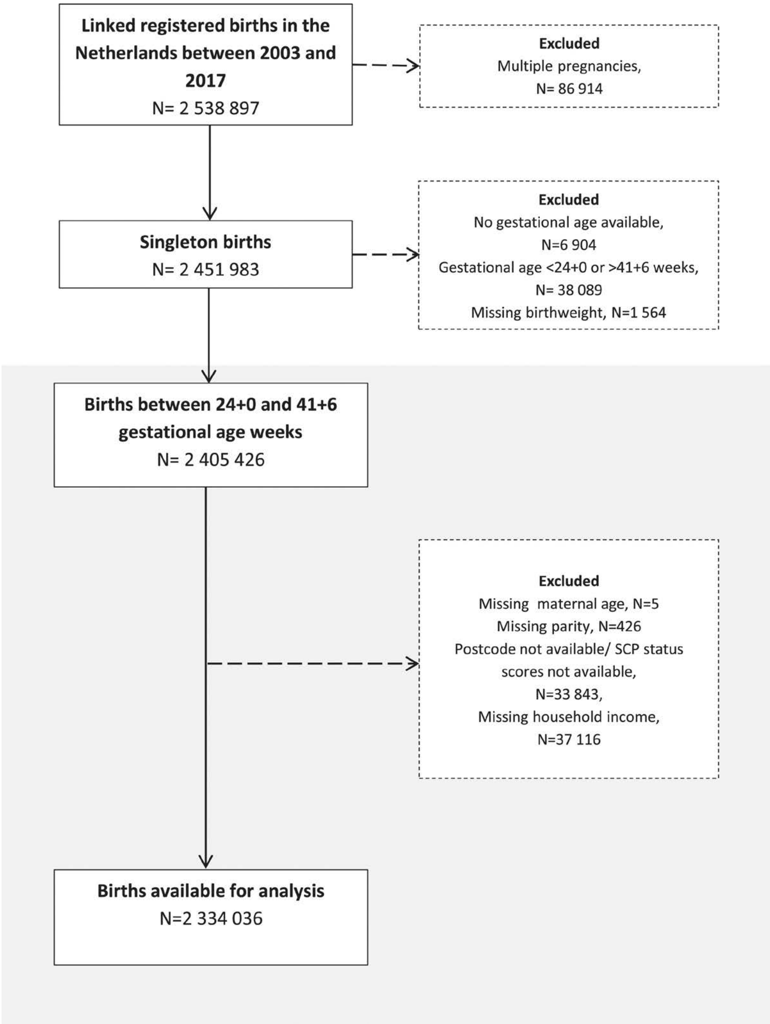

Figure 1. Study population flow diagram.

During each of the periods, roughly one-fifth (19.5%) of the neighbourhoods saw a change in their SES, while most of the areas (80.5%) remained stable (Supplementary figure 1). The mean maternal age was 30.6 (SD 4.8), it was at its lowest in Stable Low areas (29.6, SD 5.3), and highest in Stable High (31.8, SD 4.4) (Table 2). Stable Low areas showed the highest percentage of women with a migration background. The lowest and highest household incomes were observed in Stable Low and Stable High neighbourhoods, respectively. In terms of birth outcomes, Stable Low and Declining (Medium to Low) neighbourhoods had the highest prevalence of preterm and SGA births, while Stable High areas showed the lowest prevalence.

Adjusted regression models show that higher odds of having a preterm birth (OR[CI]= 1.12[1.07-1.17], p<0.0001) or SGA birth (OR[CI]= 1.29[1.15-1.23], p<0.0001) were observed for women living in Stable Low SES areas, compared to women living in (the most advantaged) Stable High SES neighbourhoods (Table 3A). Moreover, women living in areas categorised as Declining to Low SES had higher odds of having a preterm birth (OR[CI]= 1.12[1.05-1.20], p<0.0014) or SGA birth (OR[CI]= 1.12[1.06-1.18], p<0.0001), as compared to women living in Stable High SES areas. Whereas odds of preterm birth were still increased for women living in an Improving to Medium SES neighbourhood (OR[CI]= 1.09[1.02-1.18], p=0.0184), this was not the case for SGA (OR[CI]= 1.04[0.98-1.10]). There were no significant differences in the odds of preterm birth or SGA between the remaining trajectories and the Stable High areas (full adjusted results in Supplementary table 1).

Changes in the exposure-outcome relationship across time-points were assessed using interaction terms time-period × neighbourhood SES trajectory. For SGA, a downwards trend over time for the Declining to Low and Stable Low trajectories was found. For example, for the Stable Low trajectory, the odds ratios changed from 1.19 (95% 1.15-1.23) in the first period to 1.13 (95% CI 1.10 to 1.17) in the last period (Supplementary Figure 2). However, in none of the cases the interaction terms were significant. For preterm birth, the estimates remained fairly unchanged across periods (Supplementary Figure 2).

The patterns found in the main analysis remained unchanged in the sensitivity analyses where 1) models were adjusted for the time that the mother has been living in the registered neighbourhood (Supplementary table 2), 2) we excluded births that occurred in 2006, 2010, and 2014 (Supplementary table 3), 3) the analyses were restricted to women who had lived for at least one year (Supplementary table 4), or the entire exposure time, in the same residential address (Table 3B and Supplementary table 5), 4) the analyses were adjusted for maternal education (Supplementary table 6), 5) we accounted for maternal comorbidities, and lifestyle factors (Supplementary table 7), 6) the analyses were restricted to only spontaneous births (Supplementary table 8), 7) observations with implausible birthweight given gestational age values were excluded (Supplementary table 9), and 9) we fitted joint regression models (Supplementary table 10). When restricting the analysis to women who have remained in the same address for the entire exposure period (Table 3B), the association between the Stable Low SES trajectory and preterm birth was slightly larger than in the main analysis (OR[95% CI]= 1.17 [1.09-1.25], p<0.0001). For preterm birth, the results from the main analysis remained unchanged when conducting the siblings-comparison analysis (Supplementary table 11). For SGA, the results for the Stable Low (OR[95% CI]= 1.10 [1.04-1.16], p=0.0003) and Declining to Low (OR[95% CI]= 1.06 [1.01-1.12], p=0.0415) SES trajectories remained significant, however, the estimates were attenuated (Supplementary table 11).

Table 2. Population characteristics of singleton pregnancies between 2003 and 2017 by neighbourhood SES trajectory.

	Neighbourhood SES trajectory							
	Total	**Stable High**	**Stable Medium**	**Stable Low**	**Improving to High**	**Improving to Medium**	**Declining to Medium**	**Declining to Low**
N (% of total)	2 334 036	359 525 (15.4)	1 054 271 (45.2)	502 546 (21.5)	91 684 (3.9)	103 483 (4.4)	108 282 (4.6)	114 245 (4.89)
	Characteristics							
Maternal age, mean (SD)	30.6(4.8)	31.8 (4.4)	30.5 (4.7)	29.6 (5.3)	31.5 (4.5)	30.4 (4.9)	31.0 (4.6)	30.0 (4.9)
Primiparous, N(%)	1 053 956 (45.2)	155 847 (43.4)	473 158 (44.9)	231 276 (46.0)	40 771 (46.1)	50 823 (49.1)	47 818 (44.2)	52 463 (46.1)
Dutch	1 707 011 (73.1)	280 970 (78.2)	853 862 (81.0)	257 874 (51.3)	72 390 (79.0)	74 170 (71.7)	86 226 (79.6)	81 519 (71.4)
Moroccan	99 679 (4.3)	6 850 (1.9)	24 708 (2.3)	55 031 (11.0)	1 623 (1.8)	4 066 (3.9)	2 429 (2.2)	4 972 (4.4)
Turkish	80 503 (3.4)	5 743 (1.6)	18 856 (1.8)	45 084 (9.0)	1 149 (1.3)	3 422 (3.3)	1 625 (1.5)	4 624 (4.0)
Suriname	59 851 (2.6)	8 312 (2.3)	14 644 (1.4)	26 994 (5.4)	1 997 (2.2)	2 727 (2.6)	2 200 (2.0)	2 977 (2.6)
Antillean	27 572 (1.2)	2 680 (0.7)	7 587 (0.7)	12 933 (2.6)	674 (0.7)	1 300 (1.3)	839 (0.8)	1 559 (1.4)
Other non-western	141 916 (6.1)	17 205 (4.8)	46 394 (4.4)	54 610 (10.9)	4 087 (4.5)	6 796 (6.6)	4 782 (4.4)	8 042 (7.0)
Other western	217 504 (9.3)	37 765 (10.5)	88 220 (8.4)	50 020 (10.0)	9 764 (10.6)	11 002 (10.6)	10 181 (9.4)	10 552 (9.2)
Second generation	227286 (9.8)	34 111 (9.5)	76 520 (7.2)	77 695 (15.4)	8 057 (8.8)	10 542 (10.2)	8 920 (8.2)	11 441 (10.0)
Household income €, median (IQR)	22 140 (14 279)	26 504 (16 489)	22 564 (13 538)	18 068 (12 421)	26 019 (16 055)	22 057 (14 459)	22 421 (12 791)	20 478 (12 824)
	Birth outcomes							
Preterm birth, N(%)	131 521 (5.6)	18 503 (5.1)	58 623 (5.6)	30 989 (6.2)	4 807 (5.2)	5 890 (5.7)	5 983 (5.5)	6 726 (5.9)
SGA, N(%)	261 154 (11.2)	35 146 (9.8)	110 909 (10.5)	69 518 (13.8)	9 065 (9.9)	11 952 (11.5)	11 093 (10.2)	13 471 (11.8)

Time points of covariate assessment: maternal age assessed at delivery, parity is registered during the antenatal care intake, yearly household income from the year of birth of the child, and ethnicity as registered in CBS records (remains invariant across time).

Table 3. Odds ratios (95% CI) from multilevel logistic regression for the relationship between neighbourhood SES trajectory and birth outcomes.

A)	**Full sample**			
Neighbourhood SES trajectory	**Preterm birth**		**SGA**	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Stable High	REF	REF	REF	REF
Stable Medium	1.06 (1.02-1.10)	1.04 (0.99-1.09)	1.07 (1.04-1.10)	1.03 (0.99-1.07)
Stable Low	1.20 (1.15-1.25)	1.12 (1.07-1.17)	1.37 (1.32-1.42)	1.19 (1.15-1.23)
Improving to High	0.99 (0.91-1.07)	0.98 (0.91-1.06)	0.98 (0.92-1.04)	0.97 (0.92-1.03)
Improving to Medium	1.13 (1.05-1.22)	1.09 (1.02-1.18)	1.11 (1.05-1.18)	1.04 (0.98-1.10)
Declining to Medium	1.04 (0.97-1.11)	1.03 (0.97-1.10)	1.05 (1.00-1.10)	1.03 (0.98-1.08)
Declining to Low	1.17 (1.10-1.25)	1.12 (1.05-1.20)	1.23 (1.17-1.29)	1.12 (1.06-1.18)
B)	**Subsample of women who remained in the same address throughout entire exposure period**			
	Preterm birth		**SGA**	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Stable High	REF	REF	REF	REF
Stable Medium	1.07 (1.00-1.14)	1.05(0.99;1.13)	1.05(1.00;1.10)	1.02(0.97;1.06)
Stable Low	1.26 (1.18-1.34)	1.17(1.09;1.25)	1.34(1.27;1.41)	1.17(1.11;1.23)
Improving to High	1.03 (0.91-16)	1.02(0.90;1.14)	0.98(0.90;1.08)	0.98(0.90;1.07)
Improving to Medium	1.17 (1.05-1.31)	1.12(1.01;1.26)	1.07(0.98;1.16)	1.00(0.92;1.09)
Declining to Medium	1.01 (0.92-1.12)	1.00(0.91;1.11)	1.06(0.98;1.14)	1.04(0.96;1.12)
Declining to Low	1.15 (1.04-1.28)	1.09(1.01;1.18)	1.26(1.14;1.32)	1.12(1.04;1.20)

Model 1: Including only time-point dummy variables and time-period × neighbourhood SES trajectory interactions.
Model 2: Including Model 1 terms and adjusting for individual-level characteristics: maternal age, parity, migration background and household income.
Stable High trajectory (most advantaged) as reference category (REF).
First time-period (2003-2006) used as reference.
Number of preterm births and SGA births in each SES category are displayed in Table 2.
Part B corresponds to estimates from sensitivity analysis 3b.

3.4 DISCUSSION

In this study, using a large nationwide perinatal registry linked to a comprehensive measure of neighbourhood socioeconomic status, we found a detrimental (small) association between disadvantaged neighbourhood SES trajectories and adverse birth outcomes. Women living in persistently low SES areas or areas that declined to low SES had higher odds of preterm or SGA birth, compared to women living in the most advantaged areas. Also, living in a neighbourhood whose SES shifted from low to medium was associated with higher odds of preterm birth, but not SGA. Importantly, odds of preterm or SGA birth in other areas were comparable to those seen in high SES areas.

To the best of our knowledge, this is the first study to have examined the association between changes in neighbourhood SES occurring in short (four years) periods and birth outcomes in a nationwide cohort. The findings from this study are consistent with previous evidence while adding to the literature in meaningful ways. Our finding that women in stable low SES and declining SES areas have higher odds of preterm birth and SGA births is in line with studies conducted in the US by Cubbin et al. (Texas),[6] and Magerison-Zilko et al. (California).[7] They found that long-term neighbourhood poverty and poverty increase were associated with higher odds of preterm birth and SGA. Both studies used the changes in the percentage of persons below 100% of the federal poverty level as exposure, whereas we examined the changes in a broader measure of neighbourhood socioeconomic conditions. Moreover, our study furthers the existing literature by investigating changes occurring over shorter periods than those considered in the previous studies (20 to 40 years[6,7]). We also found that women in neighbourhoods rapidly improving from low to medium SES were more likely to experience preterm birth. In their study, Cubbin et al. found that living in neighbourhoods with decreasing poverty was associated with increased odds of preterm birth.[6] Additionally, Huynh et al. (New York City) found that, for disadvantaged groups, living in rapidly improving neighbourhoods was associated with an increased incidence of preterm birth.[11]

There are multiple reasons why differences in birth outcomes across neighbourhood SES trajectories were observed in our study, some of them related to potential causal mechanisms. One potential explanation relates to neighbourhood characteristics, particularly the physical environment. Several studies have observed consistent associations between high noise and air pollution levels and adverse birth outcomes, particularly in deprived areas.[52,58,59] Moreover, inhabitants from declining and continuously deprived areas might be more exposed to deteriorating or poor built environment and housing conditions, factors that have been linked to adverse birth outcomes.[59–61] Furthermore, the characteristics of areas undergoing economic improvement may still resemble more those in low SES neighbourhoods than those from more advantaged areas, which could be one explanation for the observation that improving areas (from low to medium SES) still showed higher odds of preterm birth. Living in disadvantaged areas is associated with poor healthcare uptake, which might, in turn, affect birth outcomes.[62] This mechanism is supported by the findings from a recent European study where favourable changes in neighbourhood SES were associated with higher hypertensive pregnancies diagnosis rates.[63] Untreated hypertensive pregnancies are a well-known risk for adverse birth outcomes. A different pathway could be the psychological stress triggered by perceived neighbourhood-related factors and constant exposure to poverty-related issues.[52] For example, mothers living in declining and persistently low SES neighbourhoods might perceive lower social cohesion and safety than their counterparts living in more advantaged areas. Both aspects have been linked before with adverse birth outcomes.[64–67] Neighbourhoods undergoing socioeconomic improvement may also present certain stressors,[11] such as rising rents and higher prices for neighbourhood resources (e.g., stores and food outlets).[7] Stress is hypothesised to be the main pathway for low SES neighbourhoods that are quickly improving, especially for long-term residents.[11] This could also explain the differences between preterm birth and SGA in neighbourhoods improving from low to medium, as preterm birth may be more sensitive to maternal stress.[68]

A unique strength of this study is its longitudinal approach towards neighbourhood social and economic conditions, which allows taking into account neighbourhoods' dynamic nature. Using national-level routinely collected data corresponding to an extended period (2003-2017) led to over two million individual records available for analysis. By assessing several types of declining, ascending and stable neighbourhood trajectories, our results provide more precise information about the type of change that might be the most detrimental (i.e. decline from medium to low SES) or beneficial (i.e. progress from low to medium SES). A limitation of this study is that CBS could not link some births, and therefore could not be included in the analysis. However, the impact of this is likely small as the percentage of unlinked births was only around 3%. It cannot be ruled out that the observed association can be due to compositional effects related to the selective sorting of people into neighbourhoods.[69,70] Previous research has found that income and ethnicity are the most important drivers of neighbourhood sorting,[71] characteristics we have included in our models. Moreover, including information on maternal education, hypertension and diabetes to the models in the sensitivity analyses did not change the conclusions. Additionally, the results from the siblings-comparison analysis supported the conclusions derived from the main analysis.

From a public health standpoint, this study has several implications. Our findings indicate higher odds of adverse birth outcomes for mothers living in long-term low SES neighbourhoods and areas in decline. At the same time, the odds of preterm birth for residents in improving neighbourhoods (low to medium SES) were still higher compared to those in the most advantaged areas. This suggests that longitudinal neighbourhood SES measures should also be taken into account when selecting a target population for public health interventions. Moreover, in agreement with previous research,[34] our results indicate that even though differences in outcomes between most and least disadvantaged areas seem to be narrowing, they remain persistent.[34] Therefore, it is vital to continue public health actions to reduce this gap.

Future studies should focus on how changes in neighbourhood SES affect different strata of the population, e.g. ethnic minorities. Furthermore, future research in the Dutch population needs to further investigate the underlying mechanisms driving the observed association, e.g., healthcare uptake and access, neighbourhood crime rates, social cohesion, air pollution, greenness, and walkability. To appropriately inform decision-makers when developing public health interventions, further research is necessary to pinpoint the causal pathways by which neighbourhood SES trajectories affect birth outcomes.

In conclusion, our results indicate that, in the Netherlands, women living in neighbourhoods with disadvantaged SES trajectories were more likely to experience adverse birth outcomes. Results from this study suggest that, in this context, longitudinal neighbourhood SES measures should also be taken into account when selecting a target population for public health interventions.

ONLINE SUPPLEMENTARY FILES

The supplementary files referred to in this Chapter are available online at https://github.com/LizBurgosOchoa/Mind_the_Gap_SF/blob/main/Supplementary_files_Chapter3.pdf

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Part 2:

Exploring the underlying mechanisms.


HOŞGELDINIZ

Chapter 4

Neighbourhood-related socioeconomic perinatal health inequalities: An illustration of the mediational G-formula and considerations for the big data context.

ABSTRACT

Background

Advances in computing power have enabled the collection, linkage, and processing of big data. Big data in conjunction with robust causal inference methods can be used to answer research questions regarding the mechanisms underlying an exposure-outcome relationship. The g-formula is a flexible approach to perform causal mediation analysis that is suited for the big data context. Although this approach has many advantages, it is underused in perinatal epidemiology and didactic explanation for its implementation is still limited.

Objective

To provide a didactic application of the mediational g-formula by means to perinatal health inequalities research.

Methods

The analytical procedure of the mediational g-formula is illustrated by investigating whether the relationship between neighbourhood socioeconomic status (SES) and small for gestational age (SGA) is mediated by neighbourhood social environment. Data on singleton births that occurred in the Netherlands between 2010 and 2017 (n = 1,217,626) was obtained from the Netherlands Perinatal Registry and linked to sociodemographic national registry data and neighbourhood-level data. The g-formula settings corresponded to a hypothetical improvement on neighbourhood SES from disadvantaged to non-disadvantaged.

Results

At the population level, a hypothetical improvement in neighbourhood SES resulted in a 6.3% (95% confidence interval [CI] 5.2,7.5) relative reduction in the proportion of SGA, i.e., the total effect. The total effect was decomposed into the natural direct effect (5.6%, 95% CI 5.1, 6.1) and the natural indirect effect (0.7%, 95% CI 0.6, 0.9). In terms of the magnitude of mediation, it was observed the natural indirect effect accounted for 11.4% (95% CI 9.2, 13.6) of the total effect of neighbourhood SES on SGA.

Conclusions

The mediational g-formula is a flexible approach to perform causal mediation analysis that is suited for big data contexts in perinatal health research. Its application can contribute to providing valuable insights for the development of policy and public health interventions.

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4.1 INTRODUCTION

Big Data in Perinatal Epidemiology

To design interventions aimed at improving perinatal health, causal knowledge on the effects of exposures of interest (and underlying mechanisms) on perinatal outcomes is necessary. The field of perinatal health research has generally focused on answering causal research questions using randomized controlled trials (RCT).[1] However, conducting RCTs in this field to investigate the effect of certain exposure on perinatal health is often unrealistic due to practical and ethical considerations. For example, in the study of health inequalities, it is unfeasible to randomly assign the population to advantaged and disadvantaged socioeconomic conditions. Moreover, questions regarding the underlying mechanisms cannot be answered using RCTs.[2] In these situations, researchers have supported the concept of causal inference with observational (big) data.

Recent advances in computing power enabled the collection, linkage, and processing of large amounts of data from multiple sources, i.e., big data. Big data can refer to datasets with a large number of observations (e.g., population registry data) or datasets with a large number of variables (e.g., genomics data).[3] While big data is typically not collected for research purposes, it can contribute to health research through its potential to link health records with multiple datasets or by covering a large number of observations (often entire populations). In exchange for these advantages, big data presents the challenges of being potentially incomplete, inaccurate, and computationally intensive to process. Furthermore, the observational nature of big data represents challenges for causal inference.[4]

Causal inference and the parametric g-formula

Answering causal questions with big data requires both high-quality data and robust statistical methods. The Neyman-Rubin potential outcomes framework,[5,6] provides conceptual definitions and supports analytic methods for estimating causal effects from observational data.[7] This approach uses counterfactuals (i.e., “what-if” scenarios) to define causal effects.[8]

The parametric g-formula,[9] a technique embedded in the potential outcomes framework, was first introduced in 1986 by Robins. However, its widespread application only became feasible with increasing computational power.[10] This technique is recognised as a unified and flexible causal inference approach that allows for designing custom interventions, a property available in a few other methods.[11,12] The g-formula was originally proposed for applications in settings with confounders affected by previous exposure and can naturally be extended to mediation analysis.[12]

Mediation analysis evaluates the relative magnitude of pathways by which an exposure influences an outcome.[13,14] The most utilized approach to perform mediation analysis is the Baron and Kenny, traditional, approach.[15] The traditional mediation approach has important shortcomings as it is prone to bias when exposure and mediator interact and when the outcome is non-linear (e.g., dichotomous).[16–19] The parametric g-formula, extends mediation analysis to settings involving non-linearities and interactions[10,12] and its estimates are easily understandable population-averaged effects.[11] The g-formula uses parametric regression models to predict outcomes under hypothetical intervention scenarios (counterfactuals), which are used to estimate mediation effects via Monte Carlo simulation. The parametric g-formula is referred to as mediational g-formula when used for causal mediation analysis. For simplicity, in the remaining of the manuscript we will refer to this approach as the g-formula.

While applications of the g-formula for mediation analysis have been increasing in recent years, it remains underused among substantive researchers and didactic explanation for its implementation is still limited.[12] We provide a didactic demonstration of the implementation of the g-formula by means of an example from perinatal health inequalities research. The demonstration in this paper corresponds to a simple scenario and is meant to provide a gentle introduction to the potential outcomes framework and the use of the g-formula in R software.[20]

4.2 METHODS

Illustrative example research question and dataset

Compelling evidence shows a consistent link between neighbourhood socioeconomic status (SES) and perinatal outcomes.[21,22] Although this relationship has been well established, little is known about the underlying mechanisms. One of the hypothesized pathways in the literature is neighbourhood social environment.[23,24] While SES refers to the economic conditions of a neighbourhood, social environment is defined as the relationships and processes that exist between its residents along with the social composition of a neighbourhood in terms of, e.g., life-stage.[25–27] In our example, we use the g-formula to investigate whether the relationship between neighbourhood SES and perinatal health is mediated by social environment.

Outcome

This paper focuses on small for gestational age (SGA) as the outcome, defined as birthweight below the 10th centile for gestational age and sex, according to national reference curves.[29] Data from the Netherlands Perinatal Registry (Perined) was acquired for singleton births at gestational ages between 24+0 and 41+6 weeks between 1 January 2010 and December 2017. Perined contains high-quality information on perinatal outcomes and maternal characteristics. The perinatal registry was linked by Statistics Netherlands (CBS) to several individual-level sociodemographic registries. Unfortunately, only live-births could be linked by CBS.

Exposure

Neighbourhood SES was quantified using the Neighbourhood Status Score by the Netherlands Institute of Social Research.[4] The SCP Status Score is a validated relative indicator of neighbourhood SES computed using factor analysis to summarise into a single score the following three characteristics: (i) percentage of residents with a low income; (ii) percentage of inhabitants without a paid job; and (iii) percentage of inhabitants with a low education level.[5] More information is available in supporting information file 1.

Mediator

The measure for the mediator corresponds to the Social Environment Score from the neighbourhood liveability assessment ("Leefbaarometer") by the Netherlands Ministry of the Interior.[6] The Social Environment Score (range, −50 to 50), one of the dimensions of the Leefbarometer, provides a single score based on the following indicators: residential stability (number of relocations), life stage diversity of households (e.g., single, couples, family households), population density, and social cohesion (more information in supporting information file 1). The score has shown good internal and external validity.[6] Information on other neighbourhood-level characteristics was obtained from CBS.[28] All neighbourhood-level data was linked to birth records using the mother's residential postcode and year of birth.

To facilitate the explanation of the g-formula approach, exposure, outcome, and mediator variables were dichotomised. To create the exposure categories, quintiles of neighbourhood SES were first calculated. The disadvantaged neighbourhood SES category corresponds to the lowest quintile and the non-disadvantaged category refers to the remaining quintiles, thus resulting in two categories. The same approach was taken for the social environment categories.

Mediation analysis using the parametric mediational g-formula

Counterfactuals

Under the potential outcomes framework, mediation analysis defines causal effects as the difference between two counterfactual outcomes.[5] Counterfactuals can be thought of as what would have happened under alternative histories.[8] Thus, a counterfactual outcome refers to the outcome value that *would be* observed if the exposure *would be* set to a certain value. Let Y denote the outcome of interest (SGA) and SES the exposure of interest (neighbourhood SES), which can take the (observed) values SES=1 (disadvantaged SES) or SES=0 (non-disadvantaged SES). We use upper case SES to denote the observed values of SES. If the exposure *would be* set to disadvantaged SES (ses=1), the counterfactual outcome would be denoted as $Y_{ses=1}$, and if the exposure *would be* set to advantaged SES (ses=0) the counterfactual outcome would be $Y_{ses=0}$. Lower case ses is used to denote "set" values of SES. The effect of the exposure is defined at population level as the difference between these two counterfactual outcomes, i.e., $E[Y_{ses=0} - Y_{ses=1}]$. Since these are counterfactual outcomes under alternative exposure levels, only one would be factual (observed).[7] However, through the g-formula and identification conditions (section 2.2.3), observational data can be used to extract information about the unobserved counterfactual outcome.

Adding a mediator makes the definitions of counterfactuals more complex.[9] For each value of the exposure, there is a counterfactual value for the mediator and one for the outcome. Let *M* denote our mediator variable (social environment) where $M_{ses=1}$ and $M_{ses=0}$ would be the counterfactual values of the mediator under both potential exposure values. If the value for the exposure *would be* set to *ses*=1 and the mediator would take on the value that would naturally be observed under *ses*=1, i.e., $M_{ses=1}$, the counterfactual outcome would be denoted as $Y_{ses=1\ M_{ses=1}}$. Similarly, if the exposure would be set to *ses*=0 the counterfactual outcome would be $Y_{ses=0\ M_{ses=0}}$. These so-called *nested counterfactual outcomes* are used to define the total and mediated effects.

Total and mediated effects

The counterfactual mediation approach outlines a Natural Direct Effect (NDE) and Natural Indirect Effect (NIE) that add up to the Total Effect (TE).[29] These effects are defined in table 1. As mentioned earlier, there are two counterfactual scenarios in our example: (i) setting the neighbourhood SES value to disadvantaged SES (*ses*=1); and (ii) setting the neighbourhood SES value to non-disadvantaged SES (*ses*=0). The TE is the difference in outcomes of changing the exposure value from *ses*=1 to *ses*=0 (from disadvantaged to non-disadvantaged), defined as $\boldsymbol{E}[Y_{ses=0\ M_{ses=0}} - Y_{ses=1\ M_{ses=1}}]$.[10] We refer to this change as a hypothetical intervention on the exposure where neighbourhood SES was improved.

The NIE, i.e., the effect that operates through the mediator (social environment), is interpreted as the effect of changing the mediator value from $M_{ses=0}$ to $M_{ses=1}$, while holding the exposure value constant to *ses*=1, i.e., $\boldsymbol{E}[Y_{ses=1\ M_{ses=0}} - Y_{ses=1\ M_{ses=1}}]$. The NDE is the effect from changing the exposure from *ses*=0 to *ses*=1 and in both cases letting the value of the mediator be at their potential level as in $M_{ses=0}$, i.e.,$\boldsymbol{E}[Y_{ses=0\ M_{ses=0}} - Y_{ses=1\ M_{ses=0}}$. As seen above, the nested counterfactual $Y_{ses=1\ M_{ses=0}}$ is introduced to be able to define the mediation effects. Using this counterfactual we can interpret the NIE as the observed effect of changing the mediator as if one had changed the exposure but without actually changing the exposure itself. Likewise, the NDE effect is the effect of changing the exposure, but keeping the mediator fixed at whatever level it would be, had the exposure not been changed.[14]

Table 1. Effect definitions used in causal mediation analysis.

Effect	Definition
Total Effect (TE)	$\boldsymbol{E}[Y_{ses=0} - Y_{ses=1}]$ $[Y_{ses=0\ M_{ses=0}} - Y_{ses=1\ M_{ses=1}}]$
Natural Indirect Effect (NIE)	$\boldsymbol{E}[Y_{ses=1\ M_{ses=0}} - Y_{ses=1\ M_{ses=1}}]$
Natural Direct Effect (NDE)	$\boldsymbol{E}[Y_{ses=0\ M_{ses=0}} - Y_{ses=1\ M_{ses=0}}]$

Where *Y* refers to the outcomes and *ses* to the "set" values of the exposure, neighbourhood SES, where *ses*=1 refers to the disadvantaged counterfactual scenario whereas *ses*=0 denotes the non-disadvantaged scenario. *M* refers to the mediator, i.e., social environment. Given that the effect definitions used for the g-formula refer to differences in outcome means, the formulas shown above are in the difference scale.

Causal diagram and identification assumptions

To give the total and mediation effects a causal interpretation we must make certain identification assumptions: consistency, positivity, and exchangeability.[29] These identification assumptions, described in Table 2, are not exclusive of the counterfactual framework (or the g-formula), but this framework made them explicit.

The causal diagram in Figure 1 represents the hypothesized relationships between exposure, mediator, outcome and confounding variables. In our example, the models account for exposure-outcome confounders, i.e., individual-level characteristics (maternal age, parity, ethnicity, household income and education), and area-level average home value. Additionally, the models accounted for area-level percentage of non-western migrants, an exposure-mediator confounder (which influence SES and social environment), but also a mediator-outcome confounder as it is related to perinatal outcomes.[30] More information on the confounders included in the model is available in supporting information file 2. A sensitivity analysis was conducted assessing the impact of women moving to another neighbourhood during (or shortly prior) their pregnancy (supporting information file 2).

In recent years, researchers have proposed the use of single world intervention graphs (SWIGs) as a unification of causal diagrams and the counterfactual approach.[31] In these graphs single worlds are represented, e.g., a world where *ses*=0 separate to the world where *ses*=1, are fully represented. If our main question would be related to the estimation of the total effect and not the decomposition of it, SWIGs could be used in straightforward manner. However, to address our mediation research question, the effects defined in Table 1 have cross-world references making the use of SWIGs not feasible. We refer the interested reader to the work of Richardson and colleagues for more guidance on the use of SWIGs.[31]

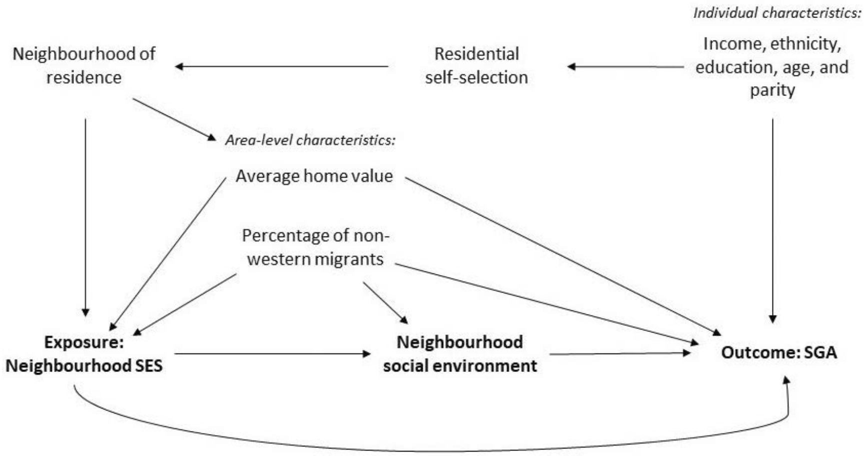

Figure 1. Conceptual Directed acyclic graph for the relationship between the exposure (neighbourhood SES) and the outcome (small for gestational age) via a mediator variable (neighbourhood social environment).

Table 2. Causal identification assumptions.

Consistency This condition connects the counterfactuals with observed outcomes by assuming that the nested counterfactuals will take the observed values when the treatment and mediator are actively set to the values they would naturally have had in the absence of an intervention.[14] To meet the consistency assumption the exposure and mediator must be well defined and there must not be multiple versions of either of them.
Positivity It assumes that for every combination of covariates the probability of observing any of the exposure values is nonzero. Furthermore, it assumes that for every combination of covariates and exposure values the probability of observing any of the mediator values is also nonzero.[14]
Exchangeability It assumes that one could exchange groups without changing the outcome of the study. Groups would not be exchangeable in settings where there is selection bias and/or confounding. Selection on certain characteristics, e.g., selection on live births, can lead to bias due to conditioning on a collider, which opens a non-causal path between exposure and outcome.[32] When selection on these characteristics is unavoidable, this bias can be reduced by adjusting for common causes of the collider variable and the outcome.[33] In our illustrative example, our dataset contains live births only. The underlying models were adjusted for known common causes of stillbirths and SGA, i.e., maternal age, parity, education, and income. In a sensitivity analysis, we also included maternal lifestyle factors and pre-existent conditions (see supporting information file 2).

Table 2. Causal identification assumptions. (continued)

Confounders are defined as covariates that are expected to be common causes of e.g., the exposure and the outcome. Thus, to interpret the total effect as causal, we assume no uncontrolled confounding for the exposure–outcome relationship. Additionally, in mediation analysis, to identify the direct and indirect effects it is also necessary to account for confounding for the exposure–mediator and mediator–outcome relationships, including mediator-outcome confounding affected by the exposure (see supporting information file 2).[34]

The g-formula procedure

The total and mediated effects (Table 1) were estimated following the g-formula steps in Table 3 (also addressed elsewhere[12]). In step 1 the observed data was used to fit suitable regression models (underlying models) for mediator and outcome variables. These models included the individual and area-level confounders described in section 2.2.3. The model for the outcome additionally included the mediator (social environment). These models may also include exposure-mediator interactions if required (we refer to other work for guidance [35]). Parametric models, i.e., logistic regression, were used for the outcome and mediator. The odds ratios for the underlying model for the outcome can be found in table S2 (supporting information). The g-formula has the benefit that in big data settings where there is a large number of candidate confounders, it can easily be combined with machine learning algorithms (e.g., the superlearner[36]) to perform variable selection for the underlying models.[37]

4

The model parameters from the first step are employed to obtain predicted probabilities for mediator and outcome variables. These predicted probabilities are used in step 2 for the Monte Carlo (MC) simulation where a dataset that resembles the observed data, natural course (NC), was simulated by keeping neighbourhood SES at its observed values. The mediator is simulated first and then its values are used in the model for the outcome. Using the same procedure, in step 3, datasets for the two counterfactual scenarios are simulated by fixing the exposure to the corresponding value (*ses*=0 or *ses*=1). Furthermore, in step 4 a mediation scenario, i.e., (Table 1) was simulated to be able to estimate the NIE and NDE.

In step 5, the mean values for mediator and outcome are saved for all simulated scenarios, which represent the proportion of births with a given outcome (or mediator) in each scenario. The simulation process involves (randomly) drawing values from probability distributions and the exact values differ across draws. This variability is known as Monte Carlo error,[38] which can be reduced by repeating the simulation process (and mean values calculation) multiple times, i.e., iteratively (step 6). The number of MC iterations must be enough (30 iterations in our case) to have stable estimates, which can be checked with the R package *cfdecomp*.[39]

In step 7, the mean outcome values saved across MC iterations were used to estimate the TE, NIE, and NDE based on definitions from Table 1. These values are the point estimates of the effects. In step 8, the 95% confidence intervals of the effects are obtained via bootstrapping, i.e., sampling with replacement of the same number of individuals in the dataset. In our example, we sampled clusters (neighbourhoods) instead of individuals to account for a multilevel data structure. Similarly, to the MC iterations, we ran a sufficient number of bootstrap iterations to obtain stable estimates (250 iterations). The computation time of the g-formula depends on the number of observations. In big data settings, as this numbers increases, researchers may consider parallel computing or taking a random subset of the sample to perform the simulation.[12,40]

The g-formula is prone to bias due to misspecification of the underlying models either by misspecifying the functional form (for mediator or outcome models) or by omitting confounders. In step 9, we performed a check against gross model misspecification where we compared the observed means (for the outcome and mediators) and the means under the simulated NC scenario.[24,25] If the means for the NC scenario are not close to observed values, then outcome and/or mediator models are likely misspecified.

Table 3. Parametric mediational g-formula procedure.

G-formula step-by-step procedure
1. Use the original data to fit the underlying models, i.e., suitable parametric models for mediator and outcome, i.e., a logistic regression model if the outcome is a dichotomous variable. These models include the confounders and the model for the outcome also includes the mediator. Exposure-mediator interactions are possible.
2. Use the model parameters from step 1 to predict probabilities for mediator and outcome. The predicted probabilities are used to draw new values from the probability distribution assumed when modelling mediator and outcome (e.g., binomial distribution for dichotomous variables) to simulate a new dataset without intervention, i.e., the natural course scenario (NC). The mediator is simulated first and then its values are used in the model for the outcome.
3. Next, using the dataset from step 1, simulate two datasets under the two counterfactual scenarios (CF). This is done by setting (fixing) the exposure to the corresponding value for each CF (*ses*=0 or *ses*=1) and following the same procedure as in step 2.
4. Additional to the CF scenarios a mediation scenario is simulated where neighbourhood SES is intervened as in *ses*=1 but the mediator values will be derived from the *ses*=0 scenario. This scenario is later used for the estimation of (natural) direct and indirect effects.
5. Save the average values for mediators and outcomes over the simulated scenarios. For dichotomous outcomes, the averages correspond to the proportion of cases with a given outcome (or mediator) in each scenario.

Table 3. Parametric mediational g-formula procedure. (continued)

G-formula step-by-step procedure
6. The simulations and calculation of the average values (steps 2-5) are repeated *J* times, where *J* is a number of iterations sufficient to produce stable estimates. This can be checked by producing stability plots, e.g., with the *cfdecomp* R package (a tutorial available via this link).[39]
7. The average of the *J* (Monte Carlo) iterations is used to obtain the point estimates of the effects. The effects are estimated based on the definitions of Table 1: the total effect (TE) is obtained from the difference between the average values of the two counterfactual scenarios. The mediation scenario is used to obtain the Natural Direct Effect (NDE) and the Natural Indirect Effect (NIE). The NDE is the difference in average values between the CF where *ses*=0 and the mediation scenario. Last, the difference between the average values for the mediation scenario and the CF where *ses*=1 is the NIE.
8. The steps above are repeated *K* times to produce bootstrap confidence intervals for the effects, the estimated effect values are saved for each bootstrap iteration, where *K* is a large enough value (200+) to produce stable estimates (use stability plots). The confidence intervals are obtained as the 2.5th and 97.5th quantiles of the distribution.
9. The comparison between the observed means and the means under the NC (no intervention) scenario is used as a check against gross model misspecification. If the NC predictions are not close to observed values, then models for outcome and/or mediators are likely to be incorrectly specified.

R code available in public repository (link in supporting information file 7)

4

For interpretability, results for the effects are presented in relative terms, i.e., the percentage change in the proportion of births with a given outcome (see supporting information file 3 for further explanation). To assess the extent to which the total effect of the exposure on the outcome operates through the mediator the proportion mediated can be calculated. As pointed out in previous work,[41] when the effects are used on the difference scale (i.e., additive scale; as in Table 1), the proportion mediated simply corresponds to the ratio of the Natural Indirect Effect to the Total Effect, i.e., PM = NIE/TE.

4.3 RESULTS

After the exclusion of non-linked births, multiple births, births with gestational age below 24+0 weeks or above 41+6 weeks, and cases with missing information (<2%), there were 1,217,626 births available for analysis. Due to the small percentage of missing data no data imputation was conducted. Population summary characteristics and a flow diagram can be found in Figure S1 and Table S1 (supporting information). The natural course scenario yielded similar mean values to the ones from the observed dataset, (Table S5, supporting information) meaning that gross model misspecification is unlikely to be an issue.

Table 4 shows the effects estimated using the g-formula. The absolute values for these effects are shown in Table S4. At the population level, a hypothetical improvement in neighbourhood SES from disadvantaged to non-disadvantaged resulted in a 6.3% (95% CI 5.2, 7.5) relative reduction in the proportion of SGA, i.e., the total effect. This effect was decomposed into direct and indirect effects as observed in Table 4. As a measure of the magnitude of the mediation, the proportion mediated was computed as specified in the previous section (please see supporting information file 3 for more information). Thus, the Natural Indirect Effect accounted for 11.4% (95% CI 9.2%, 13.6%) of the Total Effect of neighbourhood SES on SGA.

Table 4. G-formula mediation effects of neighbourhood SES improvement from disadvantaged to an advantaged category on small for gestational age births (percentage reduction).

	Mean (95% confidence interval**)**
Total Effect (TE)	6.3% (5.2, 7.5)
Natural Indirect Effect (NIE)	0.7% (0.6, 0.9)
Natural Direct Effect (NDE)	5.6% (5.1, 6.1)

4.4 DISCUSSION

Principal findings

In this didactic demonstration of the mediational g-formula, we investigated whether neighbourhood social environment mediates the relationship between neighbourhood SES and SGA. The results showed that a hypothetical improvement in neighbourhood SES from disadvantage to non-disadvantaged resulted in a 6.3% reduction in SGA births and that 11.4% of this total effect is mediated by neighbourhood social context.

Strengths of the study

Regarding the analysis performed in the illustrative example, a first strength corresponds to the ability to link several high-quality national-level datasets, leading to information on over 1.2 million births available for analysis. Another strength is related to the analytical approach. The use of the g-formula allowed us to investigate one of the potential pathways driving the exposure-outcome relationship of interest in a setting with a dichotomous outcome, helping to overcome potential non-collapsibility issues.

Limitations of the data

Foremost, our study is based on registry data, which makes it rather difficult to observe all potential confounders. For example, there might be unobserved individual-level characteristics, such as preferences, that influence both exposures to certain neighbourhood environments and perinatal health. Another limitation is that our dataset consisted of live births, which might lead to selection bias by conditioning on a collider. While we have followed a strategy to reduce this bias, this scenario may result in a violation of the exchangeability condition. A separate issue may come from violations of the consistency assumption. On the one hand, the exposure and mediator variables were dichotomised. Although the categories are well-defined, when dichotomising, e.g., the mediator, one value of the mediator measure corresponds to multiple values of the true mediator resulting in a violation of the aforementioned assumption.[42] On the other hand, both, exposure and mediator have the characteristics of compound treatments, as each of them consist of different dimensions, corresponding to potentially different versions of the exposure and mediator, where each version might lead to different outcomes. However, it has been argued that mediation effects can be interpreted even if the consistency assumption does not hold.[42]

Another potential concern is measurement error. It is likely that, e.g., the measure for the mediator is imprecise. Previous work has shown that, in the context of mediation analysis, measurement error can affect the direct and indirect effects resulting in bias towards the null for the indirect effect and bias away from the null for the direct effect.[43] Thus, the proportion mediated might be underestimated.[43] Last, the assessment of mediation involves an aspect of temporality where the exposure should be measured before the mediator, and this in turn is measured before the outcome. These conditions are relevant to prevent reverse causation and over adjustment. The model presented in the DAG reflects theoretical considerations in the study of neighbourhood health effects where the social environment is seen as a pathway for the effect of SES on health.[23] However, we cannot rule out that in this case social environment may also influence SES. To avoid this issue, ideally, one must use a measure of the exposure that temporally precedes the measure of the mediator as done in Burgos Ochoa et al.[44] However, in our real-life example, this was not feasible as only two reporting years for the mediator (2014 and 2017) were available.

The application of the g-formula approach also has shortcomings. The validity of the g-formula estimation is dependent on the validity of the underlying models used to create the simulated data. In the example, we found that observed and natural course means were practically equivalent. However, this check against gross model misspecification cannot fully rule out the presence of milder forms of this issue.[10] Another challenge is that the g-formula is very computational-intensive.[12] While there are solutions available for very large datasets (section 2.2.4), this remains a concern for researchers in settings with computational power constraints.

Interpretation

In this study we observed that the hypothetical improvement in neighbourhood SES led to a 6.3% reduction in the proportion of SGA, which corresponds to a small but meaningful effect, particularly when compared to effect estimates found in previous studies.[24,45] Regarding the proportion mediated, we observed that neighbourhood social environment accounted for 11.4% of the effect of neighbourhood SES on SGA. While this is a meaningful quantity, the results point that that a large share of the effect remains unexplained and there is need for further research on other potential mediators, e.g., crime rates or environmental pollution.

The g-formula, being a flexible approach, can be used in various scenarios in perinatal epidemiology. The g-formula can accommodate all types of outcomes of interest, e.g., continuous outcomes, such as birthweight, or survival outcomes like neonatal mortality. Furthermore, researchers in perinatal epidemiology are interested often in multiple underlying mechanisms, which might interact and even influence each other. The g-formula can handle multiple mediators at once without making the stringent assumption of them not being interrelated, as in other approaches.[46] Last, longitudinal designs are frequently used in this field, and with them comes the challenge of time-varying exposures and confounders, and the issue of adjusting for confounders affected by previous exposure. The g-formula is suitable for these challenging settings.[12] Given the wide variety of potential applications, the g-formula can be considered a promising analytical approach in the field of perinatal health research.

Conclusions

The mediational g-formula is a flexible approach to performing causal mediation analysis that is suited for big data contexts in perinatal epidemiology. This approach overcomes many of the limitations of traditional mediation analysis methods.

ONLINE SUPPLEMENTARY FILES

The supplementary files referred to in this Chapter are available online at https://github.com/LizBurgosOchoa/Mind_the_Gap_SF/blob/main/Supplementary_files_Chapter4.pdf

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Chapter 5

Does neighbourhood crime mediate the relationship between neighbourhood socioeconomic status and birth outcomes? An application of the mediational G-formula.

ABSTRACT

While the link between living in low socioeconomic status (SES) neighbourhoods and a higher risk of adverse birth outcomes has been well established, the underlying mechanisms remain poorly understood. Using the parametric g-formula, we assess the role of neighbourhood crime as potential mediator for the relationship between neighbourhood SES and birth outcomes using data on singleton births occurring in the Netherlands between 2010 and 2017 (N=1,219,470). We estimated total and mediated effects of neighbourhood SES on small-for-gestational-age (SGA), low birthweight (LBW), and preterm birth (PTB) via three types of crime (violent crimes, crimes against property and crimes against public order). The g-formula intervention settings correspond to a hypothetical improvement in neighbourhood SES. The hypothetical improvement in neighbourhood SES resulted in a 6.6% (95% CI=5.6,7.5) reduction in the proportion of SGA, a 9.1% (95% CI=7.6,10.6) reduction in LBW, and a 5.8% (95% CI=5.7,6.2) decrease in PTB. Neighbourhood crime jointly accounted for 28.1% and 8.6% of the total effect on SGA and LBW, respectively. For PTB, we found no evidence of mediation. The most relevant pathways were crimes against property and crimes against public order. The results indicate that neighbourhood crime mediates a meaningful share of the relationship between neighbourhood SES and birth outcomes.

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5.1 INTRODUCTION

Previous studies have consistently found a link between living in low socioeconomic status (SES) neighbourhoods and a higher risk of adverse birth outcomes, even after controlling for individual-level SES factors. [1–3] Furthermore, in a previous study we observed that changes in neighbourhood SES may lead to changes in the risk of adverse health outcomes. [4] These health inequalities observed at birth between inhabitants of more and less affluent areas might even prevail throughout the entire life course. Adverse birth outcomes, i.e., small-for-gestational-age (SGA), low birthweight (LBW), and preterm birth (PTB) have been found to increase the risk for subsequent lifelong morbidity. [5,6] To design interventions to reduce socio-spatial health inequalities, it is necessary to understand the mechanisms by which neighbourhood SES may influence health at birth. However, to date, the study of potential mechanisms remains neglected in the literature.

A reason why low SES neighbourhoods may be detrimental to health is that they expose their residents to disadvantaged conditions, such as higher crime rates. [7,8] A strong link has been found between neighbourhood socioeconomic makeup and local crime rates; neighbourhoods with concentrated disadvantage (e.g., high unemployment rate and low income) tend to have higher crime rates compared to advantaged areas. [9,10] At the same time, various studies have found that women living in neighbourhoods with high crime rates are more likely to experience adverse birth outcomes. [11–13] Area-level crime might influence health either by triggering a chronic stress response in unsafe areas or by promoting avoidance behaviour that affects engagement in physical and social activities. [14]

There is some evidence that neighbourhood violent crime may mediate the association between neighbourhood SES and low birthweight. [7,15] However, this prior evidence is limited by their analytical approach where the change in coefficients (particularly the significance of the estimate) is taken as evidence of mediation. As previously pointed out in the literature, such approach has severe shortcomings and can result in biased conclusions for models with a binary outcome due to non-collapsibility. [16] Furthermore, it relies on overly restrictive assumptions that do not allow for exposure-mediator interactions.[17] Given these limitations, health inequalities researchers have called for the use of more flexible methods, such as the g-formula.[18] Moreover, both previous studies, conducted in Chicago (USA), had relatively limited sample sizes and their findings may not apply to the European context due to demographic, social, economic, and health care differences.

In this nationwide study we applied the parametric mediational g-formula to investigate whether neighbourhood crime mediates the relationship between neighbourhood SES and birth outcomes in the Netherlands. Using data from the Netherlands Perinatal Registry linked to individual-level sociodemographic data and neighbourhood-level data, we estimate the share of the total effect of neighbourhood SES on birth outcomes explained by neighbourhood crime. To our knowledge, this is the first study to evaluate at a national population level the role of neighbourhood crime as underlying mechanism for the relationship between neighbourhood SES and birth outcomes.

5.2 METHODS

Approach

We used the parametric mediational g-formula to evaluate the impact of a hypothetical improvement in neighbourhood SES on birth outcomes and the role of neighbourhood crime as underlying mechanism. The g-formula is a technique embedded in the counterfactual causal inference framework,[19] which uses standardisation to overcome non-collapsibility problems that arise when comparing nested non-linear models.[20] The g-formula has gained popularity as a flexible approach for mediation analysis to answer mechanistic questions about either contextual or individual level causes.[21] The flexibility of this method comes with the trade-off of being more computationally extensive than other methods.

Study design

This study is based on nationwide individual-level birth records linked to routinely collected neighbourhood-level data and population registry data curated by Statistics Netherlands (CBS). The cohort comprises singleton births at gestational ages between 24 completed weeks and 41 weeks and 6 days in the Netherlands between 1 January 2010 and 31 December 2017.

Data sources

Birth records were obtained from the Netherlands Perinatal Registry (Perined), which provides individual-level information on maternal characteristics and birth outcomes, along the four digit postcode of the mother's place of residency at delivery. The registry covers 97% of all births in the Netherlands.[22] CBS performed individual-level linkage of Perined records to CBS national registries. Due to stillbirths being non-linkable, records available for analysis consisted of live births only. Further details on the linkage procedure are available elsewhere. [4] Information on ethnicity, educational level, and household income was extracted from CBS registries.

The Netherlands Institute for Social Research (SCP) Status Scores are a relative measure of neighbourhood SES available for four-digit postcodes areas (average of 4,000 inhabitants).[23] The scores summarise: 1) the average neighbourhood income, 2) percentage of inhabitants with a low income, 3) percentage of inhabitants without a paid job, and 4) percentage of inhabitants with a low education level. For this work we used the scores for the years between 2010 and 2017.

Neighbourhood characteristics were obtained from the postcode-level data collected yearly by CBS, which is calculated by aggregating the information of all residents from each area [24]. Neighbourhood-level yearly crime rates (per 1,000 inhabitants) were sourced from the National Crime Figures dataset by CBS (2010-2017).[25] This dataset holds information on three types of crimes: 1) violent crimes (including sexual crimes), 2) crimes against property, and 3) crimes against public order (including vandalism). Further details are available in Supplementary file 3 Web Appendix.

Data variables and measurement

The outcomes in this study were: 1) small-for-gestational age (SGA), i.e., birth weight below the 10th centile adjusted for gestational age and sex, according to national reference curves [26], 2) low birthweight, i.e., birthweight below 2,500 grams, and 3) preterm birth, i.e., any livebirth occurring from 24 completed weeks of gestational age and before 37 completed weeks.

The SCP Status Scores were used as our measure of the exposure, i.e., neighbourhood SES.[23] The SCP calculates these scores by aggregating yearly information of all neighbourhood inhabitants up to 1 January of the reporting year. For example, the scores of reporting year 2017 are based on data collected by Statistics Netherlands between 2 January 2016 and 1 January 2017, i.e., the preceding year. In the models, we used categories of the Status Scores corresponding to quintiles (going from lowest to highest). The corresponding measure was assigned to each birth record based on residential postcode and birth year, e.g., measures for reporting year 2017 were assigned to births occurred in 2017.

The mediator variables corresponded to neighbourhood crime rates per 1000 inhabitants for the following three types of crime: violent crimes, crimes against property, and crimes against public order.[25] The crime rates are calculated using the number of crimes occurred during each reporting year, e.g., the rates for reporting year 2017 include the crimes occurred between 1 January to 31 December of 2017. In a similar manner to neighbourhood SES, we created categories (quintiles) for each type of crime and these were assigned to the birth records based on postcode and year of birth.

The assessment of mediation involves an aspect of temporality where the exposure should be measured before the mediator, and this in turn is measured before the outcome. Issues like reverse causation and overadjustment may arise if these conditions are not satisfied. If we define the year of birth as our main time point (t), neighbourhood SES is measured at t-1, since for each reporting year the measure is based on data collected the preceding year. Thus, for all reporting years, the measure of the exposure precedes both neighbourhood crime and birth outcomes. Neighbourhood crime is measured at t, i.e., same as year of birth. While the situation is not ideal, we argue that for the mediator-outcome relationship the direction of the effect is clear (exposure to high neighbourhood crime rates would lead to adverse birth outcomes, not the other way around), ruling out potential reverse causation or overadjustment concerns.

5

The underlying models used in the g-formula were adjusted for factors that confound the exposure-outcome relationship, i.e., covariates that are expected to be common precursors of the exposure and the outcome (Figure 1).[27] Additionally, the decomposition of the total effect into direct and indirect effects assumes no unmeasured (and uncontrolled) confounding in the mediator-outcome and exposure-mediator relationships (apart from consistency and positivity assumptions).[21] At the individual level, the models included maternal age in categories (≤19, 20-34, ≥35 years), parity (nulliparous vs multiparous), maternal ethnicity as registered in CBS (Dutch, Turkish, Moroccan, Surinamese, Antillean, others western, other non-western),[28] maternal educational level in categories as defined by CBS (low, medium, high, unknown),[29] and equivalised disposable household income (quintiles). Household income is often preferred over individual-level income in inequalities research as it might be a more useful indicator of SES, particularly for women, who may not be the main earners in the household.[30] At the neighbourhood level, the following variables were included (quintiles): residential address density per km^2 (as a measure of urbanization degree), neighbourhood average home value, and percentage of non-western migrants. We also considered other potential confounding variables, which after further inspection were not included in the final underlying models (Supplementary file 2 Web Appendix). Year of birth (dummies) was also included in the models to account for any potential cohort effects.

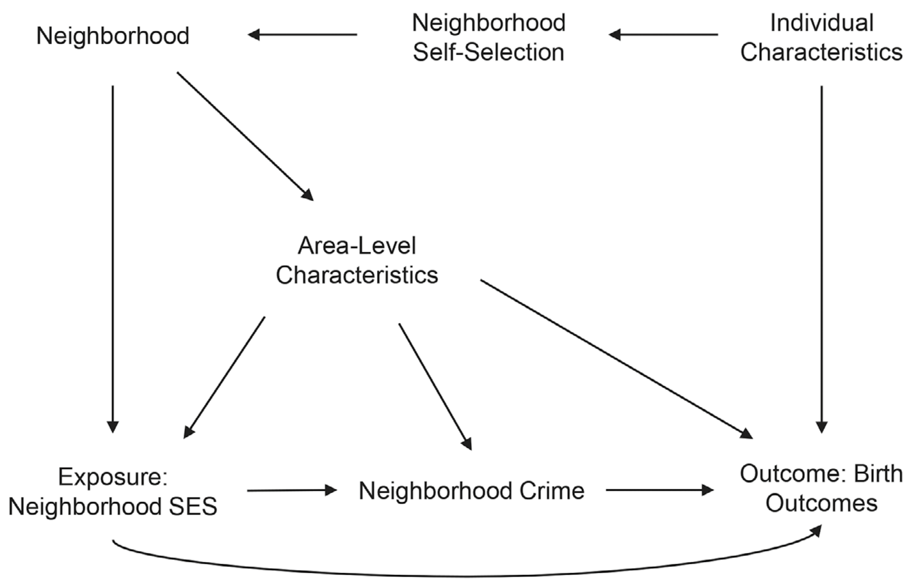

Figure 1. Directed Acyclic Graph (DAG) of the hypothesized between neighbourhood SES and birth outcomes, mediated by neighbourhood crime.

Missing data

The SCP does not calculate scores for areas with less than 100 households due to privacy concerns. Therefore, neighbourhood SES could not be assigned to births from mothers living in these areas. Values for neighbourhood level variables could also not be assigned to birth records without a postcode available. As a result, neighbourhood-level data was missing for 1.5% of the records. Data on at least one individual level characteristic was not available for 1.2% of the cases. Due to this small amount of missing data (2.7%), no data was imputed for the statistical analysis.

Statistical analysis

The counterfactual framework defines effects as the difference between two counterfactual outcomes.[31] A counterfactual outcome refers to the outcome value that would be observed when exposed to a certain exposure value (a hypothetical scenario).[31] Following previous literature,[32,33] we used hypothetical scenarios corresponding to the most and least disadvantaged neighbourhood SES categories, i.e., 1) setting the exposure values for all mothers to the lowest SES category, and 2) setting the exposure values for all mothers to the highest SES category. Thus, the total effect of the exposure (TE) is interpreted as the effect of changing the exposure value from the most to the least disadvantaged (table 1). In the remaining of the manuscript we will refer to this change as a hypothetical intervention where neighbourhood SES is improved from the lowest to the highest category.

The g-formula approach facilitates the simultaneous inclusion of multiple mediators in the models, i.e., three types of crime. The procedure allows for the estimation of mediation effects via all mediators jointly and then via each mediator individually to determine the most important pathways (see table 1). Figure 1 represents the hypothesized relationship between neighbourhood SES and birth outcomes, mediated by neighbourhood crime.

The mediation effects defined in table 1 were estimated following the g-formula steps described in Supplementary file 1 Web Appendix, which have also been extensively addressed elsewhere [32,34]. Two steps are of special interest: an estimation step and a simulation step. In the estimation step, we fitted suitable models for mediators and outcomes (underlying models), which included all measured confounders. The models for the outcomes additionally included all the mediator variables and interaction terms between exposure and mediators. The three outcomes were modelled using logistic regression.

Then, following the steps in Supplementary file 1 Web Appendix, we simulated a natural course scenario (no intervention scenario) and the two hypothetical scenarios described above. The simulation step requires drawing values of the mediators and outcomes from suitable probability distributions and the exact values assigned to individuals can change across multiple draws. This between-draws variability is known as Monte Carlo error.[35] To reduce this error, the simulations (and calculations of average values) are repeated multiple times, each time drawing a new set of mediator and outcome values.[36] The number of times (iterations) needed is based on the stability of the outcome and mediator averages, which can be checked by plotting the cumulative averages as shown in the Supplementary file 7 Web Appendix. Based on this information, 30 MC iterations were considered sufficient to produce stable estimates. For each mediator and outcome, the mean values over the simulated scenarios were saved. The mean values represent the proportion of births with a given outcome (or mediator) in each scenario. The average of the Monte Carlo iterations was then used as the estimate in effect calculations. The comparison between the observed means (for the outcome and mediators) and the means under the natural course scenario was used as a check against gross model misspecification.[32]

To determine the indirect effect of the hypothetical intervention via each individual mediating pathway, we simulated additional scenarios (table 1) following steps described in the Supplementary file 1 Web Appendix.[21] While the mediation effects are not additive due to the nonlinear nature of the models, the procedure gives insight into the specific pathways through which neighbourhood SES is related to birth outcomes.[34]

As a sensitivity analysis, we assessed the impact of women moving to another neighbourhood during (or shortly prior) their pregnancy, by restricting the underlying models used in the g-formula to women who have been living in the same residential address for at least two years at the time of delivery.

For interpretability, we report the mediation parameters in relative terms, i.e., percentage change in the proportion of births with a given outcome. Absolute values for the mediation parameters are available in Supplementary file 4 Web Appendix. The 95% confidence intervals for the mediation parameters were obtained from 250 clustered bootstrapped iterations of the g-formula. This method accounts for clustering of individuals within neighborhoods.[37] The cumulative averages of the outcomes and mediators were plotted to assess the bootstrap and Monte Carlo stability of the estimates. All the analysis were conducted in R version 4.0.5. [38] The R package *cfdecomp* was used to perform the clustered bootstrap and to produce Monte Carlo and bootstrap stability plots.[39]

Table 1. Definitions used in the mediation analysis.

Mediation effect parameter	Abbreviation	Definition[a]
Total Effect	TE	$E\left(Y_{\chi} - Y_{\chi*}\right)$ $E\left(Y_{\chi* V_{\chi} P_{\chi} O_{\chi}} - Y_{\chi* V_{\chi*} P_{\chi*} O_{\chi*}}\right)$
Natural Indirect Effect (all mediators)	NIE	$E\left(Y_{\chi* V_{\chi} P_{\chi} O_{\chi}} - Y_{\chi* V_{\chi*} P_{\chi*} O_{\chi*}}\right)$
Total Direct Effect	TDE	$E\left(Y_{\chi V_{\chi} P_{\chi} O_{\chi}} - Y_{\chi* V_{\chi} P_{\chi} O_{\chi}}\right)$
Indirect neighbourhood SES effect via violent crime	IE violent crime	$E\left(Y_{\chi* V_{\chi} P_{\chi*} O_{\chi*}} - Y_{\chi* V_{\chi*} P_{\chi*} O_{\chi*}}\right)$
Indirect neighbourhood SES effect via crime against property	IE crime against property	$E\left(Y_{\chi* V_{\chi*} P_{\chi} O_{\chi*}} - Y_{\chi* V_{\chi*} P_{\chi*} O_{\chi*}}\right)$
Indirect neighbourhood SES effect via crime against public order	IE crime against public order	$E\left(Y_{\chi* V_{\chi*} P_{\chi*} O_{\chi}} - Y_{\chi* V_{\chi*} P_{\chi*} O_{\chi*}}\right)$

[a] Where *Y* refers to the outcomes and χ to the exposure. Here χ * represent the lowest SES counterfactual scenario whereas represent the highest SES scenario. *V* refers violent crimes, *P* to crimes against property and *O* to crimes against public order.

Table 2. Demographic characteristics and birth outcomes in the Netherlands (2010-2017) by neighbourhood SES (lowest vs highest categories).

	Total [a]	Lowest neighbourhood SES category	Highest neighbourhood SES category
INDIVIDUAL CHARACTERISTICS			
Maternal age, mean (SD)	30.6 (4.8)	30.0 (5.1)	31.4 (4.6)
Primiparous, N(%)	546,765 (44)	155,405 (46)	102,114 (42)
Ethnic background			
Moroccan	30,773 (2.5)	18,918 (6.5)	2,902 (1.2)
Turkish	20,900 (1.7)	13,493 (4.6)	1,760 (0.7)
Suriname	11,575 (0.9)	6,390 (2.2)	2,000 (0.8)
Antillean	9,553 (0.8)	5,516 (1.9)	1,046 (0.4)
Other non-western	76,480 (6.3)	31,835 (10.3)	12,681 (5.4)
Other western	73,975 (6.1)	24,728 (7.6)	14,630 (6.2)
Dutch	996,214 (80.1)	225,262 (67.0)	202,581 (85.2)
Educational level			
Low, N(%)	106,213 (8.7)	49,880 (14.8)	10,693 (4.5)
Medium, N(%)	498,116 (40.8)	143,174 (42.6)	82,287 (34.6)
High, N(%)	457,102 (37.5)	104,117 (31.0)	113,193 (47.6)

Table 2. Demographic characteristics and birth outcomes in the Netherlands (2010-2017) by neighbourhood SES (lowest vs highest categories). (continued)

	Total [a]	Lowest neighbourhood SES category	Highest neighbourhood SES category
Unknown, N(%)	158,039 (12.9)	39,042 (11.6)	31,427 (13.2)
Yearly equivalised disposable household income €, median (IQR)	26,255 (15,739)	22,193 (15,693)	29,910 (15,979)
Outcomes			
Low birthweight, N(%)	54,038 (4.4)	17,690 (5.2)	9,022 (3.8)
Preterm birth, N(%)	66,783 (5.4)	19,788 (5.9)	12,195 (5.1)
Small-for-gestational-age, N(%)	131,493 (10.8)	43,310 (12.9)	22,830 (9.6)
AREA-LEVEL CHARACTERISTICS			
Residential address density per km^2, mean (SD)	1,777 (1,555)	2,408 (2,312)	1,281 (1,263)
Percentage of non-western migrants, mean (SD)	13.7 (15.0)	27.80 (19.9)	9.03 (7.2)
Average home value (in 1000 €), mean (SD)	242 (83)	179 (52)	296 (96)
Violent crime[b], mean (SD)	9.4 (12.6)	15.1 (15.5)	6.7 (11.9)
Crime against property[b], mean (SD)	60.2 (86.7)	87.26 (95.0)	51.5 (98.7)
Crimes against public order[b], mean (SD)	12.8 (13.8)	17.3 (16.3)	10.9 (13.7)

[a] Total births available for analysis: 1,219,470. Births in the lowest neighbourhood SES category N= 336,213. Births in the highest neighbourhood SES category N=237,600.
[b] Neighbourhood yearly crime rates per 1,000 inhabitants

5.3 RESULTS

Between 2010 and 2017 there were 1,334,272 linked registered births in the Netherlands. After excluding multiple births, births with gestational age below 24+0 weeks or above 41+6 weeks, and cases with missing information, there were 1,219,470 births available for the analysis (Figure 2). Supplementary figures 2 to 6 (Web Appendix) illustrate the geographic distribution of area-level SES, crime rates, and adverse birth outcomes in the Netherlands. It is observed that lower SES, higher crime rates and higher prevalence of adverse outcomes are concentrated in the largest cities.

Table 2 presents individual-level demographic and health characteristics along with area-level attributes by neighbourhood SES (lowest vs highest category). Compared to the highest SES category, the prevalence of the three outcomes was higher in the lowest category. Moreover, the crime rates for the three types of crime were higher for the lowest SES category than for the highest category. The results for the models including all mediators and confounders, showed higher odds of SGA (OR[95%CI]= 1.06[1.04,1.08]), LBW (OR[CI]= 1.10[1.06,1.14]), and PTB (OR[CI]= 1.07[1.04,1.10]) for women in the lowest neighbourhood SES category, compared to women from the most advantaged areas (Supplementary file 2 Web Appendix). The strongest associations between mediators and outcomes were observed for the highest quintile of each type of crime.

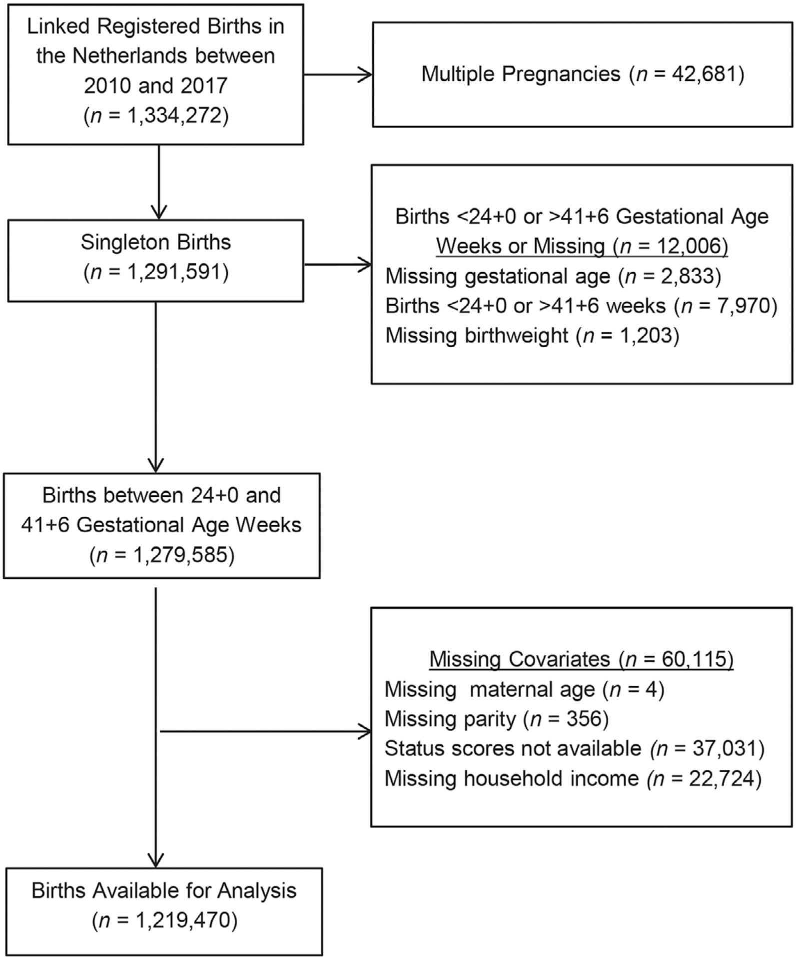

Figure 2. Population flow diagram.

Simulated outcome and mediator mean values under the natural course scenario were comparable to the observed outcome and mediator values, which is an indication that gross model misspecification is unlikely to be present in our models (Supplementary file 5 Web Appendix).

Table 3 presents the mediation effect estimates obtained from the g-formula. The TE of neighbourhood SES on birth outcomes represents the combined effect of all direct and indirect pathways. At population level, we found that a hypothetical improvement in neighbourhood SES from the lowest to the highest category would be associated with a 6.6% (95%CI= 5.6,7.5) decrease in the proportion of SGA births, a 9.1% (CI= 7.6, 10.6) reduction in births with LBW, and a 5.8% (CI= 5.7, 6.2) reduction in PTB. Absolute effect values available in Supplementary file 4 Web Appendix.

The TE was further decomposed into the TDE and NIE. The NIE accounted for 28.1% (95%CI= 24.1, 32.4) of the TE of neighbourhood SES on SGA, and for 8.6% (CI= 5.4, 11.5) of the TE on LBW. For preterm birth we found no evidence of mediation by neighbourhood crime (1.6% [-2.8, 9.0]) (Supplementary file 6 Web Appendix). When looking at the intervention effect via each of the mediators individually, it was observed that crime against property and crime against public order were the most relevant pathways (Supplementary file 6 Web Appendix).

The estimates from the underlying models used in the g-formula remained unchanged when restricting the underlying models to women who have been living in the same residential address for at least two years at the time of delivery (Supplementary file 2 Web Appendix).

Table 3. G-formula mediation effects of neighbourhood SES improvement from lowest to highest category on birth outcomes (percentage reduction).

	Total Effect (95% CI)	**Total Direct Effect (95% CI)**	**Natural Indirect Effect (95% CI)**
Small-for-gestational-age	6.6 (5.6, 7.5)	4.8 (4.0, 5.4)	1.8 (1.60, 2.1)
Preterm birth	5.8 (5.7, 6.2)	5.7 (5.2, 6.1)	0.1 (-0.2, 0.4)
Low birthweight	9.1 (7.6, 10.6)	8.3 (7.1, 9.6)	0.8 (0.5, 0.9)

5.4 DISCUSSION

In this nationwide population-based study we found that neighbourhood crime mediates the relationship between neighbourhood SES and key adverse birth outcomes in the Netherlands. Neighbourhood crime accounted for 28.1% of the total effect of neighbourhood SES on small-for-gestational-age (SGA), and 8.6% of the effect for low birthweight (LBW). However, no evidence of mediation was found for preterm birth (PTB). To our knowledge, this is the first study to examine at national level the role of neighbourhood crime as potential underlying mechanism for the relationship between neighbourhood SES and birth outcomes.

This study adds to the literature by using the parametric mediational g-formula approach to decompose the total effect of neighbourhood SES on birth outcomes into direct and indirect effects via neighbourhood crime. We found that a moderate part of the total effect of neighbourhood SES on birth outcomes was accounted by the mediators. Regarding the magnitude of the mediation, a direct comparison between our findings and previous literature is unfortunately not feasible as none of the two prior studies carried out the decomposition to be able to calculate, e.g., percentage mediated. However, the overall finding that neighbourhood crime mediated the relationship between neighbourhood socioeconomic disadvantage and low birthweight is consistent with what was previously observed [7,15]. Our work progresses from previous literature by including simultaneously three types of crime as mediators in the models to determine the most relevant pathways. The finding that crimes against property and public order (including vandalism) were the most important pathways, suggests that more visible and frequent types of crime might be the most relevant for birth outcomes. Research has found that vandalism and crime against property show stronger associations with health outcomes, in comparison to certain types of violent crime.[11,40] This could be explained in part by these types of crime occurring in a more day-to-day basis than violent crime [41]. Moreover, prior studies in Dutch population observed that particularly for women, objective measures of crimes against property translate into stronger unsafety feelings.[42]

Similar to the results from Masi and colleagues,[15] we observed that neighbourhood crime mediated the association between neighbourhood SES and SGA (along LBW) but this was not the case for PTB. The literature outlines two main pathways through which neighbourhood crime may influence birth outcomes. One way is by neighbourhood crime being an ecological stressor which leads to an activated stress response that translates into higher levels of cortisol.[11] A second explanation might be that unsafe areas may pressure women into adopting avoidance behaviours that affect their engagement in physical (and social) activities. [43,44] Both, PTB and SGA have been associated to maternal stress and health behaviours, however, previous literature argues that PTB is closely linked to maternal stress, and SGA is primarily influenced by health behaviours.[45,46] It could then be hypothesized that crime might be mainly influencing health at birth via avoidance behaviours. Nevertheless, these hypotheses would need to be further investigated.

A main strength of this study is its focus on disentangling one of the mechanisms by which neighbourhood SES may influence health at birth. Furthermore, the application of the g-formula allowed us to overcome potential non-collapsibility issues with non-linear outcomes. Additionally, it facilitated the simultaneously inclusion of multiple mediators (three types of crime), which provided more precise information about the most relevant pathways. The use of high-quality national-level routinely collected data corresponding to an extended period (2010-2017) led to over 1.2 million individual records being available for analysis which resulted in estimates that are applicable to a nationwide context instead

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of single-cities only. Given that similar conclusions to ours have been drawn in studies conducted in the USA,[7,15] it is plausible that our findings are also applicable to contexts outside of the Netherlands, particularly to other European countries with similar social and economic conditions. However, more nationwide studies are essential to confirm our main results and to build evidence regarding the magnitude of the mediation. Our findings could be valuable when designing neighbourhood-level targeted interventions. Particularly, programs targeted at reducing vandalism and crimes against property might be a promising approach to improve birth outcomes and reducing early-life health inequalities. A limitation of this study is that some births (including stillbirths) could not be linked. However, the impact is likely small as only 3% of the cases could not be linked. Related to the previous point, collider bias can arise due to selection on live-births.[47] A conventional strategy to reduce some of this bias is to adjust the model for common causes of the outcome that also influence fetal death. The underlying model used for the g-formula adjusts for known common causes of stillbirths and SGA, PTB, and LBW, i.e., maternal age, primiparity, education, and income.[48] Moreover, in sensitivity analyses, models accounted for additional potential confounders, which are known common causes of stillbirths and other birth outcomes (diabetes, hypertension, smoking, alcohol and drug use), leading to similar results.

The validity of the g-formula estimation is dependent on the validity of the underlying models used to create the simulated data. The misspecification of this models, either by omitted confounders or mis-specification of functional form would lead to bias.[21] Reassuringly, the check against gross model misspecification did not show signs of this being the case. The underlying models accounted for relevant individual and area-level characteristics, which have been found to be the most important confounders in neighbourhood-level research and drivers of neighbourhood self-selection.[49] Moreover, we explored the relevance of various other potential confounders, including potential mediator-outcome confounders that are exposure-dependent. However, our study is based on registry data which did not allow us to observe and control for all possible confounders. For example, there could be unobserved mothers' beliefs or preferences that might not only influence the exposure to certain neighbourhoods environments but also birth outcomes. At the neighbourhood level, unobserved physical neighbourhood characteristics (that could be exposure-dependent), like walkability, might influence crime rates and birth outcomes. These scenarios would bias our results upwards. Thus causal interpretation of our results needs to be done with caution.

Future research might consider using individual-level measures of perceived neighbourhood safety. These measures, which were unfortunately not available, have been found to have a stronger link to health outcomes than objective measures.[50] More research is still needed to shed light into other potential pathways through which neighbourhood may affect birth outcomes, e.g., social capital, disorder, air pollution, walkability, etc. Due to the previously described advantages of the g-formula, we encourage the application of this approach on further research attempting to disentangle the mechanisms through which neighbourhood SES may impact birth outcomes.

In conclusion, our results indicate that neighbourhood crime mediates a meaningful share of the association between neighbourhood SES and adverse birth outcomes in the Netherlands. Crimes against property and crimes against public order were the most relevant pathways.

ONLINE SUPPLEMENTARY FILES

The supplementary files referred to in this Chapter are available online at https://github.com/LizBurgosOchoa/Mind_the_Gap_SF/blob/main/Supplementary_files_Chapter5.pdf

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Part 3:

Socioeconomic conditions as modifiers for the impact of external factors.


HOŞGELDINIZ

Chapter 6

The impact of extreme temperatures on birth outcomes in the Netherlands: a nationwide population-based study

ABSTRACT

Introduction

Climate projections predict an increased frequency and intensity of extreme weather events, such as extreme temperatures, prompting concerns about their impact on early-life health and health disparities. This study aimed to investigate the causal impact of in-utero exposure to extreme temperatures on birth outcomes and effect heterogeneity across levels of socioeconomic status (SES).

Methods

We obtained data on singleton births that occurred between 2003 and 2017 from the Dutch perinatal registry (N=2 472 352). Exposure was calculated as the number of days during the gestational period in which the mean temperature fell into each of mutually exclusive bins, with the 8-12 °C bin used as reference. To identify a causal effect, we exploited the unpredictability of daily temperature fluctuations while accounting for seasonal and underlying trends. Effect heterogeneity was assessed across levels of household income, neighbourhood SES, and maternal education.

Results

In-utero exposure to an additional hot day (mean temperature > 20 °C), relative to the reference range, led to increased odds of low birth weight (LBW) (OR[95%CI]= 1.007 [1.005, 1.009]), small for gestational age (SGA) (OR[95%CI]= 1.004 [1.003, 1.005]), and preterm birth (PTB) (OR[95%CI]= 1.006 [1.005, 1.007]). Exposure during the second trimester to an additional cold day (< -4 °C) led to increased odds of LBW and PTB. The observed effects were the most detrimental for births in low-SES households.

Conclusions

In-utero exposure to extreme temperature has a detrimental impact on birth outcomes in the Netherlands. Projected increases in extreme temperatures may further exacerbate health disparities in early life.

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6.1 INTRODUCTION

The latest assessment by the United Nations' Intergovernmental Panel for Climate Change highlights that climate change has increased the intensity and frequency of extreme weather events such as extreme temperatures.[1] This increase is likely to be especially burdensome for vulnerable populations with limited capacity to respond or adapt to extreme weather events.[2] The potential adverse health effects of extreme weather events are a major concern in climate change policymaking. Researchers and public health agencies around the world have called for further research on the link between climate change and human health to develop and improve adaptation strategies that support vulnerable groups.[3–5]

Birth outcomes, such as low birthweight (LBW), small-for-gestational-age (SGA), and preterm birth (PTB) have been recognized as key influential factors in a child's life-course development and health.[6] There is a substantial body of literature showing that adverse environmental exposures during the gestational period affect health outcomes at birth;[6] but also have long lasting effects on the health, educational and economic outcomes of the affected children.[6,7] From a biological point of view, foetuses are likely affected by extreme temperatures because of the physiological changes that alter mothers' capacity to regulate body temperature.[4,8,9] Furthermore, animal models support the biological plausibility of a detrimental relationship between extreme temperature and health at birth.[10,11]

Most of the available literature looking into the relationship between temperature and birth outcomes consists of association studies. Although inconsistently, these studies provide evidence that exposure to extreme temperatures is associated with a higher risk of adverse birth outcomes.[5,12] However, most studies did not account for critical sources of confounding, (e.g., seasonality, underlying trends or self-selection), which complicates the interpretation of their estimates as causal effects. Furthermore, recent reviews concluded that the large variety in the methodological approaches and the lack of agreement on exposure definitions hinder the comparison between studies and evidence synthesis.[12–14] For example, a major criticism of earlier studies is the reliance on the concept of 'heat waves' which lacks a universal definition.[13,15,16] Recently, a small number of studies, mostly from the field of economics, have been able to establish a causal relationship between extreme temperatures and health at birth.[17–22] These studies used a "binned" approach to modelling the temperature-response function which allows for nonlinear effects of temperature on health outcomes, facilitates the control for sources of confounding, and is suitable for different types of outcomes.[23] This approach has a clear definition of exposure, i.e., the number of days in the gestational period with temperatures falling within prespecified degree ranges (bins).[23] Additionally, it enables to investigate the effects from both ends of the temperature extremes. This is of relevance as the different mechanisms through which extreme cold and heat may affect human health have also been of interest and results from previous studies have been mixed.[24]

Results from these causal studies mainly support the presence of an effect of extreme high temperatures on low birthweight; however, other outcomes have received little attention.[17,18,21,22] LBW can either be due to a preterm delivery, intrauterine growth restriction (operationalized as SGA), or a combination of the two.[25] Since the biological mechanisms through which extreme temperatures influence the risk of SGA or PTB are thought to be very different,[10,26] causal evidence on the impact of extreme temperatures on SGA and PTB is critical to better understand how extreme temperatures affect health at birth. Nevertheless, this evidence is still lacking.[19]

With the frequency of extreme weather events only expected to increase in the coming years, it is of major importance to understand the potential effects of extreme temperatures on birth outcomes and whether these consequences might differ across levels of socioeconomic disadvantage.[27] However, the largest review studies in the field point out that only a handful of studies analysed whether there is socioeconomic heterogeneity in the effect of extreme temperature on birth outcomes, and results for those that did are mixed.[13] SES could moderate the effect of extreme temperature on birth outcomes through detrimental housing conditions and living environments, disadvantaged workplace settings, awareness on risk behaviours during extreme temperatures, and limited access to mitigation strategies like air conditioning.[13]

The objective of this study is to investigate the causal effect of extreme temperatures on key adverse birth outcomes in the Netherlands. Our work expands previous literature by assessing whether any observed impact on LBW could be due to preterm delivery, intrauterine growth restriction, or both. Furthermore, we examine the role of socioeconomic status (SES) as moderator for the effect of extreme temperatures on birth outcomes. Results from this study may inform the development and optimization of existing adaptation strategies and management of pregnant women during and after extreme temperature periods.

6.2 METHODS

This is a national retrospective study based on individual-level birth records linked to routinely collected climatological data and population register data. The study comprises singleton births at gestational ages between 24+0 and 41+6 weeks that occurred in the Netherlands between 1 January 2003 and 31 December 2017.

Data sources

Birth records were obtained from the Netherlands Perinatal Registry (Perined), which includes more than 97% of all deliveries in the Netherlands. Perined provides individual-level information on pregnancy and birth outcomes, along with maternal characteristics, and the four-digit postcode of the mother's place of residence at delivery. Additionally, linkage of Perined to Statistics Netherlands (CBS) records was performed to retrieve maternal and household sociodemographic information. Detailed information about the linkage procedures can be found at the CBS website.[28]

Data on meteorological conditions was obtained from the Royal Netherlands Meteorological Institute (KNMI).[29] Meteorological data is collected by KNMI using several monitors placed across the entire country. The KNMI data informs on daily mean (along maximum and minimum) ambient temperature in °C, total precipitation (in millimetres), wind speed (in meters per second), and sunshine duration (in hours). We matched each birth record to daily weather records during the full gestational period from the nearest monitor to the place of mother's residence (postcode). The average matching distance is 15 km, which is smaller than the one observed in previous studies.[18,19]

Variables

The study outcomes are the following: 1) low birth weight (LBW), i.e., birth weight below 2,500 grams, 2) Small-for-gestational-age (SGA), i.e., birth weight below the 10th centile adjusted for gestational age and sex, according to national reference curves,[30] and 3) preterm birth (PTB), i.e., birth occurring before 37+0 weeks.

To facilitate comparison with previous studies, the exposure was set as the number of days during the gestational period in which the daily mean temperature falls into each of mutually exclusive temperature bins i.e., < -4 °C, -4 - 0 °C, 0 - 4 °C, 4 - 8 °C, 8 - 12 °C, 12 - 16 °C, 16 - 20 °C, and > 20 °C.[18,19,31] Higher temperature bins were considered, i.e., up to > 28 °C. However, the exposure during the gestational period to days with a mean temperature >28 °C was on average only 1.4 days (in comparison to the 19.0 days observed in Chen et al.[19]), often leading to very wide confidence intervals for higher bins. The gestational period was determined using the birth date and gestational age, which was used to calculate the date of conception.[32] Gestational age, obtained from the Perined dataset, is estimated by the healthcare provider using information on the last menstrual cycle and foetal scans to ensure accuracy.[33]

The linkage of Perined with CBS microdata allowed access to a set of sociodemographic variables. Information on equivalized household disposable income during the year of birth (corrected for size and composition of the household)[34] was categorized into low, medium and high where the low and high categories correspond to the lowest and highest quintiles, respectively. Mother's highest educational level is classified by CBS as low, medium, high, or unknown.[35] Moreover, we obtained maternal migration background as defined by CBS based on country of birth, i.e., Dutch, Turkish, Moroccan, Surinamese, Antillean, others western, and others non-western.[36]

Empirical strategy and challenges to causal effect identification

To estimate the effect of ambient temperatures on birth outcomes we used logistic regression models. We used a "binned" approach to model the temperature-response function,[23] where the bin 8-12 °C (which includes the yearly average temperature in the Netherlands), was excluded and used as reference category in all models.

A key challenge in the study of the causal effect of temperature on birth outcomes is that exposure to extreme temperatures is not assigned at random and there are many reasons why temperature could be correlated with outcomes even without a causal effect. Several studies have observed differences in the health of children born in different months of the year due to selection into conception based on parental characteristics and exposure to seasonal factors (e.g., influenza virus).[37,38] Moreover, regional geographic characteristics may also be correlated with both weather and outcomes.[39] Accordingly and following previous literature, the models control for differences in outcomes due to seasonality, regional variation, and time trends by including province × (conception) month fixed effects, a province × linear year-time-trend, and year fixed effects. Moreover, a broad set of climatological control variables was included in the models, i.e., the average precipitation, sunshine duration, and wind speed. The models were not adjusted for mediators such as ambient air pollution since we are interested in the total effect of ambient temperature on birth outcomes.[40,41]

Another common concern in the literature is the non-random sorting (self-selection) of families into hotter and colder regions of the country based on sociodemographic factors and preferences. However, the Netherlands is a small country with a mild maritime climate that has been historically characterized by colder rainy periods, generally moderate summers; and excessively hot weather is rare. Due to its topographic characteristics (mostly flat landscape), temperature values are rather uniform within the country. On average, the differences in temperature across provinces are up to 1°C.[42] Given the relatively small differences in climate, it is reasonable to think that non-random sorting of pregnant women into hotter and colder regions within the country might be less of a concern in the Netherlands. Therefore, due to the unpredictability of temperature fluctuations, it is sensible to assume that our exposure should be uncorrelated to maternal characteristics (and unobserved confounders) after accounting for seasonality and underlying trends. We later test this assumption in sensitivity analyses.

Previous research has warned of the mechanical correlation between length of gestation and the probability of having been exposed to environmental factors. This correlation has been observed to lead to spurious associations as children with longer gestations have a longer time in which they could be exposed.[32] To overcome this issue, we followed the approach by Currie and colleagues,[32] where the exposure (number of days in the gestational period falling into one of the pre-specified bins) is constructed using a hypothetical gestational period (counting 280 days forward from the day of conception) instead of the actual length of gestation. This approach, is now standard in the literature looking at the impact of environmental in-utero exposures.[43] To minimise survivor bias, a set of covariates correlated to the outcome and early foetal loss was included in the models,[44] i.e., maternal age in categories (≤19, 20-34, ≥35 years), parity (nulliparous vs multiparous), foetal sex, (equivalized) disposable household income, mother's educational level, and maternal migration background.

To investigate whether SES moderates the adverse consequences of extreme temperatures on birth outcomes, additional analyses were conducted including interaction terms between the temperature bins and SES indicators. The main SES indicator was defined as equivalized disposable household income in categories (low, medium, high). Additional analyses were run for mother's education and neighbourhood SES. We used SCP Status Scores to assess neighbourhood SES.[45] These scores combine yearly data on income, employment, and education for four-digit postcodes. SES categories were established using quintiles from the Status Scores: lowest and highest for low and high SES, and the middle for medium SES.

To evaluate the existence of critical windows of susceptibility during pregnancy to extreme temperatures we additionally conducted analyses exploring trimester-specific exposures, i.e., the number of days per trimester for which the temperature falls into a certain bin. Using the calculated date of conception, weeks 1–13 after conception date were assigned to trimester 1, weeks 14–26 to trimester 2, and week 27 and above to the third trimester.[19,46] Given that some births occur before the third trimester it is possible that our results for this trimester would be biased downwards, particularly for PTB (8% of PTB deliveries occur before the third trimester). Our approach treats these cases as if they were still at risk, which in many scenarios would lead to bias towards the null; however, under the rare disease assumption (prevalence <10%), it has been shown that any bias due to these sorts of strategies is minimal and generally negligible.[47]

To assess the validity of our results, an extensive set of sensitivity analyses was conducted. First, we conducted analyses with a negative control exposure (placebo test) to detect bias linked to residual unobserved confounding due to non-random sorting,[48] i.e., we used temperature exposures corresponding to 9 months after the birth instead of the actual exposure.[19] To address measurement error, models were additionally adjusted for distance to the monitor location; if distance leads to measurement error, this strategy may help reducing the bias. We assessed the heterogeneity of the results according to foetal sex by including interaction terms between exposure and sex. Finally, in a similar fashion to previous studies, we also conducted analyses using maximum and minimum temperature for the exposure bins. All analyses were conducted in R version 4.0.6. [49]

6.3 RESULTS

Between 2003 and 2017, 2 629 207 births were registered in the Netherlands. After removing multiple births, births with gestational age below 24+0 weeks or above 41+6 weeks, and births with missing data on covariates, there were 2 472 352 births available for the main analysis. Summary characteristics of the population are shown in table 1. The prevalence of LBW, SGA and PTB were 4.7%, 11.4%, and 5.8%, respectively. Also, Table 1 shows the distribution of average number of days during the gestational period falling into each of the temperature bins. On average, pregnant women during the study period were exposed to 12.4 days with a mean temperature falling > 20°C and 2.5 days corresponding to the range < -4 °C.

Figure 1 shows the estimates for the effect of in-utero temperature exposure on birth outcomes (numerical results available in supplementary file 1). In-utero exposure to an additional hot day, i.e., with mean temperature > 20 °C, relative to a day within the 8 – 12 °C range, was related to increased odds of LBW (OR[95%CI]= 1.007 [1.005, 1.009]), SGA (OR[95%CI]= 1.004 [1.003, 1.005]) and PTB (OR[95%CI]= 1.006 [1.005, 1.007]). There was also a detrimental effect of exposure to an additional day in the 16 – 20°C range that was smaller in magnitude (see Figure 1). The point estimates of exposure to an additional cold day throughout the full gestational period showed a detrimental effect for LBW and PTB, however the confidence intervals covered the null. Concerning the timing of the exposure, we observed that in all trimesters exposure to an additional day > 20 °C (relative to the reference) had a detrimental impact for SGA while for LBW and PTB an effect was only observed in the second and third trimesters (supplementary file 2). Regarding cold temperatures, we found that exposure during the second trimester to an additional day with mean temperature < - 4 °C (relative to the reference) had a negative impact on LBW and PTB, but not on SGA.

We observed that the detrimental impact of in-utero exposure to extreme temperatures was more pronounced for births in low-income households. Some of the largest differences were observed in SGA, e.g., the effect of an additional day > 20 °C for low-income households corresponded to OR(95%CI)= 1.013 (1.012, 1.014) while for high income households this was OR(95%CI)= 0.998 (0.997, 0.999). Similarly, for cold temperatures, we found that the effect of an additional day < -4 °C had a detrimental effect on births from low-income households (OR[95%CI]= 1.016 [1.012, 1.019], however, this was not the case for high income households (OR[95%CI]= 0.989 [0.986, 0.992]). Similar patterns were found in the analyses including interaction between exposure and neighbourhood SES (supplementary file 3). However, less heterogeneity was found for maternal education.

The patterns found in the main analysis remained consistent in the sensitivity analyses when the models were adjusted for distance to the monitor location. Furthermore, the patterns found in the main analysis are supported by the results using daily maximum and minimum temperature, although larger effect sizes were observed when using maximum temperature. More importantly, the patterns observed in the main analysis are not present in the placebo test (negative control exposure) indicating that women do not seem to self-select into hotter and colder regions based on unobserved characteristics. Last, when looking at heterogeneity of the effect by foetal sex, we observed that the detrimental impact of extreme high temperature was larger for males than females, particularly for PTB. Results for these analyses are available in supplementary file 4.

Table 1. Population summary characteristics.

Characteristic	n (%) / Mean (SD)
Maternal age	30.5 (4.8)
Nulliparous	1 120 638 (45.3)
Migration background	
Dutch	1 954 100 (79.0)
Moroccan	70 069(2.8)
Turkish	48 534 (2.0)
Suriname	29 661 (1.2)
Antillean	19 635 (0.8)
Other non-western	145 531 (5.9)
Other western	134 772 (5.5)
Foetal Sex	
Male	1 272 272 (51.4)
Female	1 200 080 (48.6)
Low birth weight	118 205 (4.7)
Small for gestational age	282 480 (11.4)
Preterm birth	145 628 (5.8)
Yearly equivalized disposable household income categories	
High	500 044 (21.1)
Medium	1 435 967 (60.7)
Low	429 217 (18.2)
Education	
Low	215 856 (9.0)
Medium	909 870 (37.9)
High	798 445 (33.2)
Unknown	478 742 (19.9)

Table 1. Population summary characteristics. (continued)

Characteristic	n (%) / Mean (SD)
Average number of days during gestational period with temperature	
< - 4 °C	2.4 (0.9)
-4 – 0 °C	12.0 (5.6)
0 – 4 °C	30.0 (11.9)
4 – 8 °C	56.5 (14.6)
8 – 12 °C	56.0 (18.7)
12 – 16 °C	60.7 (11.5)
16 – 20 °C	48.4 (16.3)
> 20 °C	12.4 (15.3)

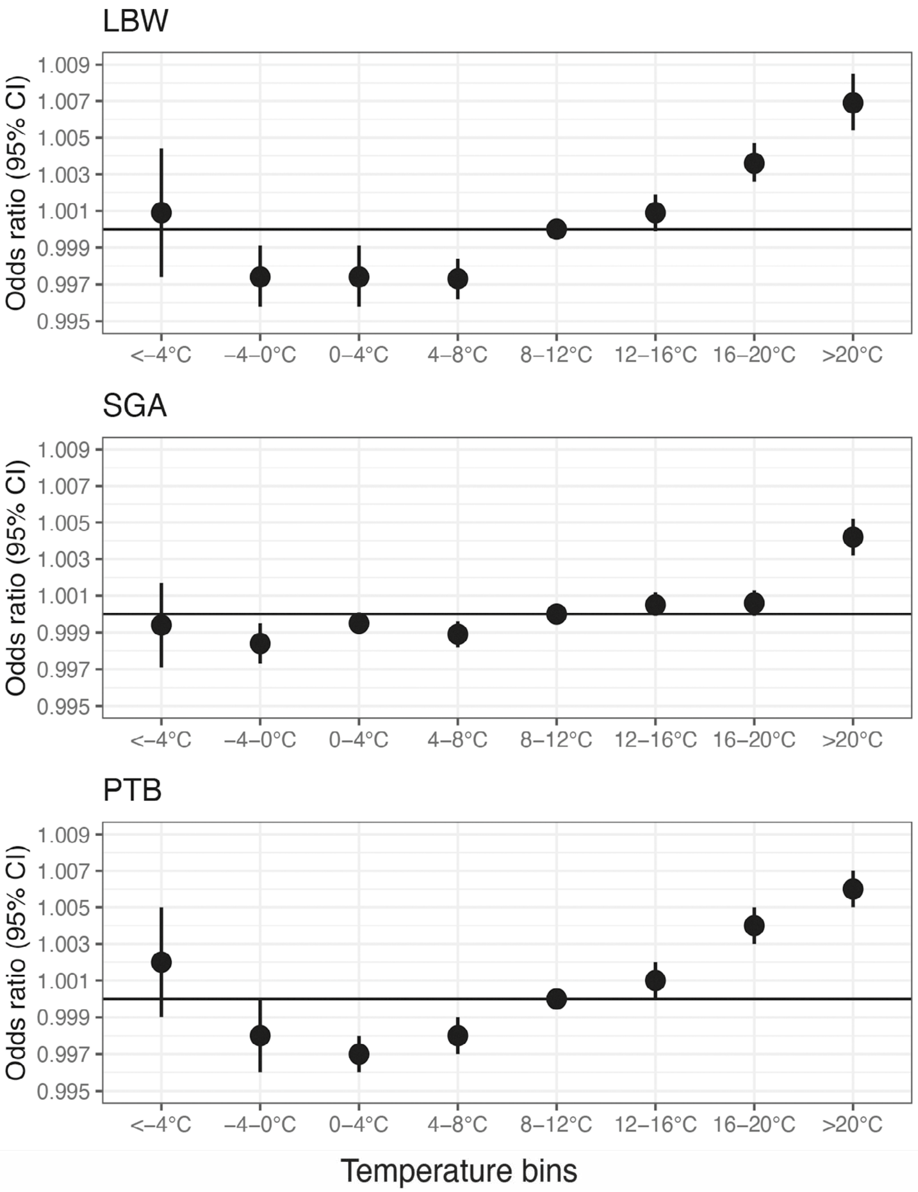

Figure 1. The effect of in-utero exposure to one additional day falling in certain temperature bin on birth outcomes (relative to a day with a mean temperature of 8 – 12 °C).

Footnote: All models include province × week-of-the-year fixed effects, province × year-time-trend, and year fixed effects. Environmental controls include mean precipitation, wind speed, sunshine duration, and relative humidity. Other covariates included were maternal age in categories, parity, foetal sex, household income, mother's migration background and education.

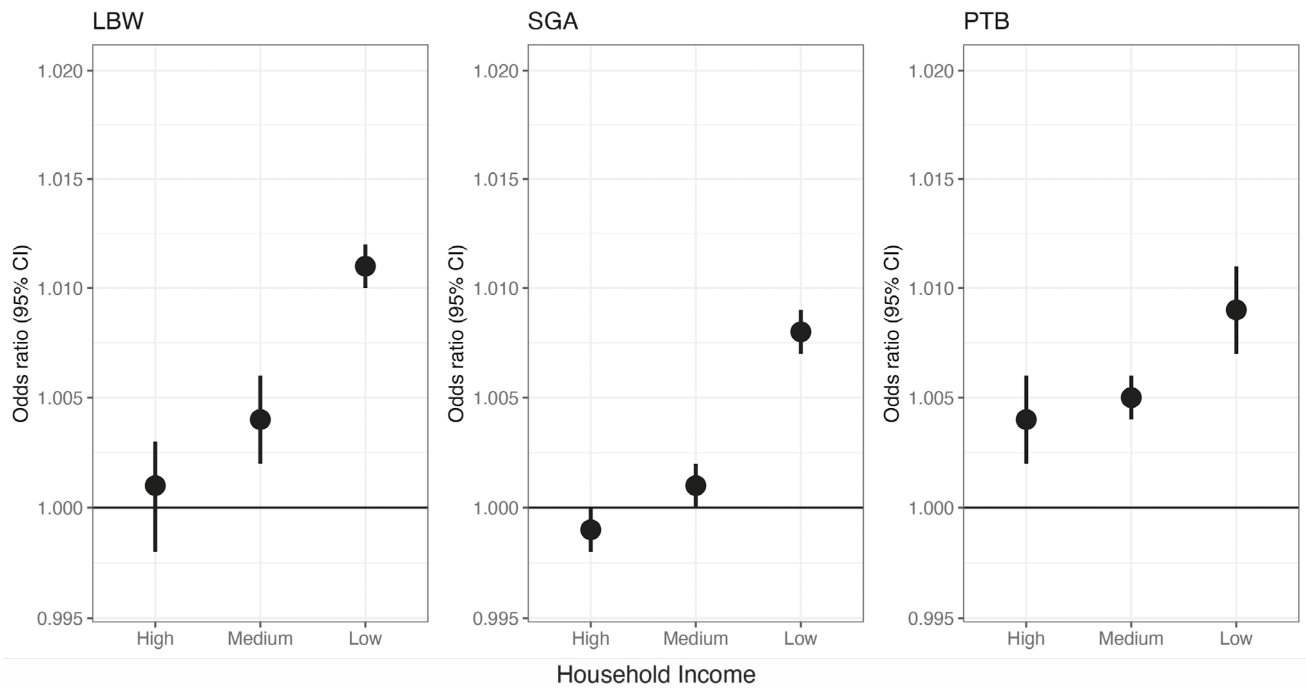

Figure 2. The effect of in-utero exposure to one additional hot day (>20 °C) (relative to a day with a mean temperature of 8 – 12 °C) by household income.

Footnote: All models include province × week-of-the-year fixed effects, province × year-time-trend, and year fixed effects. Environmental controls include mean precipitation, wind speed, sunshine duration, and relative humidity. Other covariates included were maternal age in categories, parity, foetal sex, household income, mother's migration background and education.

6.4 DISCUSSION

In this nationwide study in the Netherlands, we found evidence of a negative impact of in-utero exposure to extreme ambient temperatures on key birth outcomes. We consistently observed that an additional day with temperature > 20 °C increased the odds of LBW, SGA, PTB. We also found a detrimental effect of exposure to cold temperatures (< -4° C) during the second trimester on LBW and PTB. It was observed that household income (and other measures of SES) moderates the effect of temperature on birth outcomes and the burden of adverse effects is higher for populations in a socioeconomic disadvantaged situation.

The main objective of this study was to further the understanding of the effects of intrauterine exposure to extreme temperatures on health at birth. Our work contributes to the available literature in various ways. Foremost, it delivers presumably causal estimates of the impact of prenatal exposure to extreme temperatures on a comprehensive set of birth outcomes in the Netherlands. The finding that exposure to extreme high temperatures has a detrimental effect on birth weight and LBW, are in line with results from previous studies.[17–19,21] We also found that exposure to extreme cold temperatures had a negative impact on LBW and PTB. Although for the latter, the confidence intervals were wide and covered the null, suggesting reduced statistical power, we did however observe a clearer signal for PTB (and LBW) with second-trimester exposure. These results are in line with the conclusions from previous studies.[18,21] We expanded previous work by investigating whether the observed effect on LBW is related to a preterm delivery (PTB), growth restriction (operationalized as SGA), or both. Given that we observed an effect of exposure to hot days (> 20 °C) for both SGA and PTB, it is sensitive to think that the impact observed on LBW is related to both, preterm deliveries and growth restriction. However, for cold temperatures, an effect was found for PTB (second trimester) but not for SGA. This finding, in addition to the observed pattern that the odds ratios are larger and more consistently deviating from the reference category for PTB points that the effects could be mostly driven by preterm delivery. However, further research into other populations would be required to confirm this statement.

Our study also contributes to the literature by exploring the heterogeneity of the effect of temperature by socioeconomic conditions and foetal sex. Exploring the role of SES as moderator for the effects of exposure to extreme temperatures on birth outcomes can help to provide insights into the potential determinants of disparities in early-life health. It was observed that household income moderated the effect of temperature on birth outcomes and that the detrimental impact of extreme cold and hot days was more sizable for those in disadvantaged socioeconomic circumstances. Differences observed across SES groups could be related to, e.g., physical circumstances of living and working environment, activity patterns, resources available for the adoption of coping strategies or differences in awareness. When looking at the differences by foetal sex, we observed a larger effect for male than for female foetuses. This in line with previous findings that adverse in-utero (environmental) exposures impose larger negative effects on males.[50] The effect size may seem small at first, representing the impact of a single additional day of exposure. However, considering longer periods, especially for the low SES group, the effects become sizable.

A main strength of this study is its robust approach to investigating the potential effect of exposure to extreme temperatures on birth outcomes. To be able to identify a plausibly causal effect we have leveraged arguably random daily fluctuations in temperature with adjustment for a broad set of fixed effects and climatological variables. Our approach has the advantage over other methods that it can be applied to a wide variety of outcomes regardless of whether they are expected to have an acute-onset or not (as expected in case-crossover analysis). Furthermore, it facilitated the exploration of critical windows of susceptibility. The use of high-quality routinely collected data corresponding to an extended period (2003-2017) led to over 2.4 million individual records being available for analysis. Given its climatological characteristics, the Netherlands provides an ideal research scenario as self-selection into different climate regions is unlikely in this context (which was confirmed by a sensitivity analysis). Another advantage of the study setting is related to the role of adaptation, e.g., individuals in historically hotter places may adapt to high temperatures through the adoption of mitigating technologies, such as air conditioning, or behavioural adaptations.[19] As mentioned before, extreme temperatures have been rare in the Netherlands during the study period and adaptation strategies to warm weather, such as the use of air conditioning were not widespread throughout the country. In fact, in 2018, only 6% of the Dutch households owned an air conditioner of any sort, and this value can only be lower for the previous years. [51] For comparison, in the USA, one of the nations with the highest air conditioning adoption, almost 90% of households in 2015 had air conditioning.[52] Finally, our results are robust to various specifications as confirmed in the sensitivity analyses.

A limitation of this study is that temperature exposure was based on measurements from the nearest monitor to the residential address of the mother, which may not reflect the temperature in the exact place of residence. This might be particularly relevant for urban populations, who might be exposed to e.g., hotter temperatures than the ones registered in monitor stations due to the urban heat island effect (UHI). The UHI refers to the phenomenon when urban areas experience higher temperature compared to their surrounding non-urban areas,[53] which has been observed to be more prominent in disadvantaged areas often characterized by a lack of green spaces and poor built environment.[54] Also, exposure at e.g., the working environment could not be observed along with information on personal activity patterns, such as time spent indoors vs. outdoors. Exposure at the work place and activity patterns might explain at least in part some of the disparities observed across socioeconomic groups. Last, it is likely that our results are an underestimation of the effect of temperature on pregnancy outcomes due to selection, as early exposure to extreme temperatures might lead to spontaneous abortion of foetuses below-average health even before clinical recognition.[17,55,56] In our analysis we have adjusted our models for common causes of early foetal loss and the outcomes of interest, however, it is likely that this bias cannot be fully addressed. Thus, our estimates should be seen as a lower bound of the true effect.[17,39]

Future research needs to focus on the potential mechanisms through which temperature influences health at birth, particularly those that could be intervened on by public health policy. Previous research has proposed that aside from biological mechanisms, behavioural responses to unusually warm temperatures might also contribute to the effect observed on adverse outcomes.[21,57] For instance, pregnant women in historically cooler countries might spend more time outdoors when temperatures are unusually warm and engage in more physical activity, potentially raising the risk of fatigue and dehydration.[21,57] Furthermore, studies aiming at assessing the role of air pollution as a potential mediator (and moderators) for the effect of temperature on health at birth are needed.

Our results are particularly timely and policy relevant, in the light of the recent weather trends in the face of climate change with a rising ambient temperature and more frequent extreme weather events. With the frequency of extreme weather events only set to increase, public health adaptation strategies for climate change, on a national as well as community level, need to be developed. Furthermore, the identification of vulnerable populations and windows of vulnerability to temperature can assist healthcare providers in constructing and refining the set of recommendations given to pregnant women.

In summary, in this nationwide population-based study in the Netherlands, we found consistent evidence of a detrimental impact of intrauterine exposure to extreme temperatures on adverse birth outcomes, particularly for the exposure during the third trimester. These adverse effects were consistently larger for socioeconomically disadvantaged populations. Thus, the predicted increases in the intensity and frequency of extreme heat episodes has the potential to increase socioeconomic health inequalities at birth.

ONLINE SUPPLEMENTARY FILES

The supplementary files referred to in this Chapter are available online at https://github.com/LizBurgosOchoa/Mind_the_Gap_SF/blob/main/Supplementary_files_Chapter6.pdf

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HOŞGELDINIZ

Chapter 7

Impact of COVID-19 mitigation measures on the incidence of preterm birth: a national quasi-experimental study

ABSTRACT

Background

Preterm birth is the leading cause of child mortality globally, with many survivors experiencing long-term adverse consequences. Preliminary evidence suggests that preterm births dropped dramatically following implementation of policy measures aimed at mitigating the impact of the COVID-19 pandemic. We undertook a national quasi-experimental difference-in-regression-discontinuity approach to study the impact of the COVID-19 mitigation measures implemented in the Netherlands in a stepwise fashion on 9, 15, and 23 March 2020 on the incidence of preterm birth.

Methods

We used data from the neonatal dried blood spot screening programme (2010–2020) and cross-validated these against national perinatal registry data. Stratified analyses were conducted according to gestational age subgroups, and sensitivity analyses to assess robustness of the findings. We explored potential effect modification by neighbourhood socio-economic status, sex, and small-for-gestational-age status.

Findings

Data on 1,599,547 singleton newborns were available, including 56,720 post-implementation births. Consistent reductions in preterm birth were seen across various time windows surrounding implementation of the 9 March COVID-19 mitigation measures: ±2 months (n=531,823): odds ratio 0·77 (95% confidence interval 0·66–0·91), p=0·002; ±3 months (n=796,531): 0·85 (0·73–0·98), p=0·028; ±4 months (n=1,066,872): 0·84 (0·73–0·97), p=0·023. Decreases observed following the 15 March measures were of smaller magnitude and not statistically significant. No changes were observed after 23 March. Preterm birth reductions after 9 March were consistent across gestational age strata and robust in sensitivity analyses. They appeared confined to high-socioeconomic status neighbourhoods, but effect modification was not statistically significant.

Interpretation

In this national quasi-experimental study, initial implementation of COVID-19 mitigation measures was associated with a substantial drop in preterm births in the following months, in agreement with preliminary observations elsewhere. It is now of pivotal importance that integration of comparable data from across the globe is undertaken to further substantiate these findings and start exploring underlying mechanisms.

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7.1 INTRODUCTION

The COVID-19 pandemic and the measures taken to help prevent spread of infection and mitigate its population health effects are having an unprecedented impact on society. The sudden occurrence of the pandemic and the scale and immediacy of the policy responses taken, provide a unique opportunity to evaluate their effects as a 'natural experiment'.[1] Intriguingly, recent reports from Denmark and Ireland independently provided evidence indicating substantial reductions in the number of extremely preterm and very-low-birth-weight (VLBW) births following national COVID-19 mitigation measures.[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 are born preterm, and preterm birth is the primary contributor to mortality in early life.[4] In addition, preterm birth survivors and their families frequently experience long-term adverse consequences.[5-8] Currently, the opportunities for prevention of preterm birth are very limited.[9] As such, it is of pivotal importance that we further explore the possible link between national lockdown measures and a decrease in preterm births, and if confirmed, start identifying the underlying mechanisms to inform and optimise future approaches to help prevent preterm birth from devastating families' lives.

At present, although the link between COVID-19 mitigation measures and reductions in preterm birth identified in the pioneering aforementioned Danish and Irish studies has rightfully sparked substantial optimism globally regarding its potential to help identify new clues for effective prevention, the evidence base is still delicate.[2,3] Both previous studies had relatively limited sample sizes and the methodological approaches that were used restrict causal interpretation. In the current study we addressed these limitations by using national routinely collected data from over 1·5 million newborns to study the association between the implementation of COVID-19 mitigation measures in the Netherlands and the incidence of preterm birth. We applied a difference-in-regression-discontinuity design, facilitating casual inference over the non-quasi-experimental approaches used in previous studies.[2,3]

7.2 METHODS

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

Setting and participants

According to national guidelines,[10] women experiencing uncomplicated pregnancies are offered at least six to nine antenatal visits, the first one ideally being before the 10th week of gestation. At this visit, crown-rump length is measured to estimate gestational age. All women are offered a foetal anomaly scan at around 20 weeks gestation. In 2018, 8% of primiparous women and 23% of multiparous women had a planned home delivery.[11]

The first recognised COVID-19 case in the Netherlands was confirmed in Noord-Brabant, one of twelve Dutch provinces, on 27 February 2020.[12] The first COVID-19-related death occurred on 6 March, and from that day people living in Noord-Brabant were advised to stay indoors when experiencing possible COVID-19 symptoms. On separate occasions between 9 and 23 March, a number of national measures were then taken and widely communicated in an attempt to mitigate the impact of the COVID-19 pandemic in the Netherlands (Table 1 and appendix p 1).[12]

We obtained data on all singleton babies having undergone neonatal blood spot screening in the Netherlands between 9 October 2010 and 16 July 2020, the latter date representing the most recent data available at the time of extraction. The study period was set to include ten years and five months pre-implementation of the first national COVID-19 mitigation measures (9 March 2020; Table 1). Data were provided by the National Institute for Public Health and the Environment (RIVM) as extracted from Praeventis.[12] Praeventis is a national database containing data from all babies having undergone neonatal blood spot screening. In the national screening programme, newborns are screened for a range of diseases after 72 hours of life. Screening can take place in the hospital or at home. According to national guidelines, there is no need to delay screening for neonates born preterm or on parenteral feeding.[14] In 2018, 37% of newborns was screened within 96 hours after birth, and 99% within the first week of life.[15] Over 99% of Dutch babies undergo neonatal blood spot screening,[15] hence the Praeventis database may be considered highly representative of all births in the Netherlands. On the neonatal dried blood spot card, health professionals record several maternal and neonatal characteristics.[16]

For the purpose of this study, multiple births were excluded due to their inherent increased risk of preterm birth, this making their preterm birth risk less amendable to change following COVID-19 mitigation measures. Multiple births were identified based on having multiple records registered with identical surnames, birth dates and postcode. We furthermore excluded babies whose registered gestational age was below 24+0 weeks or above 41+6 weeks. Dutch national multidisciplinary guidelines advise against active management of babies born at gestational ages below 24+0 weeks.[17]

For validation purposes, characteristics of our cohort were cross-referenced at aggregate level against data from Perined for selected years. Perined is the national linked pregnancy and birth registry which is based on data provided by midwifery, general practice, and obstetric and paediatric practices.[11] Perined data are typically made available 1-2 years following initial registration of pregnancies and births, invalidating the use of Perined data to address our primary research question at present.

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 Strong advice for staying at home when experiencing cold symptoms or fever, or when having been in contact with COVID-19-positive person or having visited a high-risk area
12 March 2020	Strong advice against social interaction, and against visiting elderly people Events of >100 individuals are cancelled People need to work from home whenever 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 Physical distancing is introduced (1·5-meter-rule) Issuing of fines for not complying with physical distancing Municipalities may close down busy places and shops

Variables and data source

The following individual-level data were extracted from Praeventis: 1. calendar week of birth; 2. gestational age (in days); 3. birth weight (in grams); 4. sex; and 5. four-digit postcode. Four-digit postcode identifies areas with an average of 2,160 households and was used to derive: 1. province of residence; 2. neighbourhood socioeconomic status (SES); and 3. neighbourhood urbanisation level. Neighbourhood SES scores are calculated by The Netherlands Institute for Social Research (SCP) and were available for 2010, 2014, 2016, and 2017.[18] SES scores are based on: mean household income, proportion of population with low income, proportion of population with low educational level, proportion of population without paid work. Urbanisation level was dichotomised, with urban areas having >2,500 residential addresses per km^2. Individual-level sex- and gestational age-specific birth weight centiles were calculated using national reference curves.[19]

Sample size

Two earlier studies have identified a link between national implementation of COVID-19 mitigation measures and a reduction in extremely preterm and VLBW births.[2,3] In these studies, data on post-implementation births were available for 5,162 and 1,381 births, respectively.[2,3] The Netherlands has approximately 170,000 births annually. This translates into an anticipated ~60,000 births post-implementation, including ~4,000 preterm births.

Given the positive findings in earlier studies,[2,3] which had much smaller sample sizes, we anticipated that our dataset would provide ample statistical power to identify an association between the COVID-19 mitigation measures and preterm births of similar magnitude in the Netherlands.

Statistical analyses

We tabulated characteristics of the study population according to the time periods from which they were derived. We furthermore tabulated selected characteristics against published Perined annual reports, available up to 2018.[11]

We studied the association between national implementation of the COVID-19 mitigation measures and the incidence of preterm births using a variation of a difference-in-regression-discontinuity approach.[20,21] This quasi-experimental technique can be used when the exposure of interest is assigned by the value of a continuously measured random variable and whether that variable lies above (or below) some cut-off value. In this study, birth date (based on calendar week of birth) is the assignment variable and the cut-off corresponds to the implementation dates of COVID-19 mitigation measures. Quasi-experimental techniques provide a robust alternative to experimentation when randomised assignment is not possible, and facilitate causal inference over purely observational approaches.[22] We conducted separate analyses for the 9, 15, and 23 March implementation of COVID-19 mitigation measures (Table 1). A separate analysis was not possible for the 12 March measures given temporal granularity of the individual-level data (i.e. weekly rather than daily). We *a priori* hypothesised that any reductions in preterm birth would most likely have followed the 15 March 2020 measures as these were considered to be most comprehensive. We assessed four time-windows before and after the intervention in separate analyses: one, two, three, and four months pre- and post-implementation. Using such relatively short discrete time windows allows us to exclude other interventions or major influences, and make the assumption that any change observed is indeed due to the COVID-19 mitigation measures. The approach allows for comparison of the incidence of preterm birth in the period directly preceding implementation of the measures versus the period directly following implementation. With the shortest time window (i.e. one month), the estimated impact of the COVID-19 mitigation measures may be closest to the true immediate effect, but the power to detect this impact is limited. Using wider time windows, power to detect the true impact will increase, but potentially at the expense of introducing variation from temporal trends or unmeasured confounding. The analyses account for underlying temporal trends,[23] seasonal variation, and potential other time-variant factors affecting preterm birth incidence by comparing the period surrounding implementation of the measures in 2020 to the exact same time periods in each year preceding the COVID-19 pandemic (2010-2019).

The assumptions and conditions for a valid regression discontinuity were met: a) the cut-off value (9, 15 or 23 March 2020) and decision rule (exposed or unexposed to COVID-19 mitigation measures) are known; b) the assignment variable (week of birth) is continuous around the cut-off and not affected by the lockdown (appendix p 2); c) the outcomes are continuous at the threshold and are observed for all pregnancies; d) graphical analysis shows a discontinuity around the threshold, suggesting an intervention effect (appendix pp 3-14).

In the primary analyses, the outcome of interest was the overall incidence of preterm birth (i.e. number of babies born at a gestational age <37+0 weeks per 1,000 babies having undergone neonatal blood spot screening). In additional stratified analyses we assessed whether there were differential changes in preterm birth incidence following the COVID-19 mitigation measures according to the degree of prematurity: 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 socio-economic groups.[24,25] To assess possible variation in impact of the Dutch COVID-19 mitigation measures according to SES, we tested for effect modification by neighbourhood SES. In an additional post-hoc analysis we explored potential effect modification by small-for-gestational-age (SGA) status and neonatal sex.

Some mechanisms potentially underlying a link between the COVID-19 mitigation measures and preterm birth may not have an immediate impact. On the other hand, there may have been anticipatory effects as part of the population may already have changed their behaviour prior to formal implementation of the COVID-19 mitigation measures. To address this we conducted 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. Analyses were conducted using R v.4.0.2.

Ethical considerations

According to Dutch law (WMO) no formal ethical review was required. According to standard procedures and under strict conditions that were fulfilled, RIVM allows anonymised data registered as part of the screening programme to be used for research purposes with waiver of consent.[26] A protocol for the study was develop *a priori* and approved by RIVM prior to data provision.

7.3 RESULTS

There were 1,707,594 records in the Praeventis neonatal screening database in the study period. After exclusion of neonates born outside the Netherlands, duplicate records, multiple births, and neonates with gestational age missing, <24+0 weeks or >41+6 weeks, individual-level data on 1,599,547 singleton neonates were available for analysis (Figure 1). Characteristics of this population are shown in Table 2. Cross-validation against Perined data for selected years (i.e. 2011, 2014 and 2017) showed that babies born at the lowest gestational ages and those with the lowest birth weights were somewhat underrepresented in our cohort, which was stable over time (appendix p 15).

Table 2. Characteristics of the study population

Characteristic	**n (%) / Mean (SD)**
Birth characteristics	
Term birth	1,515,338 (94·8)
Preterm birth (<37+0 weeks)	84,209 (5·2)
32+0 – 36+6 weeks	72,753 (4·5)
28+0 – 31+6 weeks	8,248 (0·5)
26+0 – 27+6 weeks	2,114 (0·1)
24+0 – 25+6 weeks	1,094 (0·1)
Gestational age (weeks)	39·5 (1·7)
Birthweight (grams)[a]	3,436 (547)
Birthweight centile[a]	49·3 (29·3)
Small for gestational age[a]	171,910 (10·7)
Sex[b]	
Male	819,886 (51·2)
Female	779,654 (48·8)
Province of residence[c]	
Drenthe	39,344 (2·5)
Flevoland	45,072 (2·8)
Friesland	57,112 (3·6)
Gelderland	181,830 (11·4)
Groningen	49,643 (3·1)
Limburg	82,613 (5·2)
Noord-Brabant	221,212 (13·8)
Noord-Holland	273,616 (17·1)
Overijssel	109,762 (6·9)
Utrecht	137,630 (8·6)
Zeeland	31,278 (1·9)
Zuid-Holland	369,084 (23·1)
Living in urban area[c]	590,028 (36·9)
Neighbourhood socio-economic status[d]	
Low (<p20)	301,611 (18·8)
Medium (p20-80)	970,522 (60·7)
High (≥p80)	319,809 (20·0)

SD = standard deviation; [a]Birth weight was missing for 391 individuals (0·02%); [c]Sex was unspecified for <10 individuals – according to RIVM policy, cells containing <10 individuals are censored; [c]Postcode was missing for 1,195 individuals (0·07%); [d]7,605 cases (0·5%) could not be assigned to an SCP SES category: 1,195 due to missing postcode, 6,410 because SCP does not calculate neighbourhood SES scores for postcodes with less than 100 households

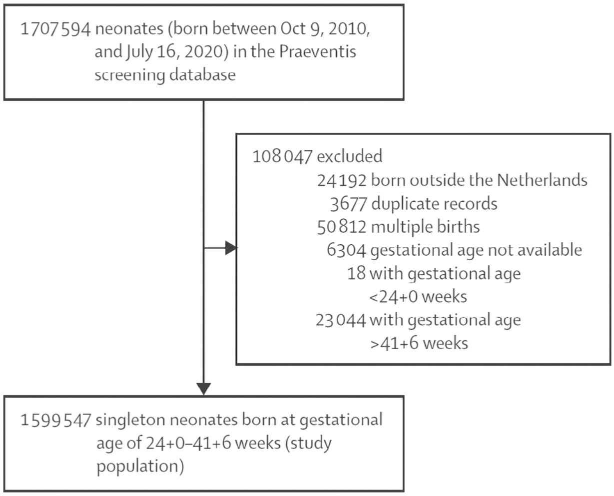

Figure 1. Flowchart of study population composition

Time trends in preterm births in the four months pre- and post-implementation of the COVID-19 mitigation measures are shown in Figure 2 and appendix pp 3-14. A clear discontinuity in the regression lines is observed when considering the initial set of COVID-19 mitigation measures introduced on 9 March 2020. Accordingly, implementation of the 9 March measures was consistently associated with substantial reductions in preterm birth across the two- to four-month time windows surrounding implementation: ±2 months (n=531,823): odds ratio (OR) 0·77 (95% confidence interval (CI) 0·66–0·91), p=0·002; ±3 months (n=796,531): 0·85 (0·73–0·98), p=0·03; ±4 months (n=1,066,872): 0·84 (0·73–0·97), p=0·02 (Table 3). These reductions in preterm births were apparent across gestational age strata, albeit statistically significant only in the 32+0 to 36+6-week subgroup (Table 3). No significant impact on preterm birth was observed when considering the dates that the initial 9 March measures were extended as the primary intervention dates (i.e. 15 and 23 March; Table 3).

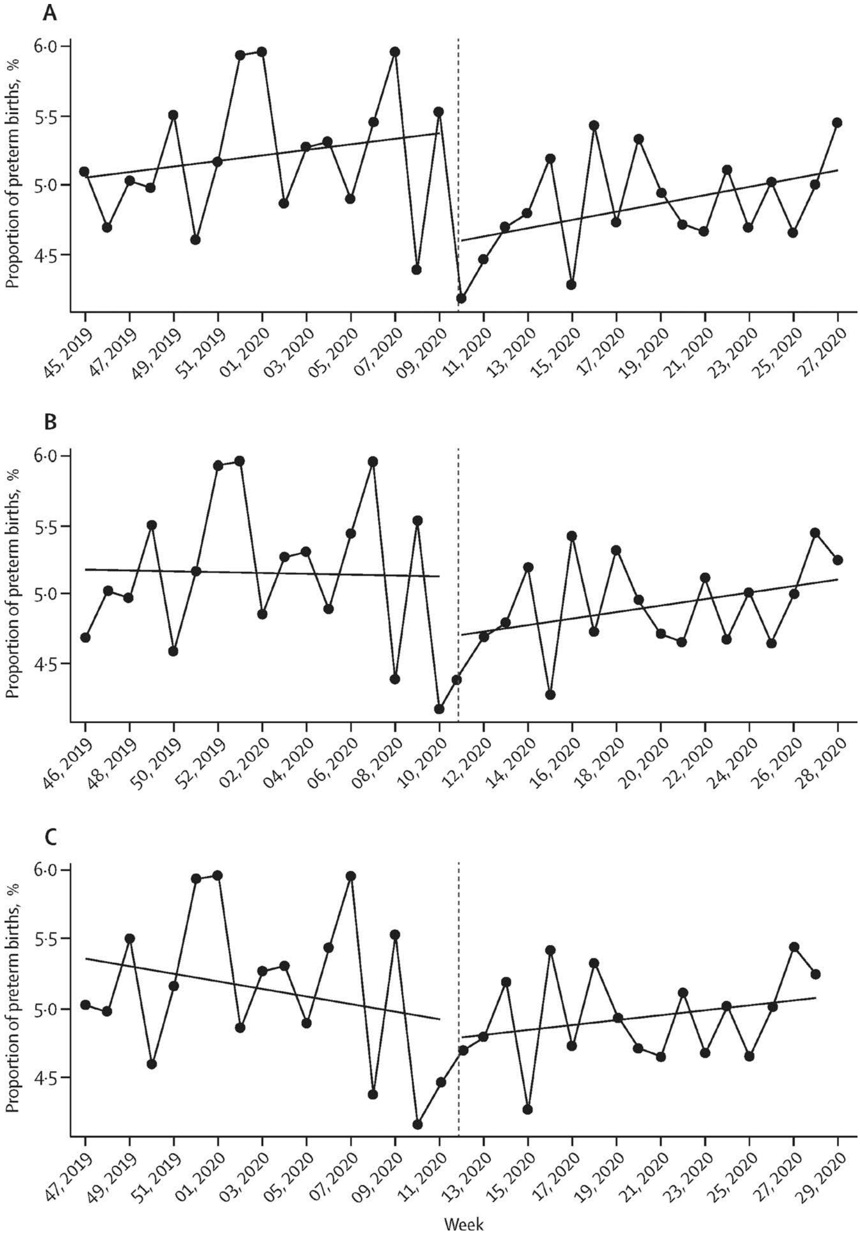

Figure 2. Regression discontinuity in weekly preterm birth incidence surrounding implementation of COVID-19 mitigation measures.

Given these findings and to restrict the number of analyses, we explored effect modification and conducted sensitivity analyses only for the 9 March COVID-19 mitigation measures, and only for the overall incidence of preterm birth. Although the reductions in preterm birth predominantly occurred in those living in high-SES neighbourhoods, effect modification by SES was not statistically significant (appendix p 16). No statistically significant effect modification by SGA status or sex was seen (appendix pp 17-18). Findings were robust to censoring of data prior to or following the 9 March measures, and remained statistically significant predominantly for the two-month time window (appendix p 19).

Table 3. Impact of COVID-19 mitigation measures on the incidence of preterm birth

Intervention / Outcome	Time window around implementation			
	±1 month OR (95%CI)	**±2 months OR (95%CI)**	**±3 months OR (95%CI)**	**±4 months OR (95%CI)**
Measures introduced on 9 March	**n=262,600**	**n=531,823**	**n=796,531**	**n=1,066,872**
Preterm birth (<37+0 weeks)	0·91 (0·68–1·20)	0·77(0·66–0·91)	0·85 (0·73–0·98)	0·84 (0·73–0·97)
32+0 – 36+6 weeks	0·91 (0·67–1·23)	0·78(0·66–0·94)	0·85 (0·72–0·99)	0·83 (0·71–0·97)
28+0 – 31+6 weeks	0·80 (0·34–1·89)	0·78(0·46–1·33)	0·88 (0·55–1·40)	0·91 (0·58–1·42)
26+0 – 27+6 weeks	1·57 (0·20–12·00)	0·66(0·21–2·05)	0·82 (0·30–2·21)	0·99 (0·38–2·55)
24+0 – 25+6 weeks	0·89 (0·10–13·00)	0·48(0·13–1·76)	0·90 (0·29–2·81)	1·00 (0·33–3·04)
Measures introduced on 15 March	**n=259,825**	**n=528,464**	**n=797,799**	**n=1,065,261**
Preterm birth (<37+0 weeks)	1·17 (0·91–1·49)	0·96 (0·81–1·13)	0·97 (0·84–1·13)	0·96 (0·83–1·10)
32+0 – 36+6 weeks	1·11 (0·58–1·45)	0·95 (0·79–1·13)	0·95 (0·82–1·11)	0·92 (0·80–1·07)
28+0 – 31+6 weeks	1·30 (0·48–2·23)	0·88 (0·51–1·50)	0·96 (0·61–1·51)	1·00 (0·65–1·55)
26+0 – 27+6 weeks	4·96 (0·68–36·05)	1·33 (0·41–4·28)	1·37 (0·50–3·69)	1·60 (0·62–4·13)
24+0 – 25+6 weeks	7·83 (0·73–83·47)	1·89 (0·48–7·29)	2·03 (0·63–6·50)	2·15 (0·69–6·68)
Measures introduced on 23 March	**n=263,098**	**n=531,720**	**n=799,511**	**n=1,067,665**
Preterm birth (<37+0 weeks)	1·27 (0·99–1·60)	1·06 (0·89–1·25)	1·05 (0·91–1·22)	1·03 (0·90–1·18)
32+0 – 36+6 weeks	1·27 (0·99–1·64)	1·07 (0·90–1·28)	1·05 (0·90–1·22)	1·01 (0·87–1·17)
28+0 – 31+6 weeks	1·18 (0·56–2·48)	0·98 (0·57–1·67)	1·08 (0·69–1·69)	1·12 (0·73–1·72)
26+0 – 27+6 weeks	1·26 (0·22–7·09)	0·89 (0·28–2·83)	1·10 (0·42–2·87)	1·33 (0·54–3·29)
24+0 – 25+6 weeks	0·45 (0·07–3·06)	0·92 (0·26–3·26)	1·22 (0·42–3·55)	1·31 (0·46–3·68)

Odds ratios (OR; 95% confidence intervals (CI)) indicating odds of preterm birth across various time windows directly following implementation of the COVID-19 mitigation measures versus the odds of preterm birth in similar time windows directly preceding the measures. Estimates derived from difference-in-regression-discontinuity analysis accounting for temporal preterm birth patterns across the same time windows in previous years (2010-2019).

7.4 DISCUSSION

In this large national quasi-experimental study spanning a 10-year period, substantial reductions in preterm births were observed following implementation of the first national COVID-19 mitigation measures in the Netherlands. These reductions were consistent across various degrees of prematurity. No significant impact of extension of the measures introduced one and two weeks later was observed. Taken together with preliminary evidence from other countries,[2,3] these findings open up important opportunities to help identify novel preventive strategies for preterm birth.

To our knowledge, our study is by far the largest to have assessed the impact of COVID-19 mitigation measures on the incidence of preterm birth. Making use of national-level routinely collected data, we had over 1·5 million individual records available for analysis, including over 55 thousand babies born after implementation of the measures in the Netherlands. Since over 99% of babies in the Netherlands undergoes neonatal dried blood spot screening,[15] and very few babies in the dataset had missing outcome data, our data are highly representative. By applying a quasi-experimental approach, our study progresses substantially from earlier uncontrolled before-after studies, thus facilitating causal interpretation of the observed link between the COVID-19 mitigation measures and reduced preterm births.[20-22] Our findings were in addition robust to various model specifications.

Our study also has limitations. Given the unanticipated nature of the COVID-19 pandemic and associated mitigation measures, we had to use a retrospective approach to data collection. As in any registry-based study, there may have been registration errors, and a very small proportion of individuals had missing data. Cross-validation against Perined suggested very little temporal variation in comparability of the data or missing variables, which − even if present − should have been captured by our difference-in-regression-discontinuity design, making any impact on our effect estimation unlikely. Extremely preterm and ELBW births were slightly underrepresented in our dataset as compared to Perined. This was anticipated because: 1. babies born between 22+0 and 23+6 weeks contributed to the aggregated birth weight data from Perined, hence explaining overrepresentation of ELBW babies; 2. Perined data include stillbirths; and 3. extremely preterm babies are at increased risk of dying in the early neonatal period.[27] For obvious reasons, stillborn babies and those dying in the first few days after birth did not contribute data to the neonatal screening programme and hence were missing from our dataset. Importantly, our validation indicates that this relative underrepresentation was not differential over time and is therefore unlikely to have influenced our findings. If anything, survival of preterm babies improved over the study period, which would have biased our findings towards the null. We excluded babies born at <24 weeks gestation as, according to national guidelines,[17] they are rarely offered active treatment in the Netherlands. Given their very low number (i.e. n=18) this is not expected to have influenced our findings. Finally, our dataset lacked individual-level information on relevant covariates including SES, ethnicity, parity, and preeclampsia. Hence, we could not discern whether changes in demographic composition of the population following the COVID-19 pandemic, for example via short-term migration, might have contributed to the findings. Lack of information on mode of delivery and labour induction limited our ability to assess whether the COVID-19 mitigation measures had a differential impact on spontaneous versus induced preterm births.

Our study progresses from earlier work in a number of ways, including using robust quasi-experimental methodology and having a much larger sample size.[20-22] Although in the Irish study none of the January-April periods in the 19 years preceding 2020 had seen proportions of extremely-low-birth-weight (ELBW) and VLBW births as low as in 2020,[3] the numbers of observed versus anticipated ELBW and VLWB births were very small (none versus four, and three versus 11, respectively). Furthermore, of the four months in 2020 across which births were evaluated against preceding data, only one-and-a-half were in fact post-implementation of the lockdown measures, complicating causal interpretation. Similar to ours, the Danish study used national data from the neonatal dried blood spot screening programme.[2] Based on figures presented in their manuscript, we calculated that only one extremely preterm birth had been observed in the first month following lockdown, where five to six were expected. Again, a striking relative reduction but a small drop in absolute terms. Intriguingly, the observed reduction in preterm births in Denmark and Ireland predominantly affected the very smallest babies,[2,3] whereas in our study the decrease was fairly constant across gestational age strata. This is important, as the vast majority of preterm babies are born moderately to late preterm (i.e. 32+0 to 36+6 weeks), and our data suggest that prevention might be possible for the smallest up to the largest groups. A comparison of birth outcomes in a London hospital before and after manifestation of the COVID-19 pandemic revealed no changes in the incidence of births before 34 or 37 weeks gestation.[28] Again, this study had a small sample size and it did not specifically investigate impact of the lockdown. Interestingly, they noted an increase in stillbirths of six per 1,000 following the COVID-19 pandemic.[28] In the Netherlands, stillbirth rates (from 22+0 weeks gestation) have fluctuated between 4·6 and 5·7 per 1,000 births between 2010 and 2018.[11] As more recent information on stillbirths was unavailable, we could not discern whether a small part of the observed reduction in preterm births might have occurred at the expense of an increase in stillbirths.

The aetiology of spontaneous preterm birth, which accounts for roughly two-thirds of all preterm births, is largely obscure and likely multifactorial, hampering effective prevention.[29] Many of the known risk factors for preterm birth may be influenced by implementation of COVID-19 mitigation measures. This includes asymptomatic maternal infection, which by means of vertical transmission can cause intrauterine infection, initiating a cascade resulting in preterm birth.[29] Physical distancing and self-isolation, lack of commuting, closing of schools and childcare facilities, and increased awareness of the importance of hygiene (e.g. hand-washing) all reduce contact with pathogens, and accordingly, risk of infection. Timing of the observed preterm birth reductions in our study suggests that hygiene measures and anticipatory behavioural changes may have been most instrumental. In addition, closure of most businesses and obligatory home assignments likely resulted in less physically demanding work, less shift-work, less work-related stress, optimisation of sleep duration, uptake of maternal exercise in- and outdoors, and increased social support, which all may have had a positive impact. Substantial reductions in air pollution have furthermore been reported following COVID-19 mitigation measures,[30] including in the Netherlands.[31] Given the recognised increased risk of delivering preterm when being exposed to air pollution,[32] this may explain part of the observed reductions. Since a large minority of preterm births is induced, usually for maternal or foetal health concerns, changes in obstetric practice or care-seeking behaviour of pregnant women may also have contributed. Relatively few women deliver via primary caesarean section in the Netherlands, and these are typically medically indicated and performed near-term.[33] Changes in primary caesarean section rates are therefore unlikely to explain the findings. Finally, substantial evidence indicates that the pandemic and associated lockdown measures have aggravated existing health and socioeconomic inequalities within populations.[24,25] In this regard, the signal in our data − albeit not statistically significant − suggesting that the reductions in preterm births were confined to people living in high-SES neighbourhoods is of considerable concern and requires further study.

Preterm birth is the primary contributor to mortality and morbidity in early childhood.[4] Survivors are at increased risk of long-term negative consequences, including adverse cognitive and motor development,[6,7] behavioural and mental health problems,[5] and respiratory disorders.[8] Globally, the incidence of preterm birth is on the rise,[4] and current options for prevention are very limited.[9] Here, we demonstrate that national introduction of COVID-19 mitigation measures in the Netherlands was associated with a considerable reduction in preterm births, substantiating preliminary findings from other countries.[2,3] COVID-19 mitigation measures have been implemented across countries with substantial variation in timing, content and comprehensiveness.[34] Similarly, levels of various risk factors for preterm delivery that might be responsive to lockdown measures also vary across populations. International collaborative efforts will be key to incorporating these sources of variation in innovative global evaluations to further study the link between COVID-19 mitigation measures and preterm births. Identification of the underlying mechanisms is an essential next step, and will require exploration of differential impact between spontaneous and induced preterm deliveries and across demographic strata including SES and ethnicity. Concomitant changes in stillbirths require evaluation and there is a need to explore possible links with changes in air pollution, mobility patterns, and care seeking and provision. These investigations are pivotal to help inform the development of much needed novel preventive strategies for preterm birth.

ONLINE SUPPLEMENTARY FILES

The supplementary files referred to in this Chapter are available online at https://github.com/LizBurgosOchoa/Mind_the_Gap_SF/blob/main/Supplementary_files_Chapter7.pdf

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Appendix A Chapter 7

COVID-19 and maternal and perinatal outcomes.

We commend Barbara Chmielewska and colleagues[1] for undertaking a timely and comprehensive systematic review on a topic of pivotal global health importance. The increase in maternal mortality and stillbirths during the COVID-19 pandemic, particularly in low-resource settings, is of considerable concern. Although a substantial number of studies were collated, many have a substantial risk of bias. For example, of the 18 included studies assessing the link between the pandemic and preterm birth, only two had a quasi-experimental design, many did not have detailed methods, few adjusted for potential confounding factors, and only three included population-level data. Only one study accounted for time trends in preterm birth,[2] which is important to ensure that any changes during the pandemic are independent of underlying temporal patterns. Of the 18 studies, that study also had the largest sample size and the maximum Newcastle-Ottawa score, indicating a high quality. Because systematic reviews serve an important role in summarising the best available evidence, it is remarkable that the meta-analysis by Chmielewska and colleagues excluded this study. Using inverse-variance rather than Mantel-Haenszel weighting allows for its inclusion,[3] with little effect on the association between the COVID-19 pandemic and preterm birth (odds ratio [OR] 0·90; 95% CI 0·83–0·98; 13 studies; n=1 919 726 [figure] compared with 0·91; 0·84–0·99; 12 studies; n=852 854).[1]

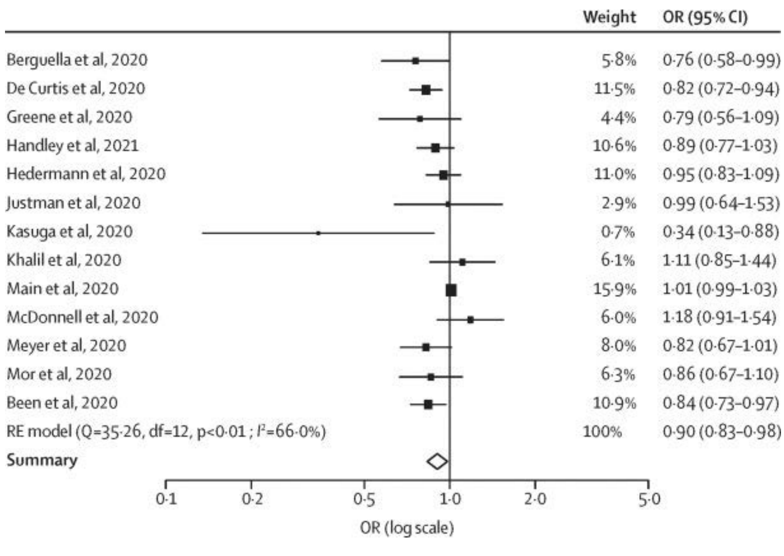

Figure. Forest plot of pooled ORs for the association between start of the COVID-19 pandemic and the incidence of preterm birth (<37 weeks gestation) within high-income countries.

Results from random effects inverse-variance meta-analysis. ORs derived from Chmielewska and colleagues[1] and Been and colleagues.[2] df=degrees of freedom. OR=odds ratio.

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A thorough assessment of how the COVID-19 pandemic and lockdowns have affected maternal and perinatal outcomes is crucial and has important public health implications. Accordingly, more robust studies are needed that are based on high-quality longitudinal data. Ideally, population-level data should be used, because the pandemic probably influenced health-seeking behaviours and access to maternity care, leading to potential ascertainment bias if institutional-level data are relied on.[4] Also, the inclusion of both pregnancy and neonatal data (rather than just one or the other) is important to assess any disparate effect of the pandemic on competing events (e.g., stillbirth and preterm birth). Applying appropriate quasi-experimental designs to population-level maternity and birth data, accounting for underlying temporal trends in the outcomes of interest, has the highest potential to attribute causality and reduce confounding.

Now is the time for the perinatal research community to collaboratively take advantage of the unique natural experiment provided by the COVID-19 pandemic to accelerate progress in maternal and child health globally. We call on researchers to undertake robust studies and contribute to joint international efforts such as the international Perinatal Outcomes in the Pandemic (iPOP) study.[5] Together we can learn from experiences from the pandemic and start identifying mechanisms that might contribute to a healthier start for future generations.

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Chapter 8

Use of natural experiments to evaluate public health policy.

A key task of public health research is investigation of the causal effect of policies aimed at improving health outcomes. However, such a task is often challenging because a study in which a population is randomised into exposed and unexposed groups is generally not feasible owing to practical and ethical constraints. In certain settings, a so-called natural experiment resulting from a policy implementation can be used to estimate the causal effect of non-experimental interventions.[1, 2]

In The Lancet Public Health, Adina Epure and colleagues[3] used the natural experiment resulting from implementation of an expansion of health insurance in Switzerland to examine the effect of full coverage of illness-related costs during pregnancy on birth outcomes. To estimate the effect of this policy, the investigators used a variation of the difference-in-discontinuity design formalised by Grembi and colleagues.[4] This approach can be used when allocation of the intervention is based on a cut-off value for a running variable that cannot be precisely manipulated by the individuals.[4] Epure and colleagues used date of childbirth as the running variable and the cut-off was the date of the policy implementation (March 1, 2014). The intervention assignment for individuals close to the cutoff value can be assumed to be as good as random, and a causal effect was estimated by comparing outcomes for groups of individuals just before and after the cutoff.[4] However, in this setting, a change in outcomes around the cut-off might also occur owing to other factors, such as seasonal patterns. To address this issue, the difference-in-discontinuity design uses the information of births that occurred during the same months around the cut-off date in control years with no policy change. 61 910 children were born 9 months before March 1, 2014 and 63 991 were born 9 months after June 1, 2014 (a 3-month censoring was used from March 1, 2014). 382 861 children were born in the same time period around the three control dates.[3]

Epure and colleagues[3] found that implementation of the policy increased mean birthweight by 23 g (95% CI 5-40) and decreased the predicted proportion of low birthweight births by 0·81% (95% CI 0·14-1·48) and of very low birthweight births by 0·41% (0·17-0·65). No statistically significant effects were observed overall for preterm birth and neonatal death. The observed effect sizes were modest, which could partly be explained by the exposed group also including births after pregnancies only partially covered by the policy, diluting the effect. Another contributing factor was that the estimation was done at a population level, whereas many pregnant women are not affected by the policy as they never need illness-related medical care. Unfortunately, the effect of the policy on health-care use, the presumed mediating variable, could not be estimated. Assessment of underlying mechanisms is still necessary to understand the pathways through which the policy might be acting.

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Although the policy provided additional health care coverage, it did not reduce socioeconomic health inequalities, and in fact even widened them, as babies with parents not at risk of poverty benefited more from the policy. That is, the policy lowered the predicted proportion of extremely preterm births (-0·19%, 95% CI -0·36 to -0·02) and neonatal deaths (-0·13%, -0·26 to 0·01) in those not at risk of poverty, but not among those at poverty risk. Although overall the intervention had a positive effect, these undesirable consequences are commonly observed when policies aimed at improving health outcomes are implemented at a population level. According to the latest European Perinatal Health Report, Switzerland achieved substantial reductions in adverse birth outcomes in the last few years.[5] Although there have been improvements at a population level, previous work has pointed out the presence of health inequalities,[6] and policies specifically targeting health inequalities at birth are needed.

To be able to make any causal claims, designs based on natural experiments require a detailed assessment of the mechanism allocating the intervention.[1] Issues like manipulation of the running variable could affect the validity of the results.[7] Such manipulation would be present if there would be a change in behaviour in anticipation of the policy intervention.[8] Bias would arise, for example, if particular groups decided to actively postpone their pregnancy to benefit from the expansion. Although the investigators cannot rule out such bias, the expansion might have been seen by the target population as a minor change that would not have led to a change in pregnancy planning.

In conclusion, the nationwide study by Epure and colleagues[3] found evidence of modest reductions in key birth outcomes after the implementation of a policy fully covering illness-related costs during pregnancy. The assessment of public health policies provides information on plausible strategies to improve perinatal health and how these could be improved. The natural experiments arising from implementation of policies can be used to estimate causal effects of public health interventions in real-world settings.

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Chapter 9

General Discussion

Socioeconomic health inequalities represent a challenge for public health and their reduction is a priority in policy making. The health gap between most and least advantaged can be observed even in the first moments of life in the form of adverse birth outcomes. Thus, health at birth can be considered one of the first indicators of health inequality in a persons' life. Given the cumulative and intergenerational nature of disadvantage, addressing health inequalities at birth and providing a healthy start to children from all backgrounds is key to the improvement of the population's health. To do this, the identification of health inequalities and their drivers is essential.[1]

This thesis contributes to the current literature in three main ways: 1) by describing the current state and evolution of patterns in early-life health inequalities by neighbourhood socioeconomic conditions in the Netherlands, 2) by exploring potential underlying mechanisms, and 3) by investigating the differential effect of external exposures on early-life health by socioeconomic status (SES). In the following paragraphs, the reflections and implications of our findings and future directions are discussed.

9.1 REFLECTION ON THE OBTAINED RESULTS

Based on the latest European Perinatal Health Report, the Netherlands is one of the countries that in recent years has made considerable improvements in perinatal health.[2] For instance, we observed that between 2003 and 2017 there has been a consistent decrease in the overall prevalence of adverse birth outcomes.[3] However, despite of this overall progress, early-life health inequalities are still present in the country. The findings from **Part 1** of this dissertation consistently demonstrated that infants born to mothers residing in deprived neighbourhoods and in areas with disadvantaged SES trajectories faced a higher risk of adverse birth outcomes, even after considering individual-level characteristics and socioeconomic factors.[3,4] The presence of such disparities indicates that previous efforts aimed at reducing the socioeconomic health gradient have not yet been sufficient. Addressing these inequalities would require not only achieving equal reach and effectiveness in policy interventions but also placing a stronger emphasis on reaching and benefiting low SES groups, which are known to be hard to reach.

In this context, neighbourhood-level interventions emerge as tools with the potential for improving health outcomes among disadvantaged populations. The exposure to certain neighbourhoods' environments is not only determined by individual-level factors but it is also shaped by large scale population and economic processes that are potentially malleable by policy interventions.[5] Successful changes implemented in these neighbourhood environments have the potential to lead to improvements in health outcomes and, consequently, reduce health inequalities. However, one important question that arises is the extent to which neighbourhood environments can be effectively influenced by policy interventions, particularly when considering changes beyond the physical environment and encompassing the social environment. Currently, there is no definitive answer to this question. A major limitation in addressing this topic is that much of the available literature on neighbourhood change relies on case studies,[6] which face challenges in terms of generalizability. Additionally, policies such as neighbourhood regeneration (renewal) programmes, which aim to reverse negative neighbourhood dynamics and promote positive change, have rarely been assessed for their effectiveness. The most robust work available has mainly focused on whether such policies succeeded on changing economic characteristics of the neighbourhood, i.e., average income or percentage of non-economically-active inhabitants.[7] While such information is valuable on the effects of such policies, it still provides a very limited picture.

To gain a better understanding of the malleability of neighbourhood environments through policy, it is necessary to conduct robust evaluations of neighbourhood renewal policy interventions in terms of improvement of neighbourhoods' environments. In this regard, the Netherlands provides a unique research opportunity as for the last decade the country has been actively implementing neighbourhood renewal policies in various areas.[8] These policies have targeted several aspects of neighbourhoods, including housing, green spaces, services, as well as addressing issues related to safety, nuisance, and cohesion.[8] Renewal policies open a door to investigate research questions pertaining to the direct effects of targeted neighbourhood interventions on various aspects, including physical changes, services, and the social environment.

It is important to note that the effects of such policies may not manifest immediately but rather require time to become observable. As a result, neighbourhoods undergoing transformation may be in a transitional phase, where their environments still retain some characteristics from their previous state, such as higher crime rates. This delay could potentially explain our findings that even after neighbourhoods experience improvements in their SES level, infants born in these areas still exhibited a higher risk of adverse outcomes.[4] By investigating the health impact of neighbourhoods undergoing change, renewal policies present an opportunity to explore potential time lags, thereby shedding light on the transitional nature of these transformations as hypothesized earlier.

Neighbourhood renewal policies may be used to further address another one of the largest knowledge gaps in the literature, i.e., the drivers of neighbourhood-related inequalities. Neighbourhoods are hypothesized to have an impact on early-life health outcomes through influencing the availability of physical and psychosocial resources the mother has access to or by increasing the likelihood of exposure to risk factors.[5] In **Part 2** it was observed that neighbourhood social environment and neighbourhood-level crime rates accounted for meaningful shares of the observed relationship between neighbourhood SES and key birth outcomes.[9,10] These results contribute to the body of evidence on how the socioeconomic characteristics of neighbourhoods can translate into potentially modifiable factors that impact health. However, there is still a need to identify in a comprehensive manner mechanisms linking area-level features and perinatal health beyond the investigation of separate mechanisms.

Examining the intricate mechanisms linking neighbourhoods and health in a comprehensive manner presents significant challenges. Particularly because when neighbourhoods change many of these changes tend to occur at the same time. Moreover, area-level factors are interrelated, further complicating the analysis. For example, the introduction of recreational green areas not only impacts physical attributes but also potentially influences social cohesion by providing spaces for neighbourhood residents to interact. To explore these mechanisms effectively, renewal policies could offer a valuable opportunity. These policies intentionally target specific factors and in many instances such changes might be implemented at various stages, allowing researchers to exploit these changes as natural experiments. By assessing the success of implemented interventions, we can investigate whether any observed changes have translated into improvements in early-life health. This utilization of information can yield insights into the causal relationship between neighbourhood interventions and health outcomes.

Such research could go beyond area-level mechanisms and can reach a deeper level by incorporating individual-level factors. It is anticipated that many of these intermediate neighbourhood attributes have indirect effects on health, such as through the experienced levels of stress, and the adoption of healthy - or unhealthy - lifestyles. Examining the specific pathways linking neighbourhood-level characteristics to birth outcomes via the health of the mother is crucial for understanding the impact of neighbourhoods on early-life health. Such research would help elucidate the contribution of various interrelated mechanisms through which neighbourhoods impact health and could help identify the modifiable mechanisms that exert the greatest influence on health. While data on lifestyle factors is not yet available at the national level, one solution could be the use of large cohorts studies, which focus on collecting detailed health information for a representative share of the population. This knowledge would enable policymakers to effectively target the mechanisms with the most significant impact through policy interventions.

The socioeconomic conditions not only have the potential to affect health outcomes via various intermediate factors, as discussed above, but they can also modify the effect of an external exposure which can result in wider inequalities. For instance, in **Part 3** of this dissertation, it was observed that exposure to ambient temperatures at the extremes of the distribution had an adverse effect on birth outcomes. Moreover, the impact was the most detrimental among births from mothers living in disadvantaged socioeconomic conditions. These differences are concerning as they have the potential to widen the gap between most and least socioeconomically advantaged populations, particularly in light of the projected increase in extreme temperature events in the face of climate change.[11]

It is likely that some of the potential explanations for the differential impact of extreme temperatures based on SES operate at the individual level. For example, the limited resources and opportunities for adaptation among low-SES mothers, such as suboptimal housing conditions with poor insulation.[12] Also, work environments with reduced ventilation, performing strenuous tasks, or working outside may exacerbate the health effects of ambient temperature.[13] Another aspect relies on the notion that higher-SES individuals, who tend to hold higher health knowledge, may make more informed decisions regarding risky behaviours during periods of high temperatures.[12] Also, differential susceptibility could also play a role, as lower-SES mothers with pre-existing conditions like diabetes or hypertension may be more vulnerable to the effects of extreme temperatures.[14]

However, it is also important to examine the contribution of area-level factors to better understand the observed disparities. For example, areas with lower building density and greater greenery have the ability to mitigate heat, and cool down more rapidly at night, offering relief during heat waves.[15] Conversely, densely populated areas, particularly in disadvantaged neighbourhoods, lack such benefits, resulting in the formation of "heat islands" that intensify the adverse effects of extreme temperatures on health.[16,17] Therefore, investigating the influence of green spaces, blue spaces, overall built environment, and land use in neighbourhoods becomes significant in comprehending the varying impact of extreme temperature events on health across SES levels. However, accurate temperature measurements at the small-area level are essential but limited. Traditional measurement stations, typically located outside urban areas, fail to capture local temperature differences adequately.[15] This limitation hampers the analysis of ambient temperature variation across neighbourhoods.

To address the questions regarding area-level contributors to the observed disparities, it is necessary to incorporate more granular measures of temperature. Local efforts, such as the curated data by the *Environmental Protection Agency Rijnmond* for the wider Rotterdam area, have aimed to collect and model more detailed climatological data. However, a concerted national-level effort is still needed to gather and make available such information for research purposes. Citizen science projects, utilizing volunteers to collect temperature data, can also provide valuable localized measurements.[15] Only with this detailed information can the contribution of the built environment to disparities in health outcomes be investigated on a larger scale. Research initiatives in this area can leverage natural experiments involving significant changes to land use in specific locations, such as the construction or expansion of public parks. Moreover, they could as well examine changes resulting from neighbourhood renewal policies, offering interesting avenues for investigation.

Beyond the influence of the neighbourhoods where mothers reside, workplace exposure is likely to make a significant contribution to the observed disparities. The potential role of the workplace has already been mentioned, considering factors such as poor ventilation and strenuous tasks. However, the area-level environment of workplaces is also likely to influence birth outcomes, which remains a substantial knowledge gap in the literature due to data availability challenges. Currently, there is a lack of information regarding the geographical location of individuals' workplaces, partly due to privacy concerns. Nevertheless, bridging this research gap is crucial for developing a comprehensive understanding of how the environments surrounding pregnant women can impact the health of their children.

In the Netherlands, for instance, women's labour force participation is around 75%.[18] The current policy allows for pregnancy leave from 6 to 4 weeks before the expected date of delivery, with a significant percentage of women waiting until the last 4 weeks before their due date to take leave. This implies that workplace environments account for a substantial portion of a woman's exposure to both protective and risk factors. Access to area-level information about the workplace, combined with detailed temperature measurements, would be invaluable for studying this matter. Ideally, individual-level temperature monitoring using wearable devices would provide the most accurate data. However, implementing such monitoring for large cohorts is likely challenging due to associated costs.

Apart from climatological factors, other external events that are beyond the control of individuals, such as policies, can have varying effects across different groups within the population. While some of these events may bring positive health outcomes at the population level, it is important to acknowledge that their impact could be predominantly benefiting already advantaged subpopulations. The global pandemic of COVID-19 in 2020 demonstrated this pattern, initially perceived as a "great equalizer"[34] but later revealing widening inequalities in COVID-19 infections and other health outcomes affected by mitigation measures. In this dissertation, we observed a decline in preterm birth rates at the population level following the implementation of COVID-19 mitigation measures.[19] Similar patterns where also observed in various other high-income countries and have been confirmed by a large meta-analysis study.[20,21] Nevertheless, the results suggested that the decline mainly occurred among births from mothers living in high-SES neighbourhoods.[19]

Although such a differential impact of the COVID-19 policies would be an unintended adverse consequence, the natural experiment created by the lockdown has unveiled mechanisms related to preterm birth that may be more modifiable than previously believed. However, the specific causes behind the observed decrease in adverse outcomes still remain unclear. Several mechanisms have been proposed, including changes in healthcare provision due to staff shortages and infection control measures, reductions in gastrointestinal and respiratory infections (excluding COVID-19), known contributors to adverse outcomes, and shifts in working conditions as remote work became the norm for non-essential professionals.

However, in closer relation to the main topic of this dissertation, area-level considerations should also be investigated. For example, changes in air pollution may have played a role in the observed outcomes, particularly regarding spontaneous preterm births. During the spring 2020 lockdown in the Netherlands, significant reductions in air pollution levels were observed.[22] However, the effects of the lockdown measures on air pollution varied across sources and areas, with urban areas, for example, experiencing more substantial decreases. Analysing these temporal and spatial variations in pollutant levels could help unravel the contribution of air quality to the observed outcomes. Furthermore, neighbourhoods with characteristics that promote physical activity, such as higher walkability or quality green spaces, could have had a positive impact on birth outcomes and potentially explain some of the observed differences across neighbourhood-level socioeconomic status.

In addition to exploring the mechanisms behind the acute effects of mitigation measures on birth outcomes, these measures could also serve as a natural experiment to investigate the impact of neighbourhood environments themselves, albeit with some limitations. Throughout the pandemic, mitigation measures have compelled the population to restrict their movements, which led individuals to experience more deeply the characteristics of their own residential neighbourhoods. This heightened experience likely prompted the inhabitants to actively interact with and utilize the physical aspects of their neighbourhoods, such as the availability of recreational outdoor spaces, the quality of infrastructure, and the accessibility of services. Additionally, social factors such as nuisance and social cohesion may have been more intensely experienced by neighbourhood residents during the lockdowns. Therefore, these circumstances present an opportunity to assess the health effects of neighbourhoods in a more isolated manner, without the interference of other environments such as the workplace. However, conducting such research poses various challenges, particularly given the many simultaneous changes occurring during the pandemic. Nonetheless, this research can benefit from the variation in mitigation measures across different regions, as it occurred within various countries during later stages of the pandemic. Although challenging, researchers must attempt to find ways to capitalise on this opportunity to investigate what could be seen as something closer to the “true effects” of neighbourhood environments.

9.2 BROADENING PERSPECTIVES: CAUSAL INFERENCE AND INCORPORATING COMPLEXITY

Asking causal questions

While significant progress has been made in the literature concerning early-life health inequalities, there remain numerous unanswered questions regarding the underlying reasons for the observed disparities. Perhaps a first step to advance our understanding in this field is to start clearly identifying the type of research questions we actually aim to address. While describing associations, serves as a legitimate research objective, especially when investigating relatively uncharted topics, the progression towards answering causal questions becomes essential. When talking about inequalities, uncovering the reasons why they arise is perhaps the most important task for researchers in the field. For instance, investigating the mechanisms through which inequalities manifest or examining how specific events, such as policy implementations, differentially impact health outcomes across population subgroups. Both scenarios necessitate probing into cause-and-effect relationships.

Various perspectives exist regarding the approach to causal inference within disciplines like social epidemiology and public health. In these fields, conducting randomized controlled trials (RCTs) presents inherent challenges due to ethical and practical constraints. For instance, it is unfeasible and unethical to randomly assign individuals to disadvantaged socioeconomic circumstances to study the impacts of such conditions on health outcomes. Traditionally, the prevailing perspective has insisted that causal inference was exclusive to RCTs, implying that analyses of observational data could only reveal associations, and any use of causal language under such circumstances was unwarranted. However, the act of removing causal language from the literature based on observational data is clearly disingenuous, as pointed out by many authors.[23–25] If researchers were genuinely interested on associations instead of casual relations, there would be no need to make the effort of matching or adjusting for confounders.[24] Such statistical adjustments, although considered standard in the literature (as seen in the first part of this dissertation), are not essential when the aim is to describe associations.[26] Moreover, the inclination to provide policy recommendations based on the obtained results, which is common practice, would be diminished if there were no underlying belief in the causality of the observed relationships and their potential for actionable interventions.[25]

The embrace of this narrow perspective on causality has not been conducive to the advancement of the field; in fact, it may have hindered progress. To date, the vast majority of research with veiled intentions of causality continues to be based on null hypothesis testing and regression-based adjustments, lacking justification from any formal causal theory.[27] Amidst this somewhat desolate landscape, recognizing a causal inquiry can signify a substantial step forward. Such recognition compels an acknowledgment of the prerequisites for interpreting results as a causal effects, motivating researchers to devise strategies that adhere to these conditions and foster a more rigorous approach. Consequently, echoing the call of numerous scholars, the need to pose *less casual causal* questions becomes evident.[23] In this context, the Rubin-Neyman potential outcomes framework[28] has proven immensely valuable, offering means to define causal effects in a manner that transcends the statistical models employed for estimation. Moreover, it has specified identification assumptions under which an effect can be interpreted as a causal relationship, i.e., exchangeability, positivity, and consistency.

In **Part 3** of this thesis, natural experiments have been employed as methodologies to address causal inquiries. These approaches are often referred to as methods grounded in the concept of selection on unobservables.[29] These methods have been traditionally used in the (health) economics literature to examine, e.g., the impact of policy changes on health outcomes. Such studies use the occurring variation in exposure to identify the causal impact of an event on some outcome of interest. As the exposure is determined by factors beyond individuals' control, these designs approximate random exposure assignment,[30] i.e., minimizing risks of violations to the exchangeability condition. However, it is essential to acknowledge that this "as-good-as-random" exposure assignment is challenging to validate, and instances may arise where its validity falters—such as cases where individuals alter their behaviour in anticipation of forthcoming policy changes. A limitation inherent in such approaches pertains to the generalizability of their findings. While this concern may be less pronounced when examining policies applied across entire populations, natural experiments often pertain to narrower population segments. This raises the question of whether effects observed in one subgroup can be extrapolated to others. For example, in the Netherlands, neighbourhood renewal policies have exclusively targeted the most disadvantaged urban areas. While studying the effects of such policies would offer valuable insights, their applicability to more rural environments would be uncertain. The inherent tension between establishing causal relationships and achieving generalizability is an inevitable aspect of research, reflecting a common challenge where trade-offs must be navigated. Natural experiments continue to serve as powerful tools for causal inference within the realms of social epidemiology and public health. Researchers should seize the occasions when such events arise, yet with an awareness of the conditions underpinning the validity of their results.

In **Part 2** of this dissertation, the g-formula[31] has been employed as a tool for answering causal questions. The g-formula operates within the ambit of methods grounded in the concept of selection on observables that have flourished in epidemiology. These methods, which encompass among others the g-formula, matching, and weighting techniques, derive their validity from the accurate specification of the data-generating mechanism. This relies on the measurement of a sufficient set of covariates that act as confounders.[24] This task is far from trivial, entailing not only expertise but also access to a potentially extensive array of information. Such availability may be constrained, particularly when relying on registry data as discussed this dissertation. Nevertheless, in the face of this challenge, results yielded by these methods can still provide valuable insights—especially when interest lies on intricate phenomena like mediation or navigating longitudinal settings.[31] Moreover, avenues to identifying lingering confounding factors are available; consider, for instance, the application of negative controls.[32] Additionally, doubly-robust methods that combine the use of, e.g., the g-formula and weighting approaches have been shown to perform well even in the presence of unmeasured confounding.[33] Approaches like the g-formula are functional when assessing the potential impact of hypothetical interventions, circumstances where natural experiments are absent. Rooted in the potential outcomes framework, these approaches foster an understanding of the necessary assumptions and underscore the importance of addressing potential violations or provide a reflection on any remaining concerns.

Broadening our perspective of causal inference can ultimately offer notable benefits, prompting researchers to adhere to a set of established causal identification prerequisites. First, by highlighting the significance of formulating precise and well-defined research questions, with an emphasis on continuous refinement as the field evolves. Related to the previous point, it underscores the crucial role of a sufficiently specific definition of the exposure, ensuring that the estimated causal contrasts accurately capture the intended effects. The field of health inequalities research has often employed composite measures of socioeconomic status, which, while valuable for monitoring, introduce challenges to causal inference due to potential violations of the consistency assumption. In this regard, it could be argued that narrower definitions of an exposure also come with further advancements in the field and certain degree of ambiguity in social exposures cannot be escaped. Further research in the area should be encouraged to narrow the definitions. Second, embracing this perspective further prompts researchers to reflect on the intricacies of the data-generating process and to actively address potential deviations from the exchangeability assumption. Third, it requires verifying the existence of a non-zero probability for exposure to the intervention of interest across subgroups within the population (positivity). Last, it encourages exploration of alternative methodologies that relax the constraints of some of these rather stringent assumptions. Approaches such as proximal causal inference hold promise as avenues that can offer more flexibility and accommodate real-world complexities.

I argue that a broader view of causality encourages a more rigorous and nuanced approach to research, ultimately enhancing the robustness and applicability of findings within the field of health inequalities research. Even when we harbour some reservations about the complete fulfilment of causal identification assumptions, findings from existing studies retain their significance and stimulate further investigation that could potentially address any lingering uncertainties. In the grand scheme of research, it's an ongoing journey, and definitive conclusions cannot be drawn from a solitary study. Instead, it necessitates persistent efforts to accumulate knowledge, ultimately paving the way for informed policy recommendations.

Incorporating complexity

Another aspect to reflect on our current perspective relates to complexity. It could be argued that the difficulty in finding suitable answers to questions regarding health inequalities stems, in part, from their dynamic nature, which has not been adequately captured by the prevailing approaches employed in existing research. In fact, a common criticism of current approaches is their oversimplification of inequalities, while these are inherently multifaceted.

To gain a comprehensive understanding of these complex issues, scholars have emphasized the application of complex systems thinking.[34] This framework acknowledges health inequalities as outcomes of interdependent elements that interact in intricate ways.[35]

Moreover, it requires researchers to explicitly elucidate how processes occur at different levels of the system and how they interact across these levels. This perspective is particularly relevant in disparities research, as differences observed along the socioeconomic gradient are influenced not only by individual-level or neighbourhood-level factors but also by macro-level factors, such as public spending.

Despite of the many possible advantages, implementing such framework in practice presents important challenges. One major challenge revolves around the plausibility of drawing causal conclusions. Each relationship depicted in the conceptual model relies on a set of causal identification assumptions, mentioned earlier in this section. However, even with simple models in health inequalities research, it becomes evident that the available data often lacks the necessary information to, e.g., account for all potential confounders. This difficulty intensifies as the number of hypothesized effects within the defined system increases. Despite this limitation, it could be argued that models based on limited information still offer valuable insights. Moreover, the process of developing conceptual models could help identifying gaps in data availability, prompting more detailed data collection efforts.

Another major challenge relates to the estimation of complex models. Despite significant advancements in computational power in the past decades, researchers still face limitations, particularly when working with large datasets encompassing an entire population. The increased complexity of models leads to computationally intensive estimation processes. Promising models within this framework, such as agent-based models and the g-formula,[36] already require substantial computational resources. Addressing the issue of computational resources would be essential for advancing the complexity of our models.

Recognizing the prevailing challenges associated with implementing the complex systems framework highlights the importance of finding a middle ground. It is crucial to acknowledge that much of the existing research has overlooked the inherent complexity underlying health disparities. Therefore, future research efforts may focus on exploring methods to incorporate complexity, and the most prudent approach may involve a gradual progression. Beginning with relatively simple models allows researchers to gain insights from the results and progressively incorporate more intricate relationships while considering the biases and limitations inherent in these models. By adopting a gradual approach, researchers could build upon their initial findings and refine their models over time. This iterative process enables a better understanding of the complex dynamics at play in health inequalities while accounting for the intricacies and nuances involved. It would also provide an opportunity to identify potential pitfalls and challenges that arise with increased complexity.

Additionally, incorporating feedback from stakeholders and experts in the field can help shape the evolution of the models and ensure they align with real-world scenarios. For this purpose, the integration of knowledge from various disciplines is key. In this dissertation, interdisciplinarity has been a fundamental element, integrating insights from epidemiology, public health, econometrics, and the medical field to address questions related to early-life health inequalities. Moving forward, future research on health inequalities should continue to embrace interdisciplinary knowledge as a promising avenue for making progress in the field.

By fostering ongoing interdisciplinary efforts and gradually incorporating complexity, we can actively work towards achieving a more comprehensive understanding of the drivers and dynamics underlying health inequalities. This effort will, in turn, contribute significantly to the development of policies and interventions to effectively address the root causes and mitigate health disparities on a broader scale. In the subsequent section, I comment on the potential policy implications that arise from the findings presented in this dissertation.

9.3 IMPLICATIONS FOR POLICY

The findings of this dissertation have important policy implications for improving early-life health outcomes and reducing health inequalities. First, there is a need to continue public health policy efforts to narrow the gap between the most and the least advantaged populations. This requires that future policies and interventions channel resources to ensure the access of disadvantaged populations to the benefits of the intervention in question. Such a task has been proven to be challenging as disadvantaged populations are often hard to reach at an individual level, but intervening at the area level may prove more effective.[37]

While the idea of implementing interventions at the neighbourhood level to improve population health is not new, recent years have witnessed various municipalities in the Netherlands, such as Rotterdam, enacting interventions specifically targeted at disadvantaged neighbourhoods to enhance the health of their residents. However, despite these local efforts, the role of neighbourhoods continues to receive limited attention in nation-wide policy implementations.

For instance, the policy program *Kansrijke Start ('Promising start')*,[38] which focuses on the first 1000 days of life, currently provides minimal attention to the influence of the environment and neighbourhoods on early-life health outcomes. The program primarily focuses on individual-level risk factors and interventions which are undoubtedly important. However, it is also crucial to consider the (neighbourhood) environmental factors that children are exposed to even before birth. Neglecting the significance of neighbourhood environments in early-life health disparities overlooks a critical aspect of improving population health. Thus, there is a need for large-scale policies to recognize and address the relevance of neighbourhood environments in shaping health outcomes, especially for those living in disadvantaged areas.

Neighbourhoods can serve as a valuable tool for selecting target populations for policy interventions. In the Dutch context, measures of neighbourhood socioeconomic conditions have been employed to identify specific populations for interventions (see Vidiella et al.[39]). In this regard, results from this dissertation highlight the potential of longitudinal measures of neighbourhood SES to provide additional insights to the ones from cross-sectional measures when looking into health inequalities By relying solely on cross-sectional cut-offs to define low SES neighbourhoods, certain policies may overlook areas that have recently experienced improvements in socioeconomic conditions and might still need support (at least temporarily). Therefore, we recommend the utilization of longitudinal measures of neighbourhood SES not only to delineate target populations for public health policy interventions but also to monitor health inequalities and assess the effectiveness of public health interventions.

Neighbourhoods can also provide an opportunity to intervene on health-related area characteristics that could be influenced by policy decisions. From a public health standpoint, potential interventions to consider would include those aimed at strengthening the social context of a neighbourhood. One might think of programmes that for example stimulate or enable activities at the neighbourhood level and meeting opportunities between residents. Additionally, area-level interventions focused on reducing crime rates, particularly those related to crimes against property and public order, may also be effective in improving health outcomes in low SES areas and helping on narrowing the gap between most and least disadvantaged groups. However, it is important to note that while the results of this dissertation suggest a mediation effect of neighbourhood social characteristics (crime and social environment),[9,10] the limited research in this area warrants caution in drawing policy implications. Further research is necessary to establish a more comprehensive understanding of the role of neighbourhood-level mediators and be able to pinpoint which factors, and which strategies may have the largest influence on health outcomes.

There is also an urgent need for action regarding adaptation strategies to address extreme temperature events. The majority of current heat action plans in European Countries, including the Netherlands, largely overlook pregnant women as a target group.[40] Considering the projected increase in the frequency of extreme temperature events, it would be advisable for national-level heat prevention measures to expand their recommendations to specifically include the antenatal period. By incorporating pregnant women into heat action plans, policymakers can promote proactive measures to protect the health and well-being of this vulnerable population during extreme heat events.

Furthermore, our results underscore the differential impact of extreme temperatures on early-life health outcomes across various socioeconomic strata, potentially exacerbating existing inequalities. A first action line would be the promotion of research to better understand the underlying factors driving these disparities. Building upon these findings, targeted policy interventions can be developed to mitigate the adverse effects of extreme temperatures among disadvantaged groups. Such policies may include enhancing the built environment and increasing the quantity and quality of green spaces in these areas, providing protective measures against extreme heat and ultimately improving birth outcomes for residents. Additionally, policies aimed at improving work conditions for mothers from low SES backgrounds may help mitigate the negative effects of ambient temperature on early-life health.

Healthcare providers also have a crucial role to play in this regard. For instance, they can consider issuing recommendations to pregnant women, with a specific focus on vulnerable groups, on how to take preventive measures against extreme temperatures. By doing so, healthcare providers can enhance their ability to help pregnant women mitigate potential risks associated with extreme temperatures.

Finally, the findings of this dissertation also suggest that policies can have differential effects across population groups and may even widen health inequalities. Therefore, policies must be carefully monitored to ensure that they benefit all population groups equally. Finally, the mechanisms underlying the observed effects of policies must be assessed to understand the channels through which policies influence health and the reasons why interventions have adverse consequences for particular groups in the population.

9.4 CONCLUSION

In conclusion, this thesis contributes to the understanding of early-life health inequality and its drivers by assessing the evolution of inequalities in the Netherlands, providing insights into potential mechanisms, and by investigating the role of SES as moderator for the effect of external exposures on early-life health. While there have been overall improvements in perinatal health in the Netherlands, health inequalities remain persistent. Thus, interventions targeted at reducing inequalities are required to reach population health goals.

Neighbourhoods offer a valuable opportunity for targeted interventions, allowing for the improvement of factors such as neighbourhood crime and the social environment through policy interventions. Moreover, our research reveals that health inequalities can also arise from the complex interplay between socioeconomic status and events outside of individuals' control, such as policy implementation and climatologic factors. Future research should continue to prioritize addressing the underlying drivers of early-life health inequalities. By adopting an interdisciplinary approach, exploring the dynamic interactions between individual and area-level factors, and utilizing advanced techniques to leverage registry data for causal inference, we can deepen our understanding and inform more effective strategies to reduce health inequalities at their earliest origin.

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HOŞGELDINIZ

Chapter 10

Summary

SUMMARY

Health differences between the most and least advantaged become apparent right from the earliest stages of life, manifesting as adverse birth outcomes. The overarching aim of this thesis was to delve into the complex relationship between socioeconomic status (SES) and early-life health, with a particular focus on the role played by neighbourhood-level socioeconomic conditions.

Part 1 describes inequalities in key perinatal outcomes by neighbourhood SES and focused on their evolution over time in the Netherlands.

In **Chapter 2**, we studied how inequalities in adverse birth outcomes have changed over time across different levels of neighbourhood deprivation in the Netherlands, using the national perinatal registry. It was observed that between 2003 and 2017, the prevalence of adverse outcomes consistently decreased over time, being the most deprived areas the ones showing the largest improvements. Although absolute inequalities seemed to narrow, relative inequalities in birth outcomes by neighbourhood deprivation level remained fairly constant.

Chapter 3 describes the relationship between longitudinal measures of neighbourhood SES and birth outcomes in the Netherlands. The findings showed that women living in neighbourhoods with disadvantaged SES trajectories (e.g., neighbourhoods in decline) were more likely to experience adverse birth outcomes. Results from this study indicate that longitudinal measures of neighbourhood SES can offer additional insights beyond those provided by cross-sectional measures, particularly when determining the target population for public health interventions.

Part 2 investigates the role of specific neighbourhood characteristics as mechanisms that can potentially explain the relationship between neighbourhood SES and birth outcomes.

A didactic application of the mediational g-formula in perinatal health inequalities research was provided in **Chapter 4**. In the illustrative example, we made use of the linkage between the national perinatal registry and routinely collected sociodemographic data to investigate whether neighbourhood social environment mediates the relationship between neighbourhood SES and early-life health. The results showed that a meaningful share (11.4%) of the observed relationship was mediated by neighbourhood social environment. In **Chapter 5**, the role of neighbourhood crime as mediator for the relationship between neighbourhood SES and adverse birth outcomes was investigated. In this nationwide study, we found that neighbourhood crime accounted for a substantive share (up to 28%) of the relationship of interest. The most relevant mechanisms were crimes against property and crimes against public order.

Part 3 explores how prenatal exposure to external factors influences birth outcomes and examines variations in the effects of these exposures based on different levels of SES.

In **Chapter 6**, we examined the effect of prenatal exposure to extreme temperatures on birth outcomes in the Netherlands. The findings showed that exposure to an additional hot day (mean temperature > 20 °C), relative to a reference range, led to increased risk of adverse birth outcomes. Moreover, exposure during the second trimester to an additional cold day (< -4 °C) also had a detrimental impact on early-life health. The observed effects were the most detrimental for births in low-SES households.

By means of a quasi-experimental design, we investigated in **Chapter 7** the impact that the first COVID-19 mitigation measures implemented in the Netherlands had on preterm birth. This study made use of data from the national neonatal dried blood spot screening programme. The findings showed that the initial implementation of COVID-19 mitigation measures led to a substantial drop in preterm births in the subsequent months. Moreover, we found some evidence that the reductions in preterm birth predominantly occurred in those living in high-SES neighbourhoods.

In **Chapter 8**, we discussed the potential of using natural experiments to assess the effects of public health policies. We highlighted the results of a specific study conducted in Switzerland that employed a natural experiment to explore the effects of extending health insurance coverage on birth outcomes, specifically focusing on the full coverage of illness-related costs during pregnancy. Furthermore, we emphasized the importance of thoroughly assessing the conditions of validity and potential biases in such approaches. Lastly, we addressed the varying effects of the policy expansion on birth outcomes within different socioeconomic subgroups, which could have contributed to a widening of health disparities.

SAMENVATTING

Verschillen in gezondheid tussen de meest en minst bevoorrechten zijn al zichtbaar in het jonge leven, zich uitend in ongunstige geboorte-uitkomsten. Het hoofddoel van dit proefschrift is het verkrijgen van een uitgebreider begrip ten aanzien van de complexe relaties tussen sociaaleconomische status (SES) en gezondheid rond de geboorte, met speciale aandacht voor de rol van sociaaleconomische omstandigheden op buurtniveau.

In **Deel 1** worden de ongelijkheden in de voornaamste ongunstige zwangerschapsuitkomsten beschreven en vergeleken volgens de SES van de buurt. Hierbij wordt er dieper ingegaan op hoe deze ongelijkheden evolueren met de tijd in Nederland.

In **Hoofdstuk 2** bestuderen we hoe de ongelijkheden in geboorte-uitkomsten evolueren in de tijd en voor verschillende niveaus van armoede in buurten in Nederland, dit gebruikmakende van de Perinatale Registratie Nederland. Er werd gevonden dat tussen 2003 en 2017 de ongunstige geboorte-uitkomsten gestaag verminderden in de tijd, waarbij de minst bevoorrechte gebieden de grootste vooruitgang boekten. Hoewel de verschillen in absolute zin een globale vermindering aantonen, blijven, relatief gezien, de ongelijkheden tussen de verschillende armoedeniveaus bij benadering gelijk.

Hoofdstuk 3 beschrijft de relatie tussen longitudinale metingen van de SES van de buurt en perinatale uitkomsten in Nederland. De resultaten tonen aan dat vrouwen die in buurten met lage SES trajecten (bijv. buurten in verval) wonen, vaker nadelige geboorte-uitkomsten ervaren. Bovendien toont deze studie aan dat longitudinale metingen van de SES van de buurt inzichten kunnen verschaffen die verder reiken dan deze verkregen uit cross-sectionele metingen. Deze informatie kan gebruikt worden voor het bepalen van de doelgroep voor interventies in de volksgezondheid.

Deel 2 onderzoekt de rol die specifieke buurtkarakteristieken spelen in de relatie tussen ongunstige geboorte-uitkomsten en de SES van de buurt.

Een didactische toepassing van de *mediational g-formula* in onderzoek naar ongelijkheden in perinatale gezondheid wordt gegeven in **Hoofdstuk 4**. In dit illustratief voorbeeld maken we gebruik van een koppeling tussen de landelijke perinatale registratie en sociaal-demografische data, om te onderzoeken of sociale omgevingsfactoren de link kunnen verklaren tussen de SES van de buurt en geboorte-uitkomsten. De resultaten geven aan dat de sociale omgeving verantwoordelijk is voor een aanzienlijk deel van de waargenomen relatie (11,4%). In **Hoofdstuk 5** wordt de rol van buurtcriminaliteit als mediator voor de relatie tussen buurt-SES en perinatale gezondheid onderzocht. In dit onderzoek op nationaal niveau vonden we dat buurtcriminaliteit een substantiële aandeel (tot 28%) heeft in de relatie tussen de SES van de buurt en ongunstige geboorte-uitkomsten. De meest relevante werkingsmechanismen hierbij waren vermogenscriminaliteit en verstoring van de openbare orde.

Deel 3 onderzoekt hoe prenatale blootstelling aan externe factoren invloed heeft op geboorte-uitkomsten en in hoeverre de effecten van deze blootstellingen variëren op basis van verschillende niveaus van SES.

In **Hoofdstuk 6** onderzochten we het effect van prenatale blootstelling aan extreme buitentemperaturen op geboorte uitkomsten in Nederland. Hierbij werd gevonden dat additionele blootstelling aan elke warme dag (gemiddelde temperatuur > 20 °C), relatief ten opzichte van een referentie-bereik, de kans verhoogde op nadelige geboorte-uitkomsten. Tevens geeft blootstelling aan een additionele koude dag gedurende het tweede trimester van de zwangerschap (< -4 °C) ook een negatieve impact op de perinatale gezondheid. Deze effecten waren het meest nadelig voor geboortes in gezinnen met een lage SES.

Door middel van een quasi-experimentele benadering onderzochten we in **Hoofdstuk 7** de impact die de eerste COVID-19-maatregelen in Nederland hadden op de incidentie van vroeggeboorte. In deze studie werd gebruik gemaakt van gegevens uit de nationale gegevensbank voor neonatale hielprikscreening in Nederland. De resultaten tonen aan dat de initiële COVID-19-maatregelen aanleiding gaven tot een substantiële verlaging van vroeggeboortes in de eerste maanden. Verder vonden we aanwijzingen dat deze daling vooral merkbaar was voor de groepswoonwijken met een hoge SES.

In **Hoofdstuk 8** bespreken we het gebruik van natuurlijke experimenten om de effecten van volksgezondheidsbeleid te onderzoeken. We bespreken de resultaten van een specifieke studie uitgevoerd in Zwitserland die een natuurlijk experiment gebruikte om de effecten van het uitbreiden van de ziektekostenverzekering op geboorte-uitkomsten te onderzoeken, waarbij werd gefocust op de volledige dekking van kosten gerelateerd aan ziekte tijdens de zwangerschap. Daarnaast benadrukken we het belang van grondige beoordeling van de voorwaarden van geldigheid en mogelijke vertekeningen in dergelijke benaderingen. Ten slotte behandelden we de variërende effecten van de uitbreiding van het beleid op geboorte-uitkomsten binnen verschillende sociaaleconomische subgroepen, wat heeft bijgedragen aan een versterking van bestaande gezondheidsongelijkheden.


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Appendices

Portfolio

List of publications

Contributing authors

Acknowledgements

Curriculum Vitae

PHD PORTFOLIO

Name: Lizbeth Burgos Ochoa
Erasmus MC Departmzent: Obstetrics and Gynaecology
PhD period: January 2019 - December 2022

Promotors: E.A.P. Steegers, T.G.M. Van Ourti
Co-promotors: L.C.M. Bertens, J.V. Been

1. Courses

	Year	Workload (ECTS)
Scientific Integrity	2021	0,3
Academic writing	2021	0,6
Empirical Policy Evaluation in Health	2020	3,0
Demographic Methods	2020	3,0
Topics in Digital and Computational Demography	2020	3,0
Population Health	2020	6,0
Data visualization – the art/skill cocktail	2021	3,0
Advanced methods for causal inference with observational data	2021	3,0
Supercomputing with R for Social Scientists	2022	0,3
Advanced Analysis of Genome-wide Association Studies ESP74	2022	1,4
Machine Learning and Interpretable Machine Learning with R	2022	0,3

2. Symposiums and conferences

Symposium on Classification Methods in the Social and Behavioral Sciences	2019	0,3
Smarter Choices for Better Health Conference (Oral presentation)	2019	1,1
16th World Congress on Public Health (Oral presentation)	2020	1,5
PHDS Annual Academy 2020 (Oral presentation)	2020	1,4
PHDS Annual Academy 2021 (Poster presentation)	2021	1,4
Pandemic Babies? The Covid-19 Pandemic and Its Impact on Fertility and Family Dynamics (Poster presentation)	2021	1,1
15th European Public Health Conference (Oral presentation)	2022	1,5
PHDS graduate workshop 2022 (Oral presentation)	2022	1,1
PHDS Annual Academy 2022 (Poster presentation)	2022	1,4
Dutch Demography Day 2022 (Oral presentation)	2022	1,1

3. Grants

- Erasmus Trustfonds,. 2020. €12.5K

Proposal: "Effects of the London Low Emission Zone on perinatal Health in Greater London." (Co-applicant)

- ZonMw, 2022, €200K

Proposal: "PREgnancy outcomes during a PAndemic REsponse (PREPARE)" (Co-applicant)

- Strong Babies, 2023, €10K

Proposal: " Assessing the complex interplay between ambient temperature, air pollution, and housing conditions in relation to inequalities in preterm birth" (Co-applicant)

4. Others

Member of the 2020 cohort of The International Max Planck Research School for Population, Health and Data Science (IMPRS-PHDS).

A

LIST OF PUBLICATIONS

Burgos Ochoa L., Rijnhart J.M., Penninx B.W., Wardenaar K.J., Twisk J.W.R. & Heymans M.W., (2018). Comparison of Methods to perform mediation analysis with time-to-event outcomes. Statistica Neerlandica. 74(1), pp.72-91.

Bertens L.C.M., **Burgos Ochoa L.**, Van Ourti T., Steegers, E.A.P., and Been, J.V., (2020). Persisting inequalities in birth outcomes related to neighbourhood deprivation. Journal of Epidemiology and Community Health. 74 pp. 232-239.

Been J.V., **Burgos Ochoa, L.**, Bertens, L.C.M., Steegers, E.A.P., Schoenmakers S., & Reiss, I., (2020). Impact of COVID-19 mitigation measures on the incidence of preterm birth: a national quasi-experimental study. The Lancet Public Health. 5(11), pp. e604-e611.

Burgos Ochoa L., Bertens, L.C.M., Garcia-Gomez, P., Van Ourti, T., Steegers, E.A. P. and Been, J.V., (2021). Association of neighbourhood socioeconomic trajectories with preterm birth and small-for-gestational-age in the Netherlands: a nationwide population-based study. The Lancet Regional Health-Europe. 10.

Burgos Ochoa L., Brockway M., Stock S.J., Been J.V. COVID-19 and maternal and perinatal outcomes. (2021). The Lancet Global Health. 9, no. 8 (2021), pp. e1063-e1064.

Burgos Ochoa L., and Been, J.V., (2023). Use of natural experiments to evaluate public health policy. The Lancet Public Health, 8(3), pp.e164-e165.

Burgos Ochoa L., van Der Meer, L., Waelput, A.J., Been, J.V. and Bertens, L.C.M., 2023. Neighbourhood-related socioeconomic perinatal health inequalities: An illustration of the mediational g-formula and considerations for the big data context. Paediatric and Perinatal Epidemiology.

van der Vliet–Torij, H.H., Bertens, L.C.M., **Burgos Ochoa, L.**, Gouman, M.J.B.M., Posthumus, A.G. and Steegers, E.A.P., (2023). Type of deliveries supported by Dutch clinical midwives. Midwifery, 124, pp. 103744.

Burgos Ochoa, L., Bijlsma, M.J., Steegers, E.A., Been, J.V. and Bertens, L.C.M., (2023). Does Neighborhood Crime Mediate the Relationship Between Neighborhood Socioeconomic Status and Birth Outcomes? An Application of the Mediational G-Formula. American Journal of Epidemiology, 192(6), pp.939-948.

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CURRICULUM VITAE

Lizbeth Burgos Ochoa was born on 18 June 1992 in Mexico City but grew up in the city of Merida, Yucatan. She completed her primary and secondary education at Escuela Modelo, one of the oldest educational institutions in Yucatan, and will always consider herself a “modelista”. After graduating, she started her Bachelor’s degree in Psychology at Universidad Autonoma de Yucatan. During her undergraduate studies, thanks to the Santander Scholarship, Lizbeth had the opportunity to study for a six-month period at Universidad de Malaga in 2014.

Following the completion of her Bachelor’s degree, Lizbeth was granted the Utrecht Excellence Scholarship, which allowed her to pursue the Research Master in Methodology and Statistics for the Behavioural, Biomedical, and Social Sciences at Utrecht University (2016-2018). As part of her Master’s program, Lizbeth completed a research internship at Amsterdam UMC, participating in the project titled “Comparison of methods to integrate mediation and survival analysis.”

In January 2019, Lizbeth began her journey as a PhD student at the Erasmus MC-Sophia Children’s Hospital in Rotterdam, the Netherlands, under the supervision of Prof. Eric Steegers (Erasmus MC), Loes Bertens (Erasmus MC), Jasper Been (Erasmus MC), and Prof. Tom van Ourti (Erasmus School of Economics). Her doctoral research focused on early-life health inequalities, with a particular emphasis on neighbourhood socioeconomic circumstances.

This year, she joined the Department of Methodology and Statistics at Tilburg University as an Assistant Professor to conduct research on g-methods and causal inference with observational data.

This photo was taken in the neighbourhood of Kanaleneiland, Utrecht, where I lived for some years. As an area undergoing transformation, Kanaleneiland provided a fair share of inspiration behind this thesis.