

From Department of Medicine, Solna
Karolinska Institutet, Stockholm, Sweden

Psychosocial Factors and Preterm Birth: National Register-Based Studies

Can Liu



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Psychosocial Factors and Preterm Birth: National Register-Based Studies

Thesis for Doctoral Degree (Ph.D.)

By

Can Liu

Principal Supervisor:

Professor Anders Hjern
Karolinska Institutet
Department of Medicine, Solna
Division of Clinical Epidemiology
Stockholm University
Centre for Health Equity Studies

Co-supervisor(s):

Professor Sven Cnattingius
Karolinska Institutet
Department of Medicine, Solna
Division of Clinical Epidemiology

Professor Viveca Östberg
Stockholm University
Centre for Health Equity Studies

Opponent:

Professor Berit Schei
Norwegian University of Science and Technology
(NTNU)
Department of Public Health and Nursing
St. Olavs Hospital, Trondheim University Hospital
Department of Obstetrics and Gynecology

Examination Board:

Associate Anna Bergström
Karolinska Institutet
Institute of Environmental Medicine (IMM)

Professor Göran Kecklund
Stockholm University
Stress Research Institute

Associate Professor Susanne Georgsson
Sophiahemmet University

博学而笃志，切问而近思，仁在其中矣。

——论语·子张

Try to learn something about everything and everything about something.

– Thomas Henry Huxley

ABSTRACT

Every year, approximately fifteen million infants are born preterm, defined as prior to 37 gestational weeks. Preterm birth is the number one cause of neonatal mortality, which kills more than one million babies every year globally. However, its aetiology remains largely unclear, hindering effective preventions. Besides genetic predisposition, the most commonly studied factors are maternal behavioural or clinical indicators measured shortly before or during pregnancy. Meanwhile, as a population health indicator in itself, preterm birth rates vary to a large extent both within and between countries, even among high-income countries. The mechanisms and processes generating unequal preterm birth rates await elucidation and action.

With an ecological perspective and a focus on the psychosocial mechanism of human disease, this thesis considers the causes of preterm birth as being embedded in the mother's living circumstances across her lifespan. To better understand the pathogenesis of preterm birth, this thesis aims to address the relationship between a mother's adverse social environment and the preterm birth of her offspring, by investigating several indicators of her living situation at different life stages. For all studies included in this thesis, this is made possible by linking data from various Swedish National Registers through the use of the personal identification number and obtaining information on all parents of infants born between 1987 and 2012.

Study I showed that severe early life adverse experience, marked by being placed in out-of-home care, was associated with preterm delivery later in life, independent of a woman's genetic or prenatal predisposition to delivering preterm. Multiple social and behavioural trajectories are hypothetically involved, including the priming of her stress response system.

The partner (expecting father of the infant) was investigated in Studies II and III, as an integral part of the psychosocial environment later in life. Depression (marked by specialized hospital care or filled prescriptions of antidepressant) and aggression (marked by convicted violent crimes) of the partner were both associated with an increased risk of preterm birth. Extensive adjustment for potential maternal confounding factors did not appreciably account for these associations.

Study IV investigated the risk of preterm birth with larger contextual changes experienced by refugee women. Migration, especially as an asylum seeker fleeing from one's homeland, is a considerable stressor that has a potentially long-lasting impact on the maternal hormonal

profile. Compared to babies born in the second year of residence, those born sooner after settlement were more likely to be preterm.

In summary, the risk of offspring preterm birth was associated with psychosocial adversities on individual, interpersonal, and macro-social levels at various stages across the lifecourse. Early life, both of the woman and of her offspring, was highlighted as being sensitive to psychosocial adversities. Meanwhile, chronic strain in day-to-day life, especially with the significant other, was suggested to impact the risk of preterm birth significantly.

Overall, the findings of these studies highlight how social disadvantages can ‘get under the skin’, taking their toll on both the affected individual and on future generations. Given this, a psychosocial approach with an extended preconception lifecourse may shed light onto future explorations of the aetiology of preterm birth. Moreover, the interdependence and interactions with other key individuals in one’s life need to be incorporated into future research agendas.

Understanding the maternal and child health in a cohesive framework incorporating social, biological, and time perspectives may help to integrate a continuum of maternal and child care. Healthcare providers are encouraged to consider a family-centred approach, which acknowledges and treats the mother, father and the infant as a triad.

LIST OF SCIENTIFIC PAPERS

- I. Liu C, Vinnerljung B, Östberg V, Gauffin K, Juarez S, Cnattingius S, Hjern A. Out of home care in childhood and preterm delivery: a Swedish national intergenerational cohort study. *Submitted manuscript*
- II. Liu C, Cnattingius S, Bergström M, Östberg V, Hjern A. Prenatal parental depression and preterm birth: a national cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2016 Nov;123(12):1973–82.
- III. Liu C, Långström N, Ekéus C, Frisell T, Cnattingius S, Hjern A. Paternal violent criminality and preterm birth: a Swedish national cohort study. *Manuscript*.
- IV. Liu C, Urquia M, Cnattingius S, Hjern A. Migration and preterm birth in war refugees: a Swedish cohort study. *Eur J Epidemiol*. Springer Netherlands; 2014 Feb;29(2):141–3.

CONTENTS

1	Introduction	1
2	Background	1
2.1	Definition and classification of preterm birth	1
2.2	The epidemiology and health outcomes of preterm birth	2
2.3	Known risk factors for preterm birth	3
2.4	The aetiology of preterm birth	3
2.4.1	Spontaneous preterm birth	3
2.4.2	Medically indicated preterm birth	5
2.5	Psychosocial mechanisms	5
2.5.1	Biological embedding of early experience	6
2.5.2	Social relations as sources of stress and support	7
2.6	Theoretical frameworks of maternal and child health	8
3	Aim and research questions	10
4	Methods	12
4.1	Study design and data materials	12
4.2	Study populations	14
4.3	Independent variables	17
4.4	Dependent variables	18
4.5	Confounding variables	18
4.6	Statistical analysis	19
5	Results	21
5.1	Adverse early life experience	21
5.2	Adverse partner relationships	23
5.2.1	Depressive partner	24
5.2.2	Aggressive partner	25
5.2.3	Subtypes of preterm birth and different indicators of adverse partner relationship	28
5.3	Time after resettlement in the host country	29
6	Discussion	31
6.1	Summary of results	31
6.2	Potential mechanisms	31
6.3	Methodological considerations	33
6.3.1	Information validity	33
6.3.2	Statistical inference and confounding	34
6.3.3	External validity	35
6.4	Implications	35
6.4.1	Population and individual health implications	35
6.4.2	Social and ecological factors	36
6.5	Ethical considerations	37
6.6	Future research	38

7	Chinese abstract (中文摘要)	41
8	Acknowledgements	43
9	References	45

LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemicals
BMI	Body mass index
CRH	Corticotropin-releasing hormone
G	Generation
HPA	Hypothalamic pituitary adrenocortical
ICD	International Classification of Diseases
IPV	Intimate partner violence
LISA	Longitudinal Integrated Database for Health Insurance and Labour Market Studies
NPR	The National Patient Register
OHC	Out of home care
OR	Odds ratio
PPROM	Preterm prelabour rupture of membrane
SDG	Sustainable Development Goals

1 INTRODUCTION

Compared to other primates, human reproduction is unique. Our neonates are proportionally larger in size and yet developmentally premature. Consequently, it is almost impossible for a human mother to safely deliver and care for the neonate all by herself as other primate mothers do. Thus, a prominent feature of human reproduction is the need for social relationships (Rosenberg & Trevathan 2002).

Babies born preterm (<37 gestational weeks) are more vulnerable to death and ill health. Despite tremendous progress in the care of preterm born babies, we are still unclear as to why and how most cases of preterm births occur (World Health Organization 2012).

This knowledge gap on the aetiology of preterm birth is the major obstacle towards effective prevention (Yamey et al. 2016). The evidence-based global solution primarily seeks to identify biological pathways predicting an increased risk of preterm birth (Lackritz et al. 2013). Undeniably, such attempts can better equip clinicians to deal with each individual case, given that there are few key purely biological pathways involved. However, environmental factors also contribute to the multifactorial origins of preterm birth, as evidenced by preterm birth rates varying between countries, socioeconomic groups and over historical time (Vågerö et al. 1999; Beck et al. 2010; Blencowe et al. 2012; World Health Organization 2012; Richards et al. 2016).

Physical and social environmental influences over an extended period of time are not only some missing pieces in the jigsaw puzzle of preterm birth aetiology, but may also represent important contexts of various processes leading to preterm birth. To better understand the influence of the physical and social environment, this thesis investigates the individual's context of living, examining several psychosocial factors over a longer time span that surrounding the pregnancy.

2 BACKGROUND

2.1 DEFINITION AND CLASSIFICATION OF PRETERM BIRTH

Preterm birth is defined as a birth occurring before 37 weeks of gestation (Goldenberg et al. 2008). Very preterm (before 32 gestational weeks) comprises about 20% of preterm births, while the remaining 80% are moderate preterm (32 to 36 gestational weeks) (Goldenberg et

al. 2008; Ananth et al. 2009). Despite the fact that this classification of preterm birth based on gestational age is well accepted in both clinical practice and research, the suggested cut-off points are arbitrarily set on the continuous duration of gestation. Additionally, the lower cut-off of gestational age for preterm birth is not definitive but rather depends on the youngest gestational age at which the foetus could survive under existing conditions and services.

The aetiological subtypes of preterm birth are generally defined as spontaneous onset of delivery, preterm pre-labour rupture of the membrane (PPROM), and medically indicated preterm birth. The first two categories are commonly unified as spontaneous preterm birth, accounting for 70% of all preterm births, while the remaining 30% comprise of medically indicated preterm deliveries (Goldenberg et al. 2008).

2.2 THE EPIDEMIOLOGY AND HEALTH OUTCOMES OF PRETERM BIRTH

Globally, more than one in ten neonates is born preterm. The overall preterm birth rate varies largely between different countries, particularly in low- and middle-income countries. (World Health Organization 2012). There is also large variation among high-income countries (Euro-Peristat Project with SCPE and EUROCAT 2013), for example, one in eight babies born in the United States were born preterm, compared to one in sixteen in Sweden in 2004 (MacDorman & Mathews 2010). There is also a huge survival gap of the extremely preterm (before 28 gestational weeks) babies in low- and high- income settings (World Health Organization 2012). Across time, there has been a slight increase in the rate of preterm birth, which consists of an increasing incidence of medically indicated preterm births and a decreasing incidence of spontaneous preterm births, especially PPRM (Goldenberg et al. 2008). Though, more recent data from several high-income countries showed that time trend of late singleton preterm birth also varies by country (Richards et al. 2016).

Approximately 50% to 75% of neonatal deaths are among those born preterm (World Health Organization 2012). Compared to moderate preterm, very preterm infants are considerably more vulnerable; their chances of survival also vary greatly, from below 10% at 22 weeks to almost 100% at 31 gestational weeks (World Health Organization 2012).

Survivors of preterm birth bear long-term health burdens, including neurodevelopmental, psychiatric and behavioural sequelae, as well as cardiovascular diseases (Bhutta et al. 2002; Saigal & Doyle 2008; Lindström et al. 2009; Lindström et al. 2011; World Health Organization 2012). Even babies born moderately preterm have a higher risk of morbidity and mortality, compared to individuals born at term (M. S. Kramer et al. 2000).

2.3 KNOWN RISK FACTORS FOR PRETERM BIRTH

Many characteristics of the mother are associated with an increased risk of preterm birth. Maternal genetic predisposition to preterm birth is suggested to explain about a quarter of the variation in risk of preterm birth (Wilcox et al. 2008; Svensson et al. 2009). Additionally, sociodemographic and clinical indicators are important markers, for example, maternal age, maternal chronic disease and related medications, maternal infections, prior pregnancy complications, maternal depressive mood, and short inter-pregnancy interval (Goldenberg et al. 2008). Maternal biometrics, such as short maternal stature, maternal BMI (indicating overweight or obesity) (Han et al. 2012; Cnattingius et al. 2013) as well as lifestyle factors, including smoking or excessive alcohol consumption, are also associated with an increased risk of preterm birth (Cnattingius 2004; Albertsen et al. 2004).

Other than these risk indicators, which are commonly measured during pregnancy, social determinants of health such as ethnicity and socioeconomic position, also impact preterm birth (Vågerö et al. 1999; M. S. Kramer et al. 2001; Lu & Chen 2004). While the link between lower socioeconomic position and preterm birth is likely explained by some of the risk indicators listed above, how the social determinants get under the mother's skin and into the womb needs to be further elucidated.

2.4 THE AETIOLOGY OF PRETERM BIRTH

Before proposing the possible mechanisms linking environmental factors and preterm birth, a summary of known biological mechanisms of preterm birth is provided below to lay the foundation for the epidemiological approach used in this thesis. Spontaneous and medically indicated preterm birth are listed separately below, although the two clinical subtypes may share some common aetiologies (Ananth et al. 2009). It may be that spontaneous preterm births, which comprise the majority of preterm births, share some of the mechanisms of a normal term spontaneous labour, while medically indicated preterm births result directly from pregnancy-related complications.

2.4.1 Spontaneous preterm birth

Understanding the mechanism of the onset of term labour in humans helps to elucidate the aetiology of preterm birth, in particular, spontaneous preterm birth. While exactly how the uterus switches from quiescence to labour activity remains uncertain (Vidaeff & Ramin 2008),

the process is believed to be regulated by joint signals from the mother, the placenta, and the foetus, in which the neuroendocrine system plays a key role (Wadhwa 2005).

The corticotropin-releasing hormone (CRH) is a stress hormone most commonly produced in hypothalamus; during pregnancy, this hormone is mainly produced by the placenta and is a key player in regulating the timing of delivery onset. CRH secretion increases with the progress of gestation; with a higher and faster increase in CRH being associated with shorter gestational age (Hobel et al. 1999; Vidaeff & Ramin 2008; M. S. Kramer et al. 2009). The downstream regulation of the endocrine and immune systems following HPA activation are described in detail below.

2.4.1.1 Regulation through sex steroids

The sex steroids oestradiol and progesterone both play a key role in regulating the periodic changes of the endometrium in preparation for implantation. While progesterone is important for maintaining gestation, oestradiol has the opposite effect (Vidaeff & Ramin 2008). Additionally, progesterone maintains cervical tissue competence and thus is important in regulating the timing of birth, thus has been considered as a preterm birth prevention measure for high-risk women (Fonseca et al. 2007). However, the effectiveness of progesterone supplementation is questionable when considering publication bias of randomized trials with positive results (Prior et al. 2017).

2.4.1.2 Regulation through the immune system

All of the milestones of reproduction, such as ovulation, menstruation, implantation, and birth, involve tissue injury and remodelling which is regulated through inflammatory pathways (Jabbour et al. 2009). This regulation is steered through the integrated endocrine and immune systems counterbalancing pro- and anti-inflammatory pathways (Vidaeff & Ramin 2008). Activation of the hypothalamic-pituitary-adrenocortical (HPA) axis may alter the balance of the inflammatory pathways in the immune system. Up-regulation of pro-inflammatory pathways may initiate the onset of labour (Jabbour et al. 2009), possibly by initiating local inflammatory process such as uterine contraction, cervix softening, and reduced membrane consistency (Peltier 2003). Thus, early activation of the pro-inflammatory pathway is a potential explanation for the spontaneous onset of preterm delivery, which is supported by epidemiological research showing the association between plasma CRH in the second trimester of pregnancy and spontaneous preterm birth (M. S. Kramer et al. 2009).

2.4.2 Medically indicated preterm birth

Medically indicated preterm birth has increased over the years, possibly affected by advancing maternal age and increasing multiple births resulted from assisted conception, especially in high-income countries (World Health Organization 2012). Based on medical and non-medical reasons, clinician-initiated obstetric intervention may also affect the occurrence of medically indicated preterm birth (Richards et al. 2016).

Preeclampsia, foetal growth restriction, and placental abruption are common pathologies leading to a medically indicated preterm birth. These conditions also share some common aetiology, often referred to as ‘placental dysfunction disorders’ (Cnattingius & Stephansson 2011), with defective spiral artery remodelling and deep placentation being the potential pathological mechanism (Brosens et al. 2011). Paternal origin aetiology is also a suggested mechanism, based on findings from a large population-based study of preeclampsia (Wikström et al. 2011). The proportion of medically indicated preterm delivery is higher among women with overweight and obese status, compared to those with normal weight status (Goldenberg et al. 2008; Cnattingius et al. 2013).

Caesarean section, the most efficient life-saving method in antenatal care, has been steadily increasing since 1990 (Betrán et al. 2016). Although on the population level, a caesarean section rate over 10% has not been associated with better perinatal health outcomes (Ye et al. 2016; World Health Organization Human Reproduction Programme, 2015).

2.5 PSYCHOSOCIAL MECHANISMS

The previous section reviewed the biological process of preterm birth, the pathophysiology of which is important for understanding individual disease processes and for elucidating how determinants of preterm birth on the population level affect disease distribution. Among the internal physiological processes, the HPA axis not only plays a key role in pregnancy and initiation of delivery but also in the stress response system, which regulates internal functioning in adaptation to the external stimuli (Selye 1955). The stress response system might aid in our understanding of how internal physiological processes may fail to adjust to the ‘fundamental hostile external environment’ (Mackenbach 2006), which in turn may also help to elucidate social inequalities in health.

Although the HPA axis undergoes profound changes during pregnancy, empirical findings on clinical samples have suggested that baseline HPA activity is associated with the stress

response profile during pregnancy. Thus, the stress response system is a potential link between the physical or social environment and pregnancy outcomes (Wadhwa et al. 1996).

Stress and allostatic load

Hans Selye has described the biological reaction of organisms to stimuli and linked environmental demands (stressors) with the pathology of human diseases (Selye 1955). The stress process is initiated when the individual experiences a stimulus as demanding and responds to maintain the physiological and psychological balance (homeostasis) (Cannon 1935).

An individual's susceptibility to stress depends on their interpretation of a potential stressor (appraisal), a process in which the cognitive and emotional functions of the brain play a major role (Richard S Lazarus & Susan Folkman 1984). An individual's possibility to cope with a stressor is also dependent on these cognitive and emotional functions (Richard S Lazarus & Susan Folkman 1984), as well as available coping resources (Folkman & Lazarus 1980). Cognitive functions of the brain, which play a key role in stress appraisal and coping, are shaped by early life experiences and social environments (McEwen 2008; McEwen 2012). Thus, the health consequences of stress responses are largely affected by the individual's history and experiences, and are entrenched in their social situation (McEwen & Stellar 1993; McEwen 2008)

Exposure to persistent external demands over a prolonged period of time (chronic stress) causes the internal biological systems to fluctuate, whereby the neural, neuroendocrine and immune systems play key roles in regulation. Chronic stress involving constant adaptation to maintain homeostasis, lead to a 'wear and tear' effect (allostatic load), which predisposes the various organs to diseases and potential ill health outcomes (McEwen & Stellar 1993).

2.5.1 Biological embedding of early experience

The socially stratified external environment creates differences in living conditions and experiences over the lifecourse. It is well-established that deprivation in early life has a profound and long-term impact on health, wherein multiple biological pathways are involved (G. W. Evans et al. 2012).

In light of the robust and well-established social gradient in health (Marmot 2005), biological embedding has emerged as a theoretical process to help explain the gradient, whereby "differential human experiences systematically affect" health throughout the lifecourse

(Hertzman 2012; Hertzman 1999; Hertzman & Wiens 1996). HPA dysregulation was one of the first examples of biological embedding (Hertzman 1999). For example, as evidenced both in animal and human studies, care in early life could alter baseline HPA axis activity and predispose the adult stress response (Plotsky & Meaney 1993; Meaney 2003; Gunnar et al. 2001; Hertzman 2012).

This biological process of embedding is of course not limited to the stress response system. Hertzman has further elaborated his theory metaphorically by the “archaeology of biological embedding”, encompassing the social patterns of population health, cell and organ function, to genetic expression, from its surface stratum to the deep stratum (Hertzman 2012). From population level to cellular and molecular levels, the in-depth excavation of biological embedding also complimented the ecological framing of human development that was already proposed by Bronfenbrenner in 1970s (Bronfenbrenner 2009). From a developmental perspective, the ecological model decomposes the social and physical environment as a nested structure of micro-, meso-, exo- and macrosystems; the micro- and meso-systems describe the proximal environmental settings of the developing individual, such as family, school and the linkages between different contexts. The exo- and macrosystems describe how the indirect environmental settings relate to the individual, such as the parents’ workplace in relation to a child within the family. Macrosystems also describe the overarching socio-cultural features that affect processes in the microsystem (Bronfenbrenner 2009).

Time is also highlighted as a dimension of biological embedding. Experiences across the lifecourse may affect health via 1) a latent effect, in which the early life experience at sensitive period of development affects later life; 2) a pathway effect, in which the early life experience is a piece of a cascade process; and 3) a cumulative effect, whereby deprived social environment is thought to entail an accumulation of adversity (Hertzman 2012). In the ecological model of human development, time refers not only to the individual lifecourse but also the chronological time that characterises the environment (Bronfenbrenner 2009).

2.5.2 Social relations as sources of stress and support

Modern human life is composed of various social relationships that coexist within an individual’s life, for example, family and workplace relationships. Observations from human and non-human primates have shown that social relations which are hierarchical in nature could generate psychosocial stress (Marmot & Siegrist 2004; Sapolsky 2005). Those in the higher social positions are much less likely to be stressed compared to those in lower positions, probably due to less exposure to diverse types of stressors by having more control

over working demands (Marmot et al. 1997). Those socially advantaged may also enjoy more social support, which can have a buffering effect on stress process, by affecting appraisal and coping processes (Cohen & Wills 1985; Adler & Snibbe 2003; Cohen et al. 2006).

Social relationships within nuclear families can create both strain and support (Walen & Lachman 2000). Regarding childbearing, the partner of the expectant mother may help to buffer the stress she faces in daily life or relieve pregnancy-related anxiety. Dissatisfactory partner relationships have been suggested to negatively influence perinatal health outcomes (Hoffman & Hatch 1996; Schetter 2010). The prospect of a new-born may also negatively impact the expectant father, by elevating depression and anxiety symptoms (Field et al. 2006; Gawlik et al. 2014). The mental wellbeing of both expectant parents is likely to be reciprocally associated with strains in their relationship (Walen & Lachman 2000). Recent empirical studies have also shown satisfactory partner relationships and partner support to be inversely associated with prenatal anxiety and distress (Giurgescu & Templin 2015; Cheng et al. 2016; Jonsdottir et al. 2017), which suggests the need for further research and attention on the father in antenatal care (Hartman 2016).

To summarize, the stress response system is an essential link between the external environment and health outcomes. The cognitive and emotional functioning might be crucial in the stress process. The early life environment may predispose both perceptions of and reactions to the external environment, as well as the reactivity of the stress response system which plays a major role in pregnancy and the onset of delivery. The social relationships of the mother with her partner or other relatives is a crucial component of her social life, and a potential source of both stress and social support. Thus, over the lifecourse and across different environmental settings, psychosocial mechanisms may help to explain how the physical and social environments affect the risk of preterm birth.

2.6 THEORETICAL FRAMEWORKS OF MATERNAL AND CHILD HEALTH

The majority of previous studies have primarily focused on proximal precursors of preterm birth. However, the broader social environment and psychosocial context also play important roles in health, as described by the developmental theory postulated by Bronfenbrenner (Bronfenbrenner 2009), and echoed in epidemiological theories and public health policy propositions developed in more recent years (R. G. Evans & Stoddart 1990; M. Susser & E. Susser 1996; Krieger 1994; Bartley et al. 1997). This vision was also integrated into the framework of perinatal health, where multiple determinants across the life span were proposed to affect pregnancy outcomes (Misra et al. 2003), especially in facing the racial-

ethnic disparities that could not be explained by conventional risk factors during pregnancy (Lu & Halfon 2003).

Intergenerational perspectives are by nature integrated into the perinatal health research, whereby the exposure of generation one (G1) directly affects generation two (G2), at least during pregnancy. A lifecourse perspective on preterm birth further extends this view by looking into the mother's (G1) early life, which is also directly affected by her parents, generation zero (G0). The different stages within the lifecourse, namely, pregnancy, neonatal and infancy period, preschool and school-age, adolescence and reproductive years, require a continuum of care for the mothers and children (Kerber et al. 2007), as factors within one period can be linked to health outcomes in another period and of the following generations.

Despite this view on lifecourse and intergenerational transmission of determinants of perinatal health, the 'continuum of care' approaches have primarily focused on clinical care (Kerber et al. 2007). Undoubtedly, from a global health perspective, such integrated health care is critical in reducing maternal and child mortality, especially in areas lacking universal access to care. Nevertheless, some of the important determinants of maternal and child health, for example, social services in other public sectors, have not been specified in the 'continuum of care' approach. The partner and other relatives, as additional primary stakeholders in maternal and child health, were generalized in the family and community, thus never mentioned.

This lifecourse perspective on women's health is replacing the previous view focusing specifically on maternal and child health, at the time when the social, demographic and epidemiologic transitions are ongoing (Langer et al. 2015). This lifecourse approach is also under the sustainable development goals (SDG), where the health of all age group relies on the efforts from all sectors. Given this transformation, the perinatal health researchers may need to rethink on how to incorporate the new visions, for example, women's role as caregivers within and outside the family context (Langer et al. 2015). Following this progress, perinatal health research requires an integrating framework, incorporating mechanisms in both the biological and the social systems, as well as their interactions across the lifecourse.

3 AIM AND RESEARCH QUESTIONS

The overarching aim of the thesis is to investigate indicators of an adverse psychosocial environment, which is hypothesized to increase the risk of preterm birth. A lifecourse perspective on the psychosocial environment was used, in which the individual woman’s life was interwoven within that of her parents, her partner, and her child, within the family sphere. Figure 1 outlines the main research questions investigated in this thesis, within the particular time and environmental dimensions.

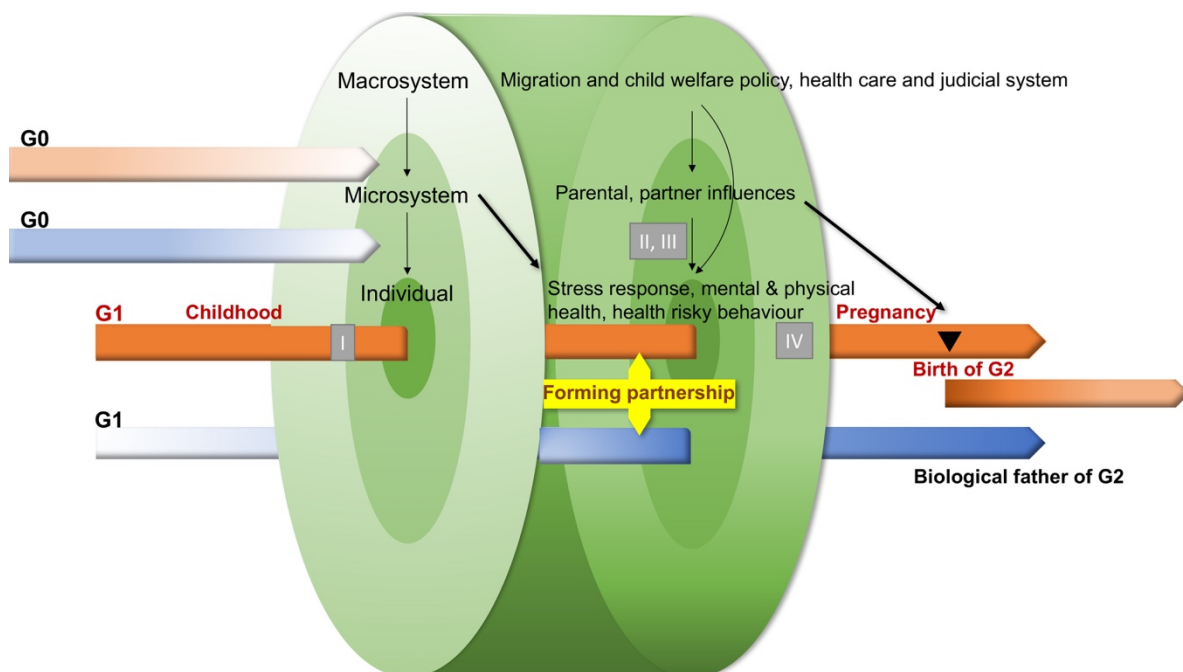


Figure 1. Schematic presentation of the thesis topic. Three generations (G) are involved in the general framework. G2 denotes the latest generation whose risk of preterm birth is of interest. G1 are the parents of G2. G0 denotes the grandparents of G2 on the mother’s side. The mother’s lifecourse is in the centre of the graph (in orange), which also represents her biological, psychological and behavioural development over time. This lifecourse also encapsulate a fourth dimension, which is the process of biological embedding, comprising the individual physiology from genetic expression, cell and organ functions to emotional and cognitive reactions and behaviours. Please note that the rings indicating different levels of systems are porous, with the more “distant” systems possibly exerting a direct impact. Roman numerals I-IV denote the primary areas of focus in Studies I-IV.

The research questions investigated within this thesis are:

- Do adverse experiences in early life, as indicated by placement in out-of-home care, increase the risk of preterm birth? (**Study I**)
- Does an adverse partner relationship increase the risk of preterm birth?
 - as indicated by depression in the partner (father of the offspring) (**Study II**)
 - as indicated by the partner's violent behaviour (**Study III**)
- Is the duration of residence in the host country among refugees associated with the risk of preterm birth? (**Study IV**)

4 METHODS

4.1 STUDY DESIGN AND DATA MATERIALS

All of the studies included in this thesis were national cohort studies, created by linking information from a number of Swedish National Registers.

Every Swedish citizen and those who have immigrated and who have resided in Sweden for longer than one year have their own a unique personal identification number (Ludvigsson et al. 2009), which was used as the key to link information from the different national registers. The National Board of Health and Welfare and the Statistics of Sweden provided all of the register information used. The datasets were de-identified by replacing the original personal number with a non-traceable identifier that was unique for the same individual recorded in the different databases.

All birth records from 1973-2012 were retrieved from the Swedish Medical Birth Register (SMBR) and linked with the Multigenerational Register (Ludvigsson et al. 2016) to collect identifier of the biological father. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) was also linked to obtain socioeconomic and demographic information of both parents in every study. Other national registers were linked to obtain information on the specific independent variables and covariates included in each study (Ludvigsson et al. 2011; Ludvigsson et al. 2016) (Table 4.1).

Table 4.1. Information about the independent variables extracted from each national register.

Study	Register	Variables	Year of measurement	Individual time/Age at measurement
I	The Child Welfare Register			
		Out-of-home care (OHC)	1973-2012	In the childhood of the index woman (G1)
		Age at first OHC	1973-2013	In the childhood of the index woman (G1)
	The Swedish Medical Birth Register (SMBR)			
		Own prematurity at birth	1973-1977	At the birth of the index woman (G1)
		Own birthweight for gestational age	1973-1977	At the birth of the index woman (G1)
		Maternal diagnosis of hypertensive disorder	1973-1977	Before birth of the index woman (G1)
		Maternal country of birth	1973-1977	At birth of the index woman (G1)
	Census 1980	Socioeconomic group (SEI) of the household	1980	3-7 years of age of the index women (G1)
	The National Patient Register (NPR)			
	Inpatient care for severe psychiatric diagnosis	1985-2012	24 months before birth of G2	
	Inpatient care for non-alcoholic addiction	1985-2012	24 months before birth of G2	
	Inpatient care for alcoholic addiction	1985-2012	24 months before birth of G2	
	Inpatient care for mood disorders	1985-2012	24 months before birth of G2	
II	The National Patient Register (NPR)			
		Parental (G1) inpatient care for depression	01/Jul/2005-31/Dec/2012	24 months before conception of the index birth (G2)
		Parental (G1) outpatient care for depression	01/Jul/2005-31/Dec/2012	24 months before conception of the index birth (G2)
The Prescribed Drug Register				
	Parental (G1) filled prescription of antidepressant	01/Jul/2005-31/Dec/2012	24 months before conception of the index birth (G2)	
III	The Crime Register			
		Parental (G1) criminal conviction	1973-2012	At any time before or after the index birth (G2)
IV	The Total Population Register			
		Parental (G1) country of birth	1992-2008	N/A
		Maternal (G1) year of immigration	1992-2008	N/A

All psychiatric and perinatal diagnoses used in the thesis were coded according to the International Classification of Diseases (ICD). The eighth revision (ICD-8) was used until 1986 and informed the coding of generation one (G1)'s perinatal diagnoses in Study I. The ninth revision (ICD-9) was used from 1987 to 1996, and the tenth revision (ICD-10) from thereafter. Detailed information of disease coding can be found in Table 4.2.

Table 4.2. Disease coding according to the International Classification of Diseases (ICD).

Diagnosis	ICD-8	ICD-9	ICD-10	Study
Perinatal				
PPROM	/	658.1	O42	I, II, III, IV
Preeclampsia	400-404	642.4-642.7	O14, O15	I, II
Gestational diabetes	250	648.8	O24.4	I, II
Placenta previa	/	641.0, 641.1	O44	I
Placenta abruption	/	641.2	O45	I, II
Chorioamnionitis	/	658.4	O41.1	I
Infectious and parasitic disease	/	647	O98	I
Psychiatric				
Severe psychiatric diagnosis	/	293-319 excluding 303-305.0	F00-F99 excluding F11-F19	I, III
Substance abuse				
<i>Non-alcoholic addiction</i>	/	292, 304, 965.0, 968.5, 969.6, 969.7	F11, F12, F14, F16, F19, Z503, Z71.5, Z72.2, O35.5, P04.4, T40, T43.6	I, III
<i>Alcoholic addiction</i>	/	291, 303, 305.0, 357.5, 425.5, 535.3, 571.0-571.3	F10, K70, G621, I426, K292	I, III
Mood disorders	/	296, 311	F30-F39	I
<i>Depression</i>	/	/	F32-F39	II

4.2 STUDY POPULATIONS

Studies I, II and III were based on all births recorded in the Swedish Medical Birth Register from 1973 to 2012, with additional linked register information updated until 2012. Study IV was based on a similar database but only updated until 2008.

Various national registers may differ by year of initiation as well as the variables that are included in the registers over time. To insure the largest sample size with register-based information with national coverage, the study population was constrained by year of birth. In all studies the index births were constrained from 1992 onwards, when the antenatal care information (e.g. maternal smoking), was more complete.

The study population in Study I and II was further designed to have the largest sample size within the available timeframe. Study I had two generations' birth information collected between 1973 and 2012. The study population was designed to have the largest index birth (G2) population delivered by G1, with every G1 having the same time of observation. The grey area in Figure 4.1 illustrates how the G1 (index mother) and her child G2 was defined, when; 1) the oldest G1 was born in 1973 and the youngest G2 was born in 2012; 2) every G1 was observed between 13 to 35 years of age in the observation time. The study II population was constrained by the available information in the Prescribed Drug Register, which started on July 1, 2005. More detailed information can be found in Table 4.3.

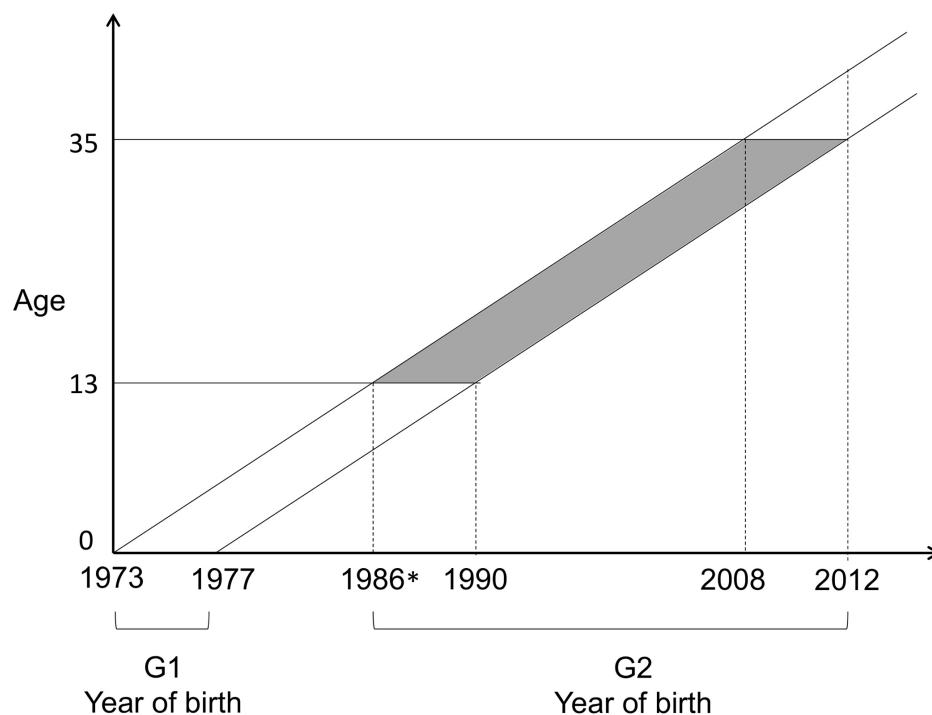


Figure 4.1. Birth cohort of Study I.

*No G2 was recorded to be born in 1986. The G2 cohort (Study I) was born during 1987 and 2012.

Table 4.3. Study population and variables.

Study	Study population	Independent variable	Dependent variable	Confounders specific to the study	Potential mediators
I	343 828 live singletons deliveries in 1987-2012 of women who were before 36 years of age and was themselves born in Sweden during 1973-1977	Out-of-home care in childhood	Preterm delivery (further classified by length of gestation and onset of delivery)	Index woman's perinatal indicators (including own preterm birth, her mother's pregnancy diagnosis, and intrauterine growth), her mother's country of origin and socioeconomic index of the household in early childhood	Education achievement, height, BMI, smoking, psychiatric problems and pregnancy-related complications
II	366 499 live singleton births conceived after 20 June 2007 and born before 31 December 2012	Paternal prenatal depression	Preterm birth (further classified by length of gestation, onset of labour and their combination)	Paternal age and education, maternal depression occurred before paternal depression	Smoking, BMI status measured in early pregnancy
III	1 478 703 live singleton births in Sweden during 1992-2012	Paternal violent criminality	Preterm birth and gestational age	Paternal and maternal age and education, maternal conviction status, maternal invariant confounders shared between siblings, maternal characteristics that may change between pregnancies (including smoking and BMI)	Paternal psychiatric problems
IV	20 723 live singleton births to women during their first five years of residence, who migrated after 13 years of age from Former Yugoslavia (1992-2000), Iraq (1992-2004), Somalia (1992-2004), or Afghanistan (1992-2004) with a spouse of the same origin	Duration of residence	Preterm birth (further classified by length of gestation)	Maternal country of origin	N/A

4.3 INDEPENDENT VARIABLES

Study I: Out of home care

Information on out of home care (OHC) in childhood was used as a proxy of early life adversity. Having the first experience of OHC before or after turning ten years of age was used as a marker of household dysfunction or manifested behavioural problems in older ages.

Study II: Parental depression

For each parent of the index birth, in- and out-patient care of both parents with a diagnosis of depression and a filled antidepressant prescription (according to World Health Organization's Anatomical Therapeutic Chemicals (ATC) classification of N06A) were used jointly as the indication of depression (the specific ICD coding used for depression and other covariates in each of the studies can be found in Table 4.2.). The time interval of each indication of depression to the estimated conception date was calculated. Based on this interval, every 3-month time period, within the period 24 months before or 6 months after conception can be defined as exposed or not exposed to paternal depression. Having an indication of depression at any time within 12 months before conception, and up until 24 weeks of gestation was used as an indicator of prenatal depression. This indicator was further classified as being a "new depression" (depression after 12 months of no depression indication) or a "recurrent depression" (all other cases) (see Figure 4.2).

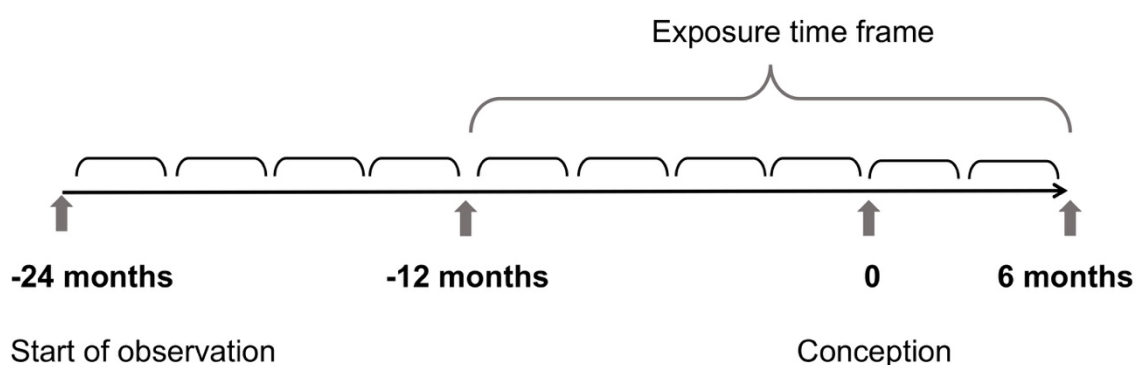


Figure 4.2. Definition of parental prenatal depression in Study II.

Study III: Paternal conviction for violent crime

The father having a violent criminal conviction before the index birth was used as a proxy exposure indicating violent behaviour. Having three or more convicted violent crimes

(persistent violent convictions) was an indication of a higher level of aggression, compared to those fathers convicted of less than three violent crimes.

Study IV: Duration of residence

The number of years from gaining permission of residence to the birth of the index infant was calculated using the year of birth and the year in which the Swedish residence permit was granted. Residence in Sweden was then categorized as 0, 1, or 2-4 years. A very short duration of residence was considered as it may reflect a higher level of migration-related stress compared to those with a longer duration of residence.

4.4 DEPENDENT VARIABLES

Preterm birth (or preterm delivery, as termed in Study I) was defined as being born (having delivered) before 37 gestational weeks/ 259 gestational days. By length of gestation and onset of delivery, preterm birth was further sub-classified as being very preterm or moderate preterm, and as being spontaneous or medically indicated preterm birth (Table 4.4).

Table 4.4. Classification of preterm birth in this thesis.

	Sub-classification of preterm birth	
	By length of gestational	By onset of labour*
Preterm birth <37 gestational weeks	Very preterm birth <32 gestational weeks	Medically indicated preterm birth Vaginally induced labour or planned caesarean section
	Moderate preterm birth 32-36 gestational weeks	Spontaneous preterm birth Spontaneous onset of labour or having diagnosis of premature rupture of membrane (PPROM)

*Categorized as spontaneous preterm birth in records where the labour was recorded as having both spontaneous and induced onset.

Gestational age in days was also used as a dependent variable in the sibling comparison design of Study III where statistical power was limited.

4.5 CONFOUNDING VARIABLES

Table 4.3 lists variables considered to introduce possible bias due to confounding in each of the studies. To improve estimation precision, the age of the mother at delivery, parity, and calendar year of index birth were included in the models for each study. In study IV, country of origin was also adjusted as a confounder. Since the refugee migration from each country

was associated with the calendar year, and duration of residence was the independent variable, the calendar year of birth was not included, as it was collinear with the two former variables.

4.6 STATISTICAL ANALYSIS

Depending on the form of the dependent variable, different regression models were performed to estimate the main effect of the exposure on the risk of preterm birth (or shortened gestational age) (Studies I, II, IV) (Table 4.5). For sibling comparison (Study III), fixed effect linear and logistic regression models were used when the dependent variable was continuous and dichotomized, respectively. Cluster robust estimation of standard errors was used to account for the independence of births/deliveries of the same woman.

Table 4.5. Choice of regression model according to the study design and dependent variable.

Dependent variable		Form of dependent variable	Population analysis	Sibling comparison	
			Conventional regression models	Fixed effect regression models	
Gestational age in days		Continuous	Linear regression	Fixed effect linear regression	
Preterm birth		Binary	Logistic regression	Fixed effect logistic regression	
Preterm birth sub-classified	Duration of gestation	vs. Term birth	Categorical	Multinomial logistic regression	N/A
	Very preterm birth				
	Moderate preterm birth				
	Onset of labour				
	Spontaneous preterm birth				
	Medically indicated preterm birth				
	Both criteria				
	Spontaneous very preterm birth				
	Medically indicated very preterm birth				
	Spontaneous moderate preterm birth				
Medically indicated moderate preterm birth					

5 RESULTS

The main empirical findings of the thesis are briefly presented here. The odds ratios (OR) of very and moderate preterm birth are presented for each study on a logarithm scale.

5.1 ADVERSE EARLY LIFE EXPERIENCE

In Study I, maternal early life adversity was associated with an increased risk of preterm birth. OHC after ten years of age was in particular associated with an increased risk of very preterm birth.

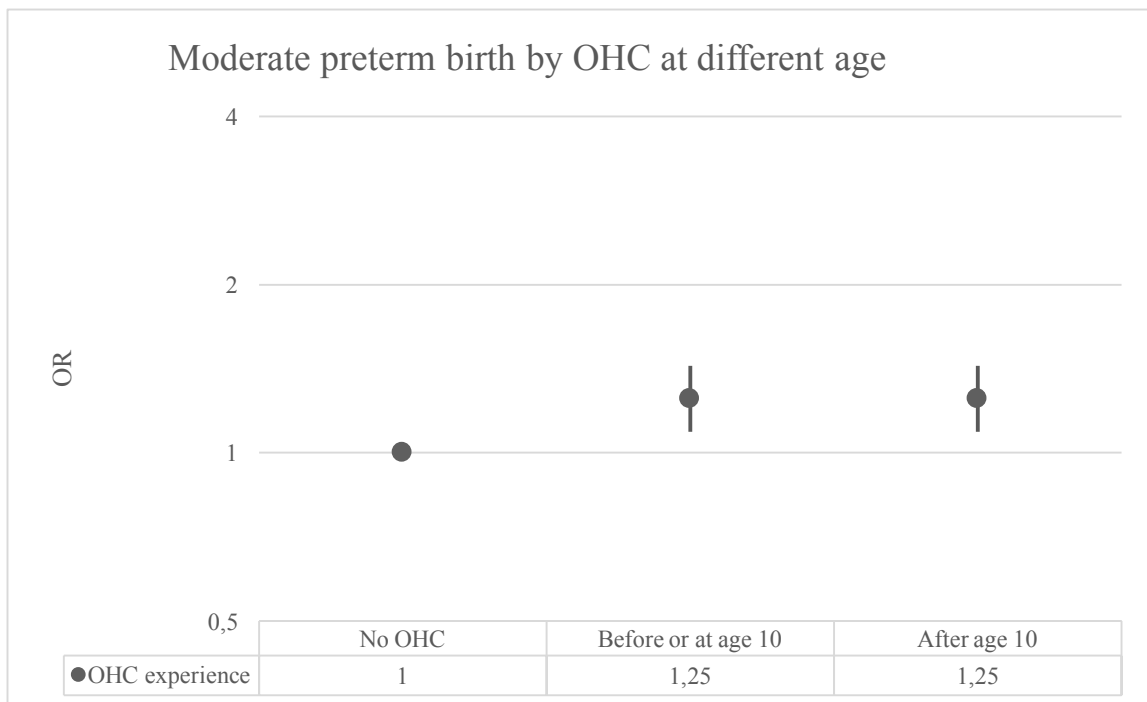
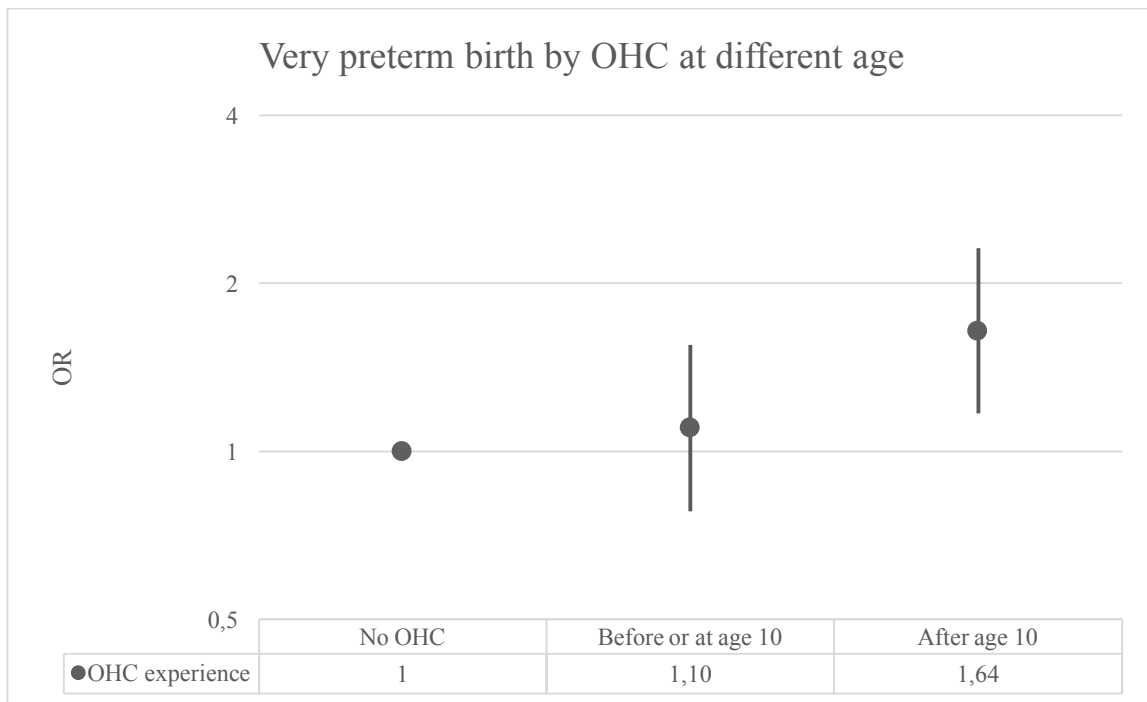


Figure 5.1. Odds ratios (OR) of very and moderate preterm birth among women who experienced OHC in comparison to those who did not (N=343,828).

Experiencing OHC after ten years of age was also notably associated with increased risk of medically indicated preterm birth.

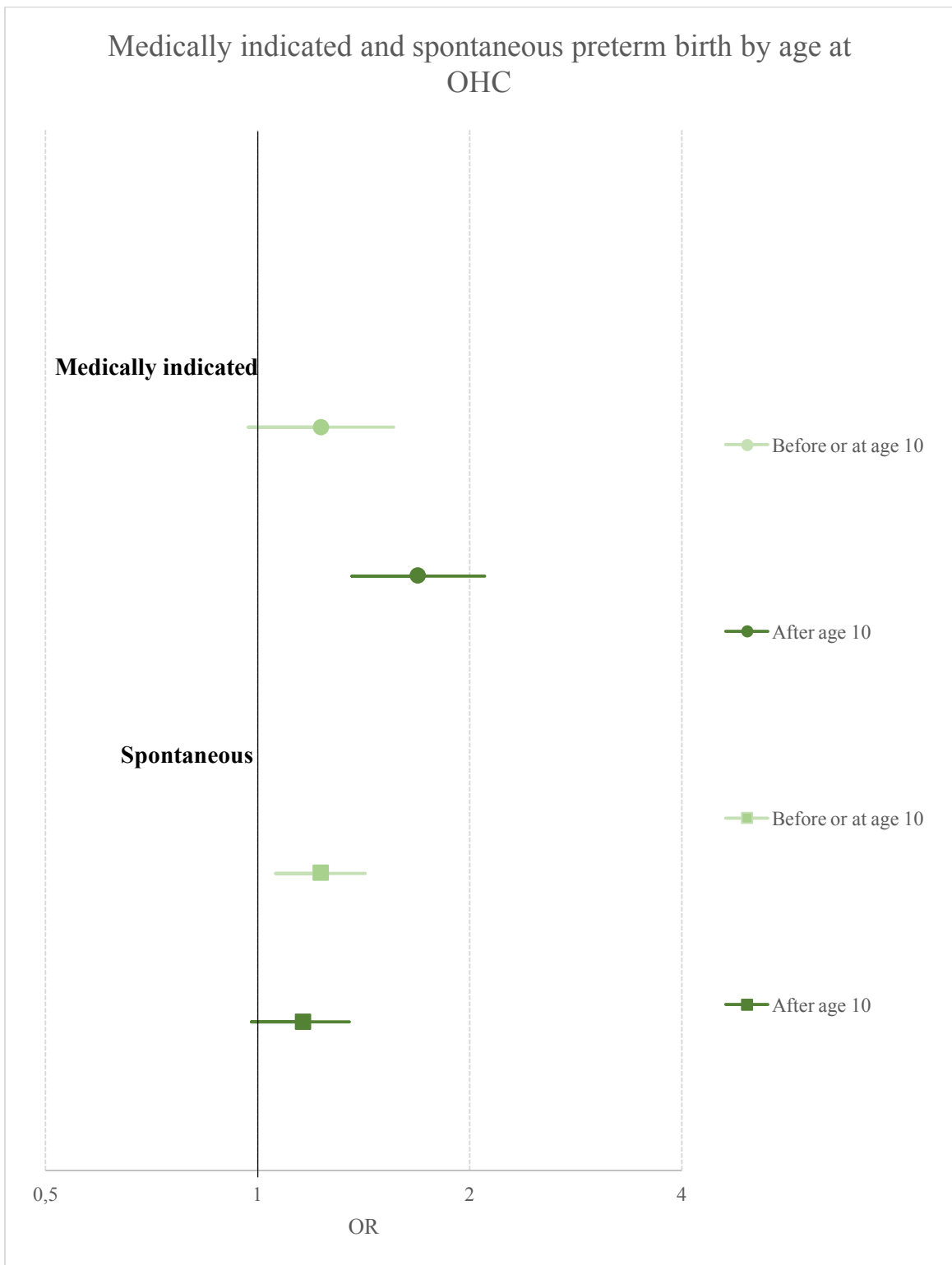


Figure 5.2. Odds ratios (OR) of medically indicated and spontaneous preterm birth among women who experienced OHC in different age groups.

5.2 ADVERSE PARTNER RELATIONSHIPS

Prenatal depression and convicted violent crime of the partner, or the father of the index birth, were investigated as two indicators of problematic partner relationships.

5.2.1 Depressive partner

Newly occurred paternal depression before or during pregnancy was associated with an increased risk of preterm birth.

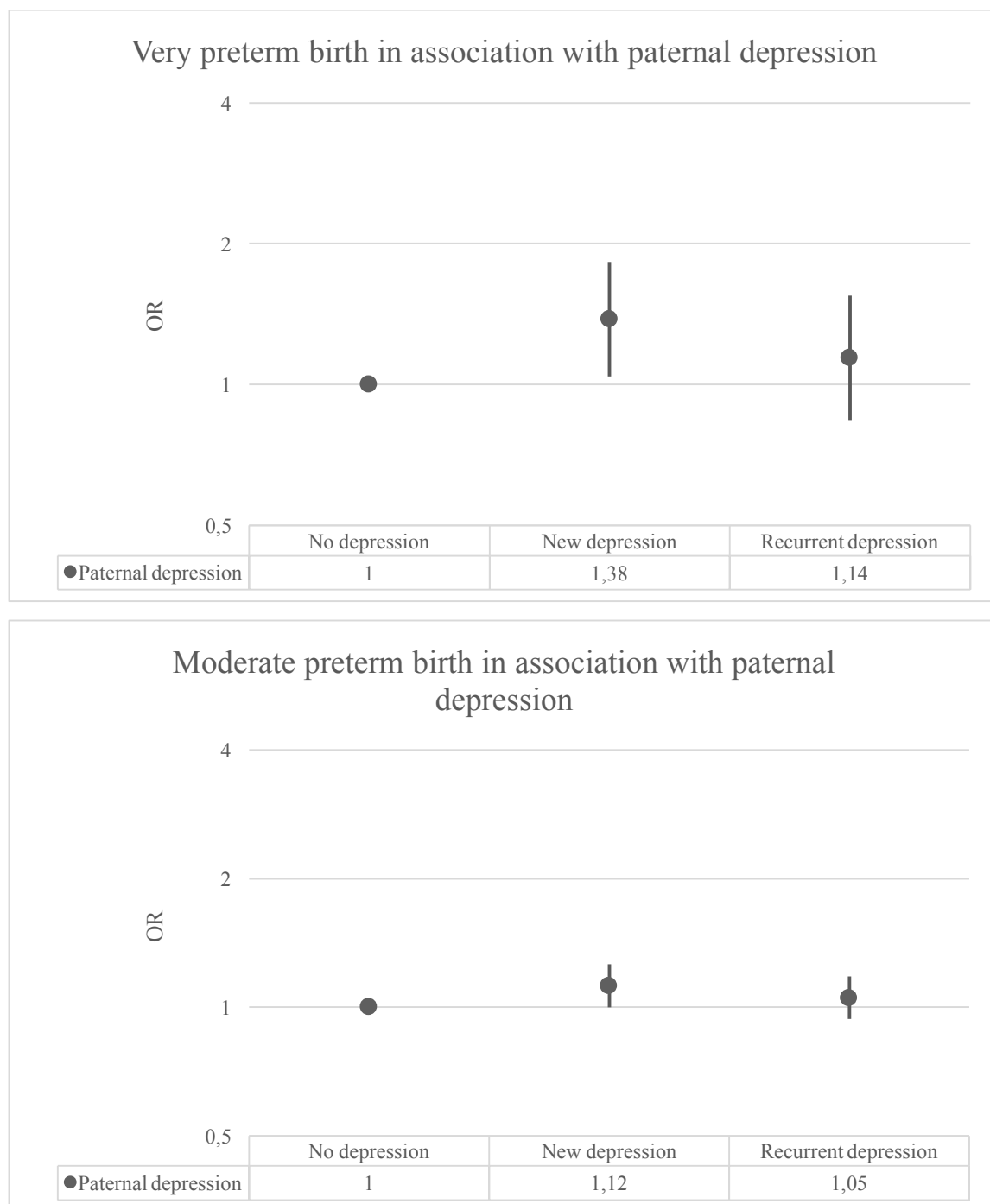


Figure 5.3. Odds ratios (OR) of very and moderate preterm birth among infants of fathers who had a clinical indication of depression shortly before or during pregnancy, in comparison to those without depression (N=366,499).

5.2.2 Aggressive partner

Persistent paternal violent criminality was associated with an increased risk of preterm birth, with this result remaining robust after conditioning on consistent maternal characteristics, which was shared between maternal siblings. Linear regression modelling (see Figure 5.5) of gestational age is also presented, in correspondence to the logistic regression model (see Figure 5.4).

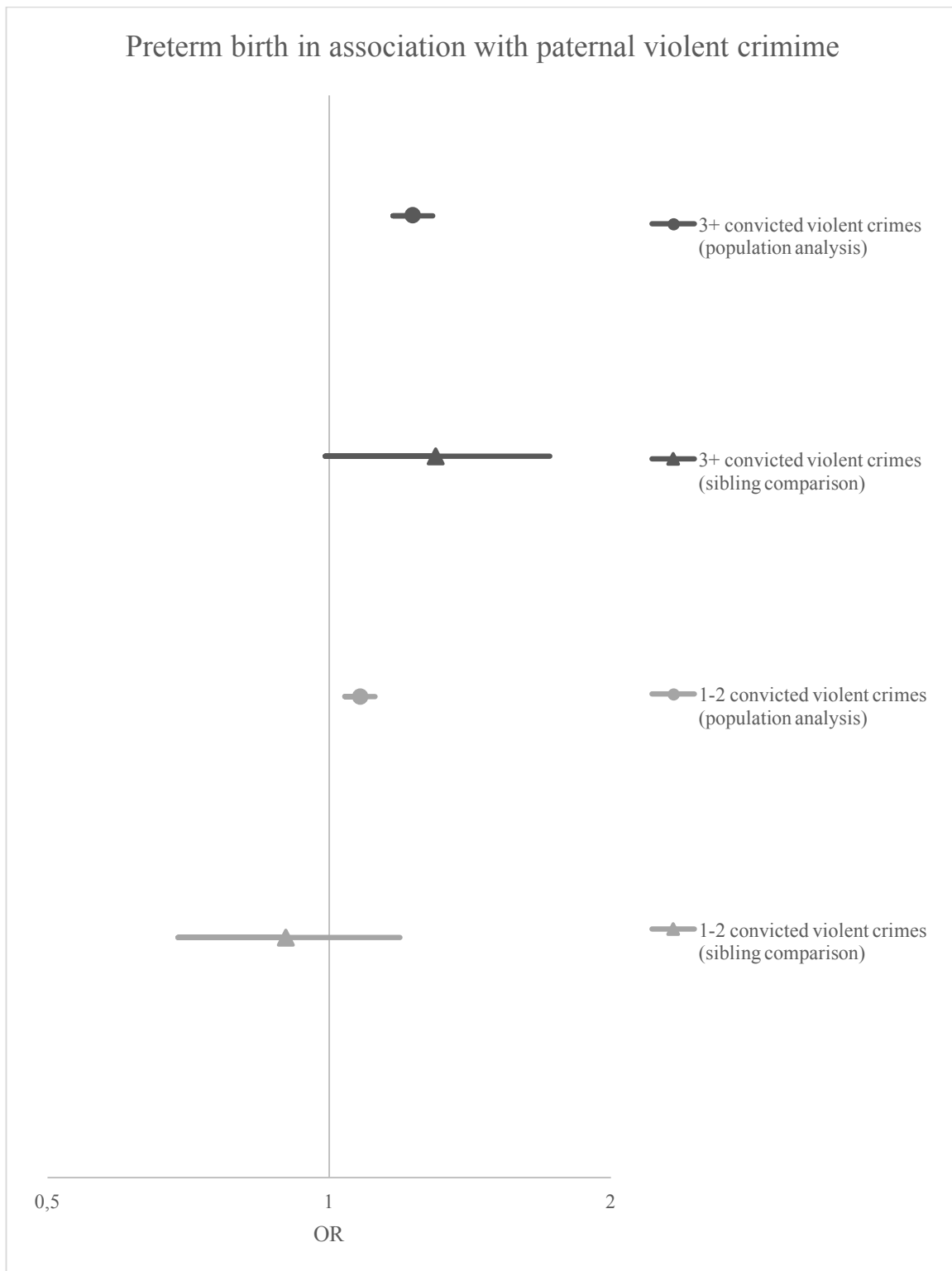


Figure 5.4. Odds ratios (OR) of preterm birth among infants of fathers who were convicted of a violent crime in comparison to those without a crime conviction (N= 1,046,986 in population analysis; N=1,528 in maternal half sibling comparison).

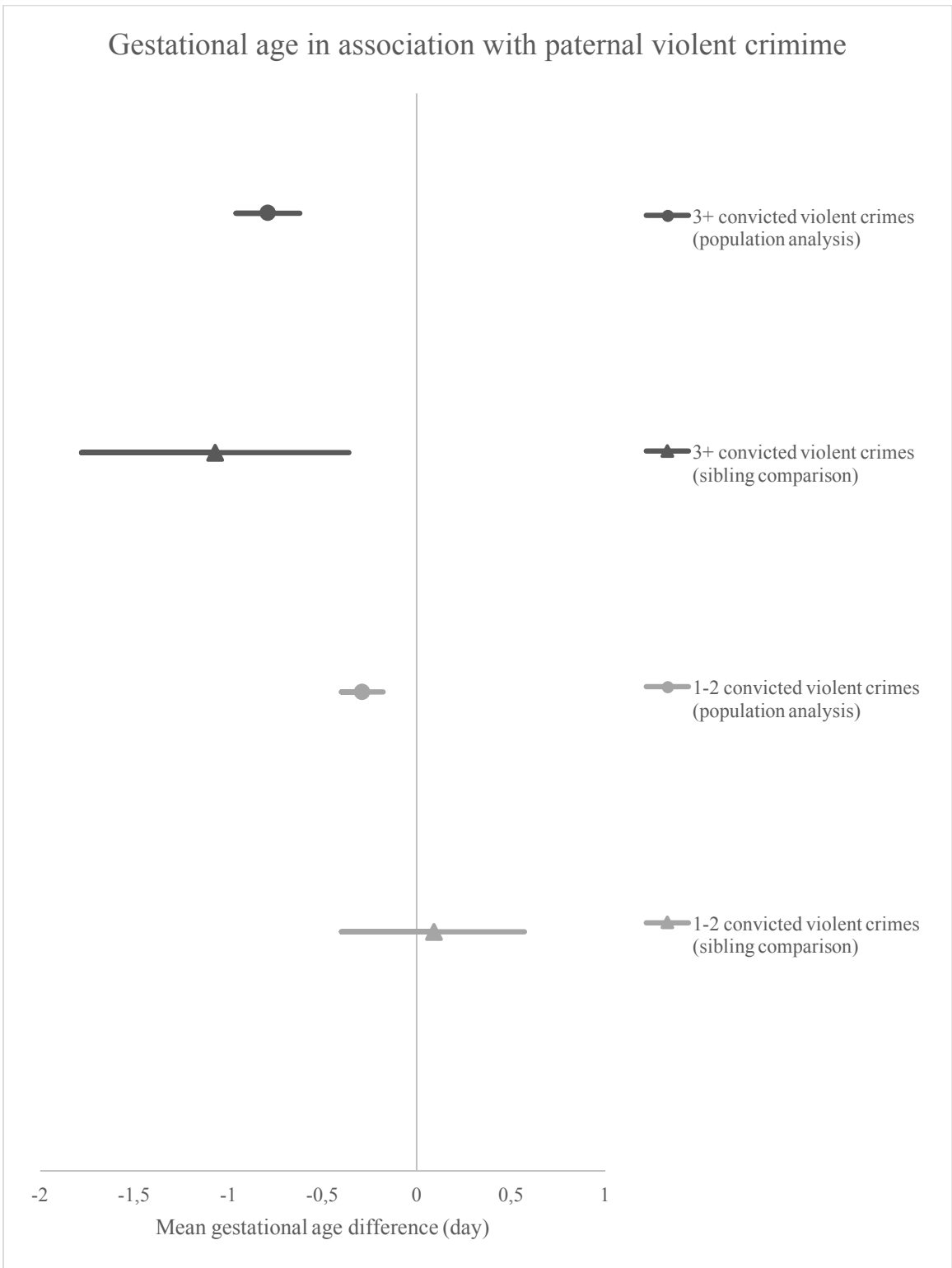


Figure 5.5. Mean differences in gestational age of infants whose fathers were convicted of a violent crime, in comparison to those without a conviction (N=1,046,986 in population analysis; N=14,229).

5.2.3 Subtypes of preterm birth and different indicators of adverse partner relationship

The ORs for medically and spontaneous very/moderate preterm birth among births exposed to paternal new depression (vs. no depression) and paternal persistent violent convictions (vs. no convictions) are presented to compare the two indicators of problematic partner relationships. The association between paternal prenatal depression was more pronounced for medically indicated preterm birth than spontaneous preterm birth. However, the association between high paternal aggression (as measured by 3+ violent crime convictions) was most pronounced with risk of spontaneous preterm birth.

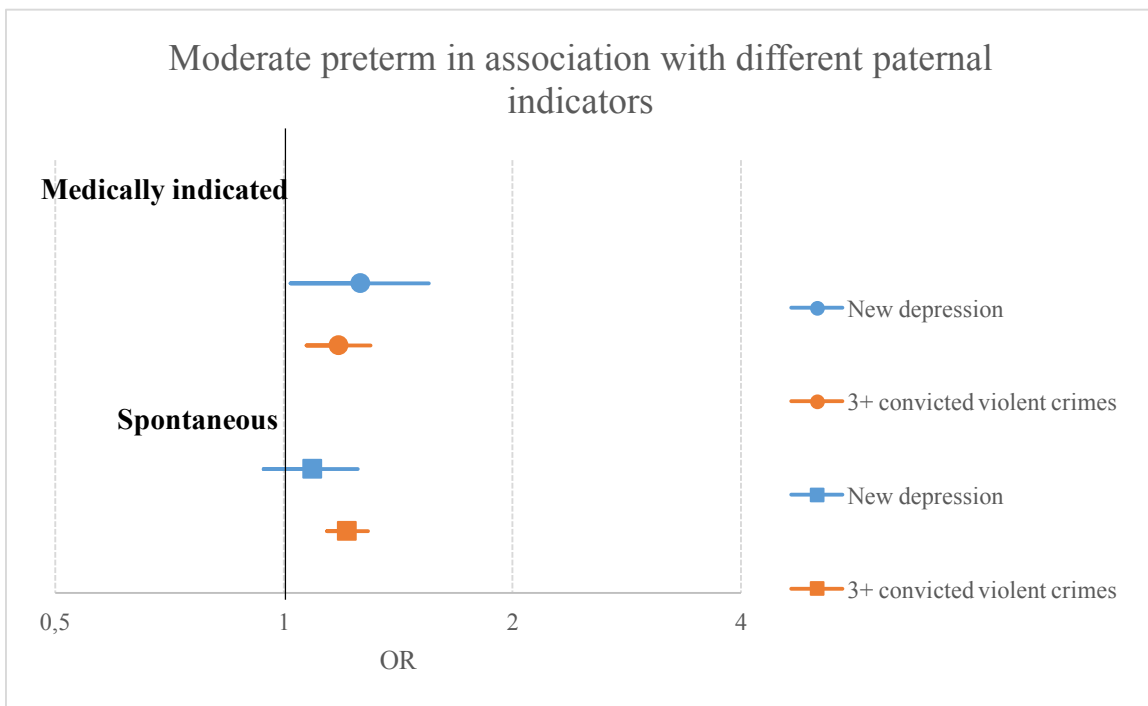
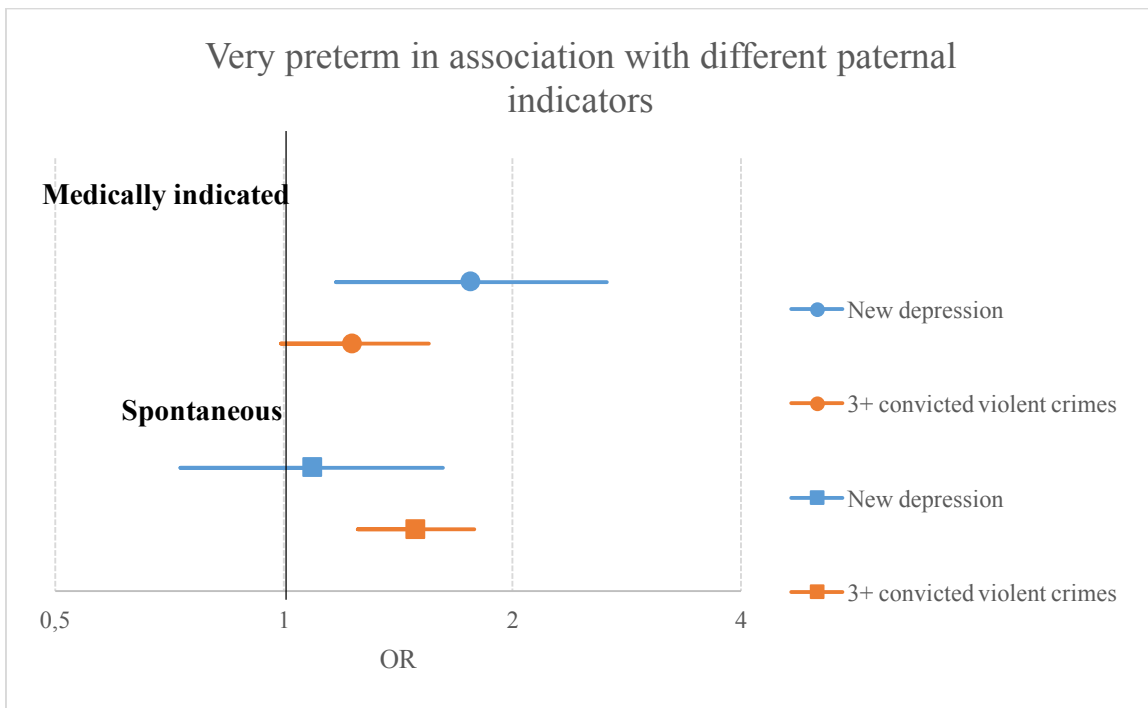


Figure 5.6. Odds ratios (OR) of medically indicated and spontaneous preterm birth among neonates whose fathers had prenatal new depression or persistent violent convictions, in comparison to those without depression or crime convictions.

5.3 TIME AFTER RESETTLEMENT IN THE HOST COUNTRY

Migration related stress (as measured by duration of residence) was associated with increased risk of preterm birth, with this association weakening with duration of residence.

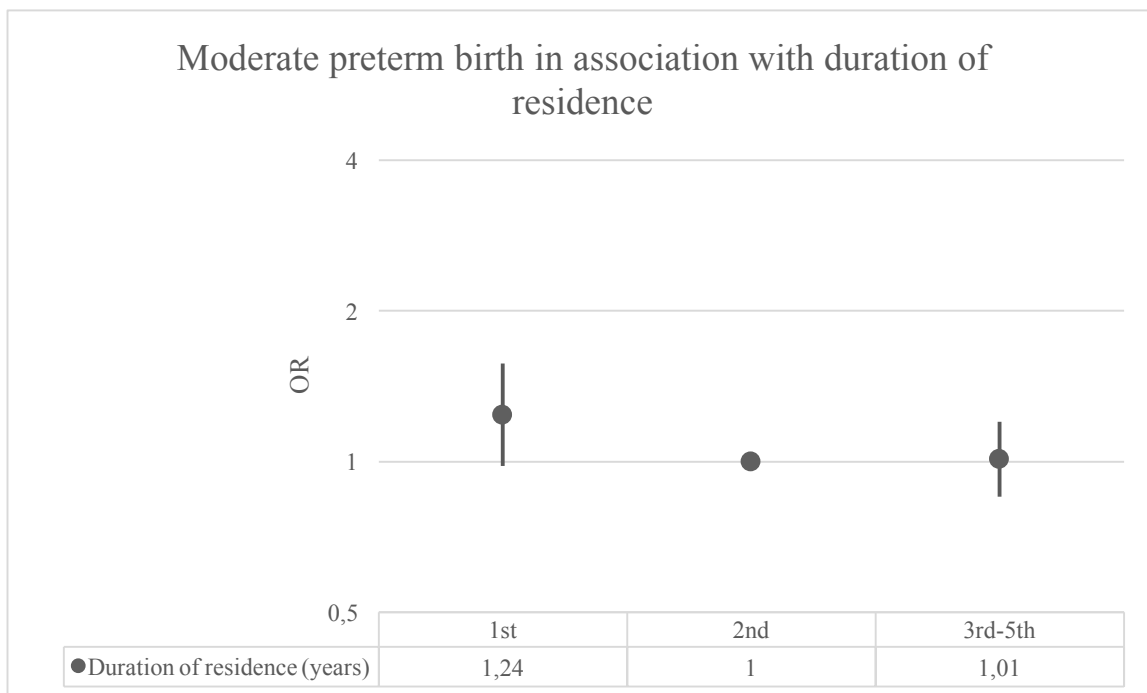
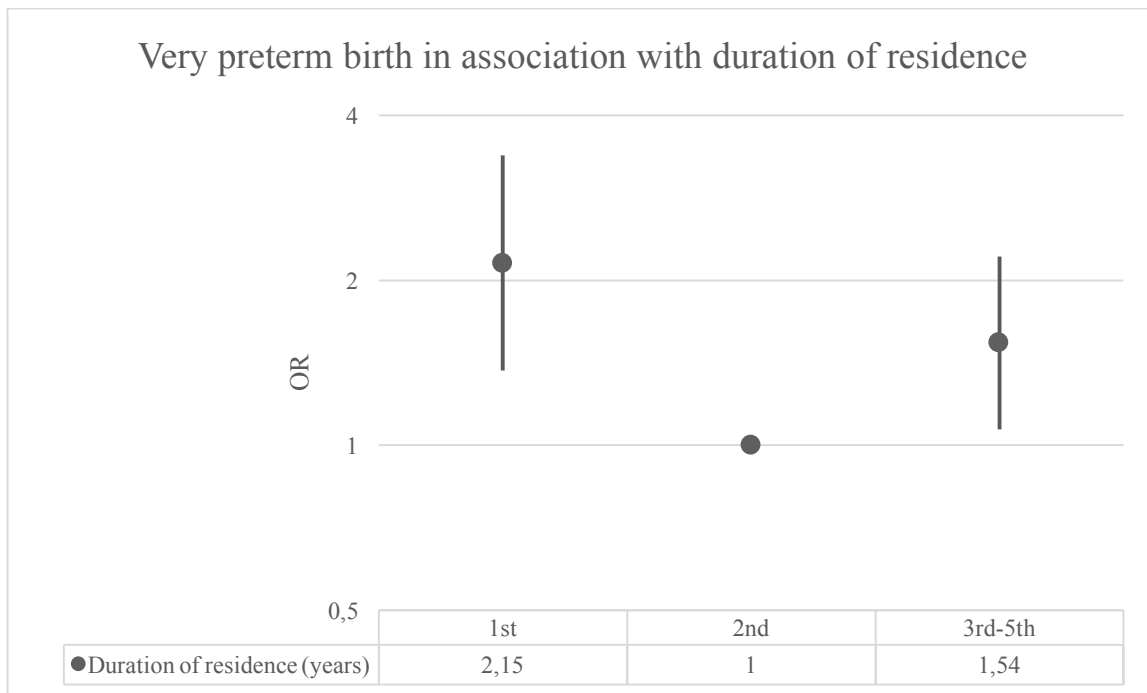


Figure 5.7. Odds ratios (OR) of very and moderate preterm birth in association with duration of residence (N=20,723).

6 DISCUSSION

6.1 SUMMARY OF RESULTS

The studies included in this thesis investigated the impact of several psychosocial factors across the lifecourse on preterm birth, a multi-factorial birth outcome. Adverse early life experiences, problems related to the quality of partner relationship, and migration as a refugee shortly before childbearing were investigated as indicators of physical and psychosocial stressors. The findings of the studies suggest that OHC experience in early life, having a depressed or aggressive partner, and recent migration as a refugee might potentially increase the risk of preterm birth, especially very preterm birth.

More specifically, the aetiological subtypes of preterm birth differed by both the timing and specific characteristics of the psychosocial exposures. OHC after ten years of age was more strongly associated with risk of medically indicated preterm birth, which was also more prominent when the partner had newly onset prenatal depression. In contrast, the risk of spontaneous preterm birth was slightly more pronounced among women whose partner had been convicted of violent crimes repeatedly.

6.2 POTENTIAL MECHANISMS

The examined indicators of the adverse psychosocial conditions were conceptualized as stressors that may have an impact on the mother's psychosocial stress response. The investigated stressors are located at different stages in life or at different level of the social environment.

An adverse family environment in childhood may predispose an individual's stress response system, and health-related behaviours, as well as their physical and psychological conditions in adulthood (Anda et al. 2006; Vinnerljung et al. 2006). Biological embedding (the hidden fourth dimension in the proposed framework in Figure 1), especially in relation to stress response predisposition, may increase the susceptibility to inflammation and hence the risk of preterm birth. Cognition, emotional reactivity, and behavioural regulation is also very likely shaped by early life experiences (McEwen 2012), which in turn may affect social trajectories following adversity experienced in early life, as epidemiological research has shown (Berlin et al. 2011; Vinnerljung et al. 2005).

Finding a partner is a major step in one's social trajectory that influences the lifecourse and family environment. In the process of family formation, the social environment may place constraints on the individual through assortative mating, whereby people with more similar social backgrounds are also more likely to form the partnership with one another (Ermisch et al. 2006). As an integral part of the familial psychosocial environment within the family, the partner is one important source of social support, both before, during, and after pregnancy. Thus, when the partner experiences mental health problems, such as depression, it can affect the psychosocial environment of the expectant mother both by reducing the social support she needs and by adding on her duty of providing care to the sick partner.

Having an aggressive partner, indicated by repeated violent crime conviction, is both a form of social selective mechanism through family formation, and an indicator of adverse family environment over an extended period of time. Exposure to this stressor may affect the risk of preterm birth both through psychosocial pathways and, in the cases where it occurs, through a direct impact of intimate partner violence (IPV).

Migration in and of itself can be a stressful procedure, as it implies a dramatic change in the broader physical and social environment. Migration related stressors may be even more severe for asylum seekers or other forced migrants, who likely experience multiple pre-migration adversities and stressors in the country of origin as well as potentially difficult or dangerous migration journeys. The migration-related stress may contribute to the elevated risk of preterm birth in the short term. The macrosocial environmental change, followed by long-term challenge in adapting to the new social surrounding, may have a consequence on health, illustrated by the increasing risk of preterm birth in the third to fifth year of residence.

The risks of spontaneous and medically indicated preterm birth were explored in Studies I-III. Pre-adolescent adversity is suggested to alter maternal stress reactivity, as a study on both human and rodent samples showed recently (Morrison et al. 2017). This experimental evidence is in line with our finding of increased spontaneous preterm birth risk among women experienced OHC before or at age ten. Maternal psychosocial stress has been suggested to increase the risk of spontaneous preterm (M. S. Kramer et al. 2009). Our large national cohort study not only supports this hypothesis, but also draws the attention to early life adversity in priming of prenatal stress.

Nevertheless, only using stress mechanism seems not sufficient to explain the observed variation in the risks of spontaneous and medically indicated preterm birth, in particular when comparing the two partner indicators, which may both be stressful. Furthermore, the risk of

medically indicated preterm birth of OHC experience after age ten was more pronounced. The adverse social and behavioural trajectories following early life adversities might in part explain the association. Social and behavioural factors may also hypothetically affect clinician's initiation of obstetric intervention, which in turn may influence the risk of having spontaneous vs. medically indicated preterm birth.

In summary, the collective findings of this thesis provided some evidence suggesting that the psychosocial adversity can increase the risk of preterm birth. From a lifecourse perspective, individual's lives are linked and affected by the macrosocial context. The stress response system may be the nexus of the social environment and perinatal health.

6.3 METHODOLOGICAL CONSIDERATIONS

Most previous studies that investigate the role of a mother's early life experience and aim to elucidate the role of the family on birth outcomes are restricted by the data available. Survey-based studies have the potential to provide great insight into both the biological and psychological indicators of the pregnant women. But for a rare outcome like preterm birth, it is expensive to obtain a sample size sufficient for reliable statistical inferences in a prospective cohort study. Besides, the introduction of selection bias is almost guaranteed. The use of national population registers provided an opportunity to investigate the relatively rare outcome of preterm birth on a minimally selected population.

6.3.1 Information validity

The registered data provided opportunities to investigate the social circumstances of all residents in Sweden. However, the information included in the register is limited, and may not comprise a perfect match with the concepts studied in this thesis, particularly when the variable of interest is hard to measure with register-based information, such as violent or aggressive behaviour. The validity of the measure used was not quantitatively analysed (Greenland 1996; Lash et al. 2011) in this thesis. Further studies on the specific psychosocial risk factors should perhaps use alternative measurements which may have higher validity. For future register-based studies, validation of the registered information and quantitative bias analysis (Greenland 1996; Lash et al. 2011) may help to strengthen the validity of the findings.

A second problem related to information validity pertains to the way that the data was collected. It can take several years for the national registers to achieve total information

coverage for the whole of Sweden, as is the case with the NPR (Ludvigsson et al. 2011). Thus, it is likely that some individuals suffering from certain conditions have not received a diagnosis. Such misclassification may dilute the very effects that are estimated.

6.3.2 Statistical inference and confounding

To investigate hypothesized causal relationships, various study design and statistical analyses were employed. Despite minimal selection bias, confounding is still of concern when using observational data to make causal inferences for the associations under investigation in this thesis.

In Study I, experiences of OHC were used as an indicator of adverse experiences in early life, although this indicator is effectively a measure of social services attempts to alleviate the distress of the child and the family. As an early life indicator, this variable has the advantage of not being confounded by covariates commonly associated with preterm birth, such as prenatal behavioural and psychological factors that are difficult to measure. Based on previous findings, a causal effect of underlying adversity on preterm birth is highly possible. However, OHC in itself may potentially have a protective effect, which is the intention of such an intervention. Thus, a causal interpretation based on this marker may be misleading and is therefore not claimed.

Study II had a similar limitation to that of Study I. Since depression is mainly treated in the primary care setting, and such incidents and treatment are not included in the national registers, the definition of depression used was based on records of anti-depressant medication dispensation. Thus, it is difficult to isolate and estimate the effect of depression and the effect of being treated with medication for depression.

In Study III, the causal effect of paternal violent behaviour on the risk of preterm birth was investigated using a sibling comparison design, which extensively accounts for the possible confounding effect of unchangeable maternal characteristics. Despite this, assortative mating and other underlining social confounding may also explain the results found.

Study IV investigated whether migration-related stress increased the risk of preterm birth. Although the results were in line with such an interpretation, estimating a causal effect was not the aim of the study. The associations found simply highlight a relationship between the two, which is important in itself to understand the aetiology of preterm birth.

In summary, using register data to construct psychosocial indicators increased statistical power and minimised selection bias. However, causal inferences were limited due to the way in which the indicators were constructed, as exemplified in Study I and Study II. Nonetheless, the associations found suggest potential causal relationships between psychosocial indicators and preterm birth.

6.3.3 External validity

The macro-social environment not only impacts an individual's life but research practice as well. The register-based information used was generated and collected within social institutions, such as child welfare, health care, judicial, and migration management systems. Which individuals are admitted, treated, convicted, or settled in these systems is influenced by the specific policies of the various Swedish institutions. This selection process is likely context-specific and differs by country, thus limiting the external validity of our findings. We speculate that, in comparison to Sweden, social and health services are less publicly-funded in many other contexts. Future studies should validate and compare such findings within different cultural contexts.

The findings in this thesis were based on the Swedish population, where the rate of preterm birth is among the lowest globally (Euro-Peristat Project with SCPE and EUROCAT, 2013). The four studies highlight several adverse psychosocial factors influencing preterm birth, using an expanded array of social-environmental indicators. Such individual attributes, however, are not necessarily the same as the determinants of health and rates of disease within the general population (Schwartz & Carpenter 2011). Thus, the findings of the thesis cannot directly address striking variation in the rate of preterm birth among different populations. Nevertheless, the mechanisms discussed in this thesis probably have their implication for discovering the underlying structural factors in the macro-environment that affect preterm birth rates in the population. The following section will discuss the implication of the findings, from both population and individual health perspectives.

6.4 IMPLICATIONS

6.4.1 Population and individual health implications

Population health

The studies included in this thesis provide evidence of an adverse effect of the social environment on health, both from an individual and inter-generational lifecourse perspective.

To promote population health and reduce social inequalities in health, efforts should be made to incorporate a lifecourse perspective and address all age groups, as prioritised in the World Health Organization's Sustainable Development Goals (World Health Organization 2015). To achieve this goal, it would be beneficial to integrate services, including health care and social welfare, which are currently organized in different public sectors.

Individual health

Actions to prevent preterm birth at an individual level require comprehensive information to predict cases. Social and environmental factors may also provide information for better prevention and prediction of preterm birth, as biomarkers do. Nonetheless, generating reliable, personalized medicine using findings from epidemiological studies is considerably challenging, if even possible (Smith 2011).

Future scientific knowledge could perhaps fuel algorithms that will sufficiently predict the outcomes of individuals. In this direction, some progress has been made using more data-informed approaches, such as machine learning (Pan et al. 2017), which will likely reshape future decision making in various contexts, including health care. Presently, it remains to be questioned and explored just how such emerging tools will shape medical practise and research. In my opinion, the human side of perinatal care will never be outdated, regardless of future possibilities. Providing compassionate care is continuing to be a demand on midwifery, which faces the need of all childbearing women (Renfrew et al. 2014).

6.4.2 Social and ecological factors

6.4.2.1 Gender

The influence of the male partner on the woman and her child's wellbeing is undeniable, particularly in traditional nuclear families comprised of one mother and one father. Sweden is known for having a high, active level of paternal participation in child rearing, thanks to generous, publicly-funded parental leave entitlements for both parents. Despite this, fathers are largely neglected in the perinatal health research field. From a physiological perspective, the mother is of primary importance, since the foetus grows within her body throughout pregnancy. Given this, her physiology before and during pregnancy are likely most relevant to the birth outcomes in her offspring.

The social cultural norm of the importance of the mother is deeply rooted in our way of thinking, both in daily life and in research. An individual, mother-centric approach will

perhaps continue to prevail in perinatal research until we fully understand the health impact of the interactive relationships between individuals and their environment. This thesis draws attention to the neglected role of the partner during pregnancy. Continued efforts, both within research and societal institutions, are needed to acknowledge and investigate the influence of partner on childbearing and rearing, as they are yet to be considered as involved as the mother-to-be.

In drawing attention to risk factors for preterm birth, the intention is not to make either parent feel responsible for this negative outcome. Rather, the distinct gender roles of the women and their partners are taken into consideration, for example women's dominance in care-giving. The different social expectations of men and women may partly explain gender differences in health, such as susceptibility to aggression or depression. The role men and women are expected to take within the family may also play a major role in relationship satisfaction and hence affecting psychosocial stress experiences.

6.4.2.2 Violence

Violence permeates ordinary life, and yet the health costs of violence are mostly invisible. Violence is connected to every adverse psychosocial factor investigated within this thesis. In Study I, both being a victim of child abuse and juvenile offending could be a potential reason for OHC. Depression, as investigated in Study II, is a risk factor for self-directed violence, such as self-harm or suicide. Intimate partner violence (IPV) is potentially related to the partner's violent behaviour, which was investigated in Study III. In Study IV, war is the primary cause of becoming a refugee in the first place, but can also be seen as a form of collective violence. Being an asylum seeker is also related to pre-migration exposure to violence.

While violence is a global public health problem, population research within this area is primarily limited by the availability of data, particularly in relation to health outcomes (World Report on Violence and Health 2002). Thus far, violence has not been claimed as one of the main causes of preterm birth, aside from IPV specifically. As evidenced throughout this thesis, violence might be a potent cause of preterm birth at a population level.

6.5 ETHICAL CONSIDERATIONS

Reductionism, a helpful simplification of the reality, is the building block of natural science and technology. It also triumphed the birth of epidemiology, marked by John Snow's original

categorisation of the source of the London cholera epidemic (Cameron & Jones 1983). Nevertheless, simplification can be misleading when analysing human characteristics, which cannot simply be broken down into molecules. More caution need to be taken when the hypothesized mechanism involves a dynamic interaction between individuals. In this thesis, some aspects of the adverse psychosocial environment were effectively defined with another person (the partner).

In combination with extrapolating population study findings to individual cases, individualism and a deterministic way of thinking could lead to the dangerous tendency of victim blaming (Marantz 1990); it could be more tempting to blame the other person, here the parents or the father-to-be. Such mistaken conclusions could be avoided by recognising that the causes of diseases and health originate from different levels- from the social environment to internal biological system - and are formed throughout the lifecourse, and over generations. Acknowledging the complexities in space, time, and social context may help to avoid blaming individuals.

The data used in this thesis include sensitive personal information from national registers, which has some legal and unique ethical concerns (Ludvigsson et al. 2015). As researchers, it is our obligation to do no harm when using such information. To avoid potential harm, protection measures were taken when handling the data, including; de-identification of individuals, secure data storage, and avoiding sub-categorizations that would generate very low cell counts and make individuals more identifiable.

Careful interpretation of study results is essential. Epidemiology is based on a population approach; therefore, the implication and interpretation of findings should only be drawn at a population level and not for individual cases. To better incorporate fathers into the area of maternal and child health, changes in society's attitudes towards masculinity and men's involvement in pregnancy and childrearing are needed (Barker et al. 2007). At an institutional level, building more collaborations between different public services might boost efficiency in protecting the individual across the lifecourse

6.6 FUTURE RESEARCH

Paradigm shift in vision

Advocating for a paradigm that adopts an ecological way of thinking has been ongoing for decades (Krieger 1994; March & E. Susser 2006). Such ecological thinking was taken in

some of the perinatal research topics, for example, in elucidating racial-ethnic and socioeconomic disparity in perinatal health outcomes (Lu & Halfon 2003; Lu & Chen 2004; M. R. Kramer & Hogue 2009). Despite this, a perspective linking social and biological processes has not been fully appreciated by researchers and practitioners within the field of perinatal epidemiology.

Biological embedding and social/ behavioural trajectory

Early life experiences may predispose the individual to poor health in a similar way as inheritable factors. In combination with the individual's social trajectory, biological embedding together with social conditions in later life may synergistically affect later life risk of disease and health. Further analysis of the interaction between various risk factors in early and later life may shed light on multiple disease processes.

Social inequality is a pressing concern in modern society. The findings included in this thesis suggest ways in which inequality in health is produced through the lifecourse and reproduced across generations. While this thesis mainly focused on dimensions of family life, many other aspects of G1's life have been associated with an increased risk of preterm birth in their offspring. The workplace psychosocial environment has been demonstrated to affect health (Marmot et al. 1997). A better understanding of how the different dimensions of life intersect and affect health would be beneficial in illuminating how health and diseases are produced within the context of the physical and social environment.

More confidence in causal relations

Currently, there is a heated discussion on the development of causal inference, which may have an implication for the future of the epidemiology (Vandenbroucke et al. 2016; Krieger & Davey Smith 2016). The research field of epidemiology, in particular peer-reviewed publishing, has been influenced by developing knowledge in human genetics, epigenetics, the -omics, and causal inference techniques; and most likely will also be shaped by the emergence of artificial intelligence. Following this trend, it is believed that precision/personalized medication and more rigorous scientific analysis are on the horizon. Conversely, the trend might also navigate the research focus further away from aspects that have a more profound impact on population health, such as the social determinants of health, where the causal mechanisms remain to be conceptually clarified.

Acknowledgement of the broader scope of origins of disease (Krieger 1994) and use of more rigorous analyses does not need to stand in contradiction. Advances in methodology might

facilitate greater confidence for decision-making when tackling determinants of population health.

How much we can draw a causal inference from an observational study should be questioned. Careful utilization of statistical models, and acknowledging underlying assumptions can help to confirm findings. At the same time, studies using various designs and data materials contribute to the idea of causation that we seek ultimately.

7 CHINESE ABSTRACT (中文摘要)

社会心理因素与早产

刘灿

据世界卫生组织估计，每年全世界范围内约有一千五百万早产儿在 37 孕周前出生。其中至少一百万的新生儿死于早产相关的疾病或并发症。但是由于大多数早产的诱因并不明确，很难对其开展有效的预防措施。目前大多数的研究侧重于母亲怀孕前后的健康状态和身心疾病以及遗传因素。另一方面，从人群的角度观察，国家之间甚至是高收入国家之间的早产率都相差甚大，同时各个国家内部居于不同社会经济地位的族群之间也有很大差异。以上差异说明社会环境和社会心理因素对早产的发生有很大的影响。这些社会环境因素对早产的影响机制需要进一步的研究，以便施行有效预防措施。

从社会流行病学的社会心理机制理论出发，我认为早产的病因植根于母亲的生命历程中每个阶段的社会心理环境。因此，本文旨在阐明母亲的成长过程中的不良社会心理环境和早产之间的关系。瑞典从 70 年代至今的社会登记系统记录了每一个居民的信息，覆盖了生活的多个方面。本论文中的各个研究材料都是基于匿名的全国性的登记记录，并且经医学伦理委员会批准，将所有生于 1992 至 2012 年的新生儿的父母信息联系起来进行分析。

第一项研究结果显示，妇女在儿童时期被儿童保护机构带离并送寄养家庭的经历与成年后产下早产儿有显著联系。本研究矫正了妇女本身在胎儿时期的环境暴露以及遗传等干扰因素。除此之外，原生家庭产生的问题可能对成年后的社会经济，心理，行为均有不良影响。这些因素也有可能参与早产的机制。

准爸爸也是准妈妈的社会心理环境中不能忽视的一个组成部分。第二项及第三项研究针对了现行围产期流行病学研究领域忽略父亲的倾向，显示了父亲在母亲的怀孕前后的临床抑郁症状，以及父亲的暴力犯罪记录与早产的相关关系。

第四项研究展示了在更宏观的社会环境变化下，申请避难的移民母亲在移民后不同时间段早产的风险变化。在异乡立足的过程可以带来相当大的压力，特别对那些逃离战火肆虐的家乡的难民来说更是如此。研究结果显示那些在移入瑞典第一年生育比起过一年以后才生育的难民女性更有可能早产。

上述研究探讨了妇女在生产前的生命历程中个人，人际之间的因素，以及不同层面的社会环境对早产的影响。这些研究结果凸显了儿童期和围产期社会环境对健康的关键影响。与此同时，源自配偶的日常生活中的压力特别值得进一步研究。

本篇论文描述了社会因素影响生理疾病的可能机制。社会环境不仅仅施加在个体，更可通过个体的繁殖过程影响后代的健康和疾病。今后对早产病因学的研究需要把个体放在社会环境和时间背景中，更要注意女性生活中重要的他人的影响，尤其是配偶的影响。

一个跨社会与生理机制以及时间维度的理论框架有助于妇女儿童健康研究，从而进一步发展具有连贯性的健康促进措施。以家庭为中心的医疗服务应该把母亲，父亲及其子女作为一个整体考虑。

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