Delayed umbilical cord clamping and maternal COVID 19 - Implications for child neurodevelopment and perinatal practice

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Delayed umbilical cord clamping and maternal COVID-19

Implications for child neurodevelopment and perinatal practice

Johan Berg is a paediatrician currently undertaking his fellowship at the Department of Neonatology at Skåne University Hospital in Sweden.

Focusing on the first years of life, this thesis examines umbilical cord clamping practices and maternal SARS-CoV-2 infection as early-life exposures that may influence neurodevelopment. By showing how the COVID-19 pandemic shaped cord clamping recommendations and practice, and assessing associations between maternal infection and child neurodevelopment, the work helps inform and safeguard evidence-based perinatal care.

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Abstract:

Objective: Although delayed umbilical cord clamping at birth (CC) and maternal SARS-CoV-2 infection in pregnancy may influence child neurodevelopment, the evidence remains limited. This thesis aimed to explore the impact of CC practices and maternal SARS-CoV-2 infection on early child neurodevelopment, and to examine CC practices in SARS-CoV-2-positive mothers.

Methods: This thesis comprises a single-centre randomised controlled trial in Nepal comparing neurodevelopment at 36 months in healthy term children randomised to delayed (≥180 s) or early (≤60 s) CC (paper I); a systematic review and meta-analysis of reported CC practice and guideline recommendations in SARS-CoV-2-infected pregnancies from December 2019 to July 2021 (paper II); and two prospective multicentre cohort analyses from the Swedish 'COVID-19 in Pregnancy and Childhood study' (COPE, papers III–IV). These cohort analyses included children born between June 2020 and December 2022 and examined the association between maternal SARS-CoV-2 infection during pregnancy and child neurodevelopment at four and 24 months using regression analyses adjusted for multiple confounders. In paper IV, postpartum depression and mother–child bonding were examined as potential mediators. Papers I and III–IV measured neurodevelopment using the Ages and Stages Questionnaire (ASQ).

Results: In paper I, ASQ scores at 36 months did not differ between delayed and early CC among 180 and 170 children, respectively. In paper II, 48 studies comprising 1 476 children and 40 guidelines were included. While 70% of the guidelines recommended delayed CC, early CC was reported twice as often in cohort studies. Neonatal SARS-CoV-2 positivity was similar after delayed (1.2%) and early (1.3%) CC, with 93% of transmissions classified as in utero. In papers III–IV, adjusted regression models in cohorts of 1 446 children at four months and 745 children at 24 months showed no overall association between antenatal maternal SARS-CoV-2 infection and ASQ scores. Mediation analyses at 24 months found no evidence of indirect effects through postpartum depression or mother–child bonding.

Conclusion: Delayed CC appears safe when the mother has suspected or confirmed SARS-CoV-2 infection and should be recommended given its established benefits. Antenatal exposure to maternal SARS-CoV-2 infection was reassuringly not associated with adverse neurodevelopmental screening outcomes during the first two years of life, although interpretation remains limited by attrition and relatively short follow-up.

Key words: Child Development; Neurodevelopmental Disorders; SARS-CoV-2; Pregnancy; Pregnancy Complications, Infectious; Prenatal Exposure Delayed Effects; Infant; Infant, Newborn; Umbilical Cord; Umbilical Cord Clamping; Infectious Disease Transmission, Vertical.

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Dedication: To my family, and to the generations to come

Table of contents

List of figures

List of tables

List of papers

This thesis is based on the following four papers

I. **Effect of delayed cord clamping on neurodevelopment at 3 years: a randomized controlled trial.**
Berg JHM, Isacson M, Basnet O, Gurung R, Subedi K, Kc A, Andersson O. Neonatology. 2021:1-7.

II. **Umbilical cord clamping in the early phases of the COVID-19 era – a systematic review and meta-analysis of reported practice and recommendations in guidelines.**
Berg JHM, Thies-Lagergren L, Svedenkrans J, Samkutty J, Larsson SM, Mercer JS, Rabe H, Andersson O, Zaigham M. International Journal of Infectious Diseases. 2023;137:63-70.

III. **The Association between Antenatal SARS-CoV-2 Exposure and Infant Neurodevelopment at Four Months of Age: A Prospective Multicenter Cohort Survey within the COPE Study.**
Berg J, Linden K, Zaigham M, Domellof M, Ahlsson F, Elfvin A, Aden U, Abrahamsson T, Ohlin A, Berg J, Hjertberg L, Graner S, Wendel SB, Iorizzo L, Arnkil S, Carlsson Y, Veje M, Bergman L, Sengpiel V, Andersson O. Int J Infect Dis. 2025:107973.

IV. **Child neurodevelopment at 24 months after antenatal SARS-CoV-2 exposure: findings from the prospective multicentre COPE cohort study**
Johan Berg, Karolina Linden, Mehreen Zaigham, Fredrik Ahlsson, Magnus Domellöf, Ulrika Ådén, Thomas Abrahamsson, Linda Hjertberg, Linda Iorizzo, Ylva Carlsson, Malin Veje, Sophia Brismar Wendel, Sofie Arnkil, Lina Bergman, Verena Sengpiel, Ola Andersson. *Manuscript*

List of abbreviations

ASQ	Ages and Stages Questionnaire
BMI	Body mass index
CC	Cord clamping
COVID-19	Coronavirus disease 2019
EPDS	Edinburgh Postnatal Depression Scale
HIC	High-income country
ICD-10	International Classification of Diseases, 10th Revision
ICU	Intensive care unit
IgM	Immunoglobulin M
LMIC	Low- and middle-income country
PBQ	Postpartum Bonding Questionnaire
PCR	Polymerase chain reaction
RCT	Randomised controlled trial
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SEM	Structural equation modelling
SGA	Small for gestational age
SmiNet	Swedish Register of Notifiable Infectious Diseases
SNQ	Swedish Neonatal Quality Register
SPR	Swedish Pregnancy Register
WHO	World Health Organization

Preface

My first assignment with Médecins Sans Frontières in the Central African Republic in 2017 decisively awakened my desire to pursue research. There, I became acutely aware of the grotesque health manifestations of extreme poverty. It gave a human face to the statistics that describe the vast global inequities in health. That experience led me to a central question: how do we value a human life? We are all born human, and I believe that a fundamental principle must be that all people have equal value and, consequently, equal rights to health. Since then, I have striven to let this principle guide my professional life.

In late 2018, I started collaborating with Ola, my main supervisor, with the objective of developing a doctoral research project. I was fascinated by Ola's work on delayed umbilical cord clamping at birth. It was a method that could make a significant difference without requiring expensive technical equipment, making it accessible even in low-resource settings. Paper I in this thesis examines the effect of delayed cord clamping on later child neurodevelopment in a cohort from Nepal.

During the development of paper I, the emergence of the COVID-19 pandemic posed both new challenges and opportunities for research in child health and neurodevelopment. The overall aims of the PhD project were shaped in this context in discussion with my main supervisor, Ola, and my co-supervisors Mehreen and Karolina. The thesis came to encompass not only the effects of cord clamping on neurodevelopment, but also how the pandemic affected cord clamping practices (paper II) and how maternal SARS-CoV-2 infection during pregnancy affected child neurodevelopment (papers III–IV).

The COVID-19 pandemic profoundly affected health systems, social structures, and economies worldwide. It became clear that one cannot study child health and development by considering the direct effects of the virus alone. The broader societal consequences of the pandemic must also be taken into account. We kept this in mind when designing papers II–IV. In particular, papers III–IV were supported by an infrastructure that made it possible to adjust for potential sociodemographic confounders.

The research field examining the effects of COVID-19 on child health and development is evolving rapidly. While we now know considerably more than we did at the start of this PhD project, it is important to remember that the full consequences of the pandemic for the health and development of the generation born during this period will only become apparent over a longer time horizon. Developmental trajectories early in life shape health across the entire life course.

A doctoral thesis is not only a body of completed work, but also a process of learning. Through this work, I have learned how to identify and critically appraise new findings. I have developed a solid understanding of statistics, including both its possibilities and its limitations. Above all, I have gained a deeper appreciation of how knowledge is generated as a continuous and evolving process. Most importantly, I have learned how to contribute to that process by generating new scientific knowledge.

Now, at the end of the thesis work, it is fitting to reflect not only on what has been done, but also on what should come next and why. In that reflection, the principle of equal value and equal rights to health for all people should remain central. Since I began my doctoral work, recent developments in the world have further underscored the importance of this principle. Authoritarianism is gaining ground, international collaboration is declining, and it is becoming increasingly acceptable to claim that not all human lives have equal value or should have equal rights to health and wellbeing. Many governments are reducing official development assistance, international humanitarian law is being violated, and humanitarian actors are criminalised in some contexts. I have three children, and this development has made me question what kind of world I have brought them into.

Children occupy a distinct position because they depend on adults. Their right to survival and development should therefore be prioritised, and their views should be respected, in accordance with the United Nations Convention on the Rights of the Child. It is the responsibility of the adult generation to help change the world for the better. I believe we must hold on to the conviction that it is within our power to do so. Authoritarian leaders want us to either believe in an absolute truth or to believe that we cannot trust anyone, that everyone lies, and that what we do does not matter. That is how control is maintained: through division.

Science offers the opposite message. Through international collaboration, we can generate knowledge with the aim of making the world better for all. Even if truth is never absolute and we know nothing with complete certainty, what we know now is the best understanding we can achieve.

Ola's enthusiasm has been a major source of inspiration throughout this work. His belief, together with that of my co-supervisors, that what we do and say matters and that we can change the world for the better through science has been deeply motivating to me. They have been an important source of inspiration, and I am grateful for that.

I hope that this thesis has contributed to expanding access to the benefits of delayed cord clamping for children worldwide, and to a more nuanced understanding of the potential effects of SARS-CoV-2 infection during pregnancy on child health and neurodevelopment. In doing so, it may offer reassurance to affected families and clinicians, and help guide future research. I am grateful for the tools that I have acquired during my PhD training, not least through collaboration with my

supervisors and other research colleagues. I will strive to use this knowledge to help make the world a little better.

2026-08-13

Johan Berg

Table 1. Summary of thesis

	Aim	Design	Results	Conclusion
I	To assess the effects of delayed CC (≥180 s) vs early CC (≤60 s) on neurodevelopment at 36 months of age.	Single-centre RCT, Kathmandu, Nepal; healthy term children randomised 1:1 to early vs delayed CC; outcome ASQ at 36 months (phone interviews).	No differences in ASQ mean scores between groups; no association between ASQ scores and prior IDA at 8 months; more girls in the early CC group at risk of gross motor impairment (p = 0.02).	No overall neurodevelopmental screening differences between early and delayed CC. Early CC may increase risk of gross motor delay among girls.
II	To review CC guidelines and reported CC practice in SARS-CoV-2–infected pregnancies and examine associations between CC timing and mother-to-child SARS-CoV-2 transmission.	Systematic review and meta-analysis of studies and official guidelines on CC in women with SARS-CoV-2 infection (Dec 2019–July 2021).	48 studies and 40 guidelines (1 476 children); early CC reported roughly twice as often as delayed CC; similar neonatal SARS-CoV-2 positivity rates after delayed vs early CC; most transmissions classified as in utero.	Delayed CC did not seem to increase mother-to-child SARS-CoV-2 transmission and should be encouraged even when the mother has SARS-CoV-2 infection.
III	To investigate the association between antenatal maternal SARS-CoV-2 infection and neurodevelopment in 4-month-old children.	Prospective multicentre cohort; exposed vs unexposed children; exposure: maternal SARS-CoV-2 infection during pregnancy; outcome parent-reported ASQ at 4 months with background data from national registers.	1 446 children included; no overall group differences in ASQ mean scores; exposure associated with lower risk of fine motor scores below cutoff; severe maternal COVID-19 associated with higher risk of abnormal ASQ results.	Antenatal maternal SARS-CoV-2 infection was not associated with overall impaired neurodevelopmental screening at 4 months. Severe maternal disease may be linked to adverse neurodevelopment in exploratory analyses.
IV	To investigate the association between antenatal maternal SARS-CoV-2 infection and neurodevelopment in 24-month-old children, accounting for maternal postpartum depression and mother–child bonding.	Prospective multicentre cohort; exposed vs unexposed children; exposure: maternal SARS-CoV-2 infection during pregnancy; outcome parent-reported ASQ at 24 months with background data from national registers.	745 children included. No overall group differences in ASQ mean scores or scores below cutoff. Mediation analyses found no indirect effect through postpartum depression or bonding.	Antenatal maternal SARS-CoV-2 infection was not associated with overall impaired neurodevelopmental screening at 24 months.

Abbreviations: ASQ, Ages and Stages Questionnaire; CC, cord clamping; RCT, randomised controlled trial

Introduction

Despite remarkable progress in nearly halving the under-five mortality rate over the past 25 years[1], an estimated 250 million children under five years worldwide (about 40%) will not reach their full developmental potential[2]. This number is particularly high in low- and middle-income countries (LMIC)[2].

The first 1 000 days of life, i.e. from conception to two years of age, have been emphasised as fundamental for human development[3-6]. Functional and anatomical studies of the brain indicate that the concept should expand to include the third year of life[4]. Nevertheless, the principle remains the same: the basis for the individual's long-term health trajectory and overall neurodevelopment is largely determined by early life events[3-5,7].

The period from the last quarter of gestation through the first 2–3 years of life is a time of high plasticity in brain organisation, characterised by rapid synapse formation, corpus callosum overgrowth and myelination[6]. Specific functions such as sensory and perceptual processing, language and the foundations of cognitive processing develop in interactions with the environment during different 'critical periods' of development early in life[3,5]. When a critical period for a certain function is closed, the brain circuit is stabilised, and the function can no longer be obtained[3,5]. Even if the brain can adapt across the whole lifetime, interactions with the environment early in life affect basic brain processes, which can profoundly change how we interpret and interact with the world around us[5].

The first 1 000 days of life therefore constitute a window of opportunity but also of vulnerability for child health and development[2,3,7]. While interventions during pregnancy, childbirth and infancy can have a major positive lifelong impact on health and development, environmental disturbances can damage the brain and the body with irreversible consequences for wellbeing and development[2,3,5,7]. Early child health and development are also closely linked to maternal health[7].

Foetal and early-life macro- and micronutrient deficiencies increase the risk of poor growth and negatively affect long-term health, cognitive development, and economic outcomes on a global level[4,7-10]. Early initiation of breastfeeding and exclusive breastfeeding reduce neonatal mortality in LMICs[11] and has been associated with improved performance on intelligence tests, especially in high-income countries (HICs)[12].

Infections during pregnancy can affect the foetus through placental compromise, severe maternal disease, vertical infection, induction of preterm birth, or maternal or foetal immune and inflammatory responses resulting in long-term impacts on subsequent neurodevelopment[13-17]. Postpartum infections early in life have also been associated with adverse neurodevelopmental and cognitive outcomes[18-21].

After birth, the child needs an emotionally responsive, supportive and developmentally stimulating environment to reach their full developmental potential[2]. Maternal and paternal postpartum depression, as well as maternal stress, anxiety and postpartum post-traumatic stress, affect the quality of parent-child interactions and have been associated with lower cognitive scores and adverse emotional and behavioural problems up to school age and worse school performance and increased risk of depression in adolescence[22-26].

Within this broader framework of early-life influences on child health and brain development, this thesis primarily examines two exposures: delayed umbilical cord clamping (CC) at birth and maternal SARS-CoV-2 infection during pregnancy. Both are considered in the wider context of the COVID-19 pandemic and its impact on perinatal practice. The remainder of this introduction first outlines iron deficiency and placental transfusion in relation to early brain development, then reviews the potential impact of delayed CC and maternal SARS-CoV-2 infection on child neurodevelopment and finally situates these exposures within the broader context of pandemic-related changes in perinatal care and health-seeking behaviour.

Iron deficiency and brain development

Iron deficiency, usually defined as a serum ferritin <10–12 mcg/L, is the most prevalent micronutrient deficiency globally, and is a leading cause of disability-adjusted life years in children under five years of age[27,28]. A late manifestation of iron deficiency is iron deficiency anaemia, which affects approximately 25% of preschool children worldwide[28].

Iron is essential for numerous physiological processes and plays a central role in haemoglobin synthesis, oxygen transport, DNA synthesis, and muscle metabolism[28]. Beyond its haematopoietic function, iron is critical for brain development, where it contributes to myelination, synaptogenesis, hippocampal dendritogenesis, the development and function of dopaminergic, serotonergic, and noradrenergic systems, and epigenetic regulation of the brain[27,28].

Rapid somatic growth and central nervous system development during the first year of life result in substantial iron requirements[27]. Due to the low iron content in breast milk, infants depend on their iron stores to meet these demands until approximately six months of age, when dietary diversification introduces additional iron sources[27]. Untreated, iron deficiency during the first two years of life can lead to irreversible adverse effects on cognition and behaviour[4,27]. Prevention is therefore preferable to

treatment, with earlier protection of brain iron status giving optimal neurodevelopmental outcomes[4].

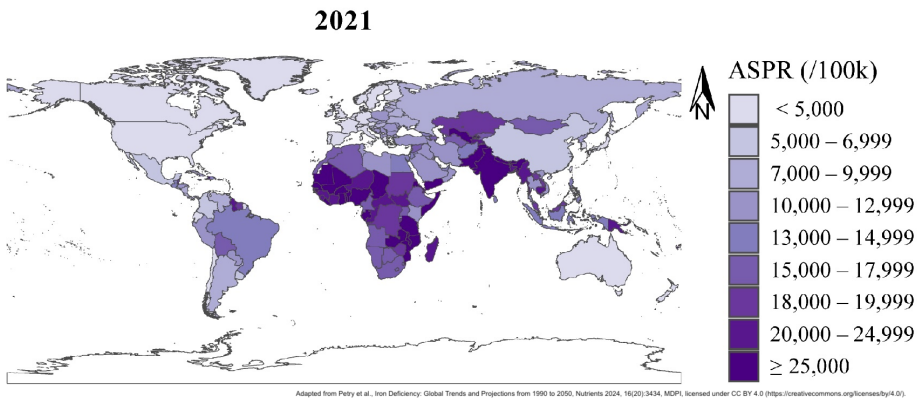


Figure 1. Age-standardised prevalence rate of iron deficiency at the national level in 2021

The fetoplacental circulation

The relationship between delayed CC at birth and infant iron status is grounded in the dynamics of fetoplacental blood flow. Therefore, a brief description of the fetoplacental circulation is needed to contextualise the physiological basis of this relationship. During foetal life, the placenta delivers oxygen and nutrients to the foetus while removing metabolic waste to the maternal circulation. The proportion of foetal blood volume it contains decreases from ~50% at 30 weeks' gestation to ~25% at term[29,30]. At birth, umbilical arteries close within 15–45 seconds while venous flow persists, resulting in a net placental-to-child blood transfusion of approximately 15–30 ml/kg of within the first 3–5 minutes. This process was first described by Budin in 1875 and later confirmed in studies from the 1960s and 2010s[30-34].

The rate at which this net blood transfusion occurs depends on several factors: the position of the child relative to the placenta (a lower position facilitates faster transfer), placental contractions (increasing net flow to the child), and the onset of the child's breathing, which reduces pulmonary vascular resistance[33,35]. In utero, foetal pulmonary blood flow is limited because placental gas exchange predominates. After birth, the transition to pulmonary respiration is accompanied by a marked decrease in pulmonary vascular resistance which increases pulmonary blood flow and redistributes the circulatory volume[33].

Delayed umbilical cord clamping – effects on child health and neurodevelopment

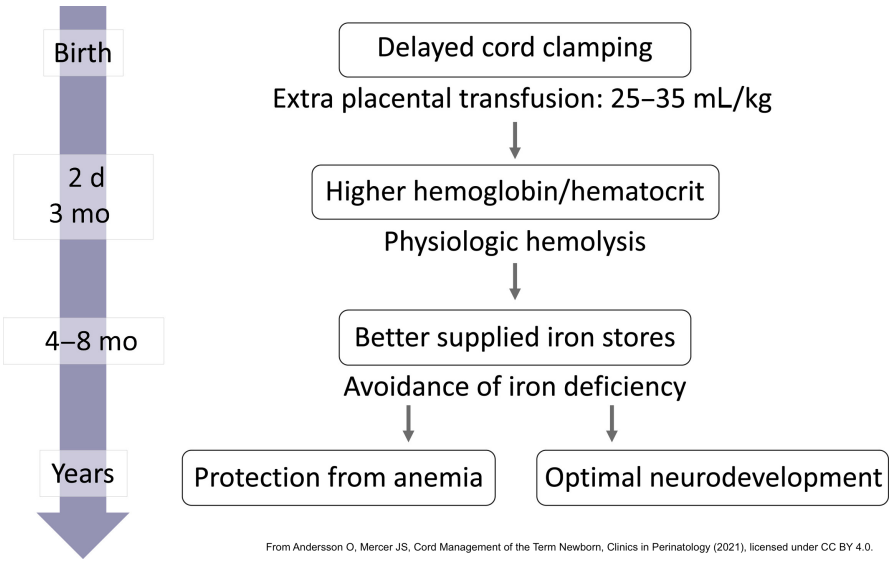


Figure 2. The placental transfusion model

The additional placental transfusion from delaying the clamping of the umbilical cord at birth provides an important iron reservoir during early infancy, when iron demands are high and dietary intake is limited. In term children, delayed CC has been associated with higher haematocrit and haemoglobin concentrations after two days of life[30,36]. Delayed CC for three minutes further reduces the risk of iron deficiency anaemia at 3–8 months[35-37], providing a plausible mechanism for its neurodevelopmental benefits (Figure 2). Several studies have suggested neurodevelopmental benefits of delayed CC in healthy term children. Mercer et al. examined brain myelination using magnetic resonance imaging in children randomised to delayed CC (>5 minutes) versus early CC (<20 seconds) [38,39]. They reported higher ferritin levels at four months and increased myelination in brain regions associated with motor, visual, and sensory function at both four and 12 months in the delayed clamping group[38,39]. Even so, neurodevelopmental testing at 12 months showed no between-group differences[38]. In a Swedish cohort, CC after three minutes versus ten seconds reduced iron deficiency prevalence at four months but there were no differences in neurodevelopmental outcome at four- or 12 months[36,40,41]. However, at four years, the delayed CC group had better scores in the Ages and Stages Questionnaire third version (ASQ) personal-social and fine-motor domains, the prosocial subscale of the Strengths and Difficulties Questionnaire, and the Movement ABC bicycle-trail task; boys also had improved processing speed on

the Wechsler Preschool and Primary Scale of Intelligence (WPPSI)[42]. No difference in attention deficit hyperactivity disorder risk was observed at age ten years[43].

Beyond the additional iron supply, keeping the umbilical cord intact during the first minutes after birth also contributes to stem cell transfusion and cardiovascular stability, which may have additive effects on child health and development[35,44]. In children born preterm, delaying CC for more than one minute reduces mortality[45], with the largest effect seen in those clamped after at least two minutes[45]. Delayed CC has been associated with improved neurodevelopment at seven months and 18–22 months in preterm children[46,47].

SARS-CoV-2 infection during pregnancy – effects on the foetal brain and later child neurodevelopment

The widespread exposure to SARS-CoV-2 during pregnancy has raised important questions about its possible effects on neurodevelopmental trajectories in early life. Building on the earlier discussion of maternal infection and immune activation, SARS-CoV-2 infection during pregnancy is of particular concern because it may affect foetal neurodevelopment through inflammatory and placental mechanisms.

Pregnant women were identified early as a group at increased risk of SARS-CoV-2-related complications, including severe maternal disease, preterm birth, and admission of both mother and her newborn child to the intensive care unit[48,49]. Evidence suggests that maternal SARS-CoV-2 infection might lead to maternal–foetal immune activation, persistent epigenetic reprogramming, direct foetal infection, and placental pathology with hypoxia, stillbirth and preterm birth[15,50-52]. Taken together, these processes constitute biologically plausible pathways by which antenatal exposure to SARS-CoV-2 could cause acute perinatal morbidity and longer-term neurodevelopmental impairment. In this section, these mechanistic pathways are first summarised, followed by an overview of observational studies assessing associations between maternal SARS-CoV-2 infection in pregnancy and subsequent child neurodevelopment.

Direct viral infection of the foetus

There is some evidence that SARS-CoV-2 has neurotropic potential, and transplacental transmission has been confirmed[15,53,54]. Consequently, direct infection of foetal neural tissues is biologically plausible. Nevertheless, available evidence suggests that mother-to-child SARS-CoV-2 transmission occurs in less than two percent of cases and that confirmed transplacental transmission is even less frequent[55].

Placental compromise

SARS-CoV-2 infection in pregnancy has been associated, in a small subset of cases, with placentitis leading to severe placental dysfunction and adverse foetal or neonatal outcomes, including stillbirth and preterm birth[56-58]. The virus can infect the placenta because the syncytiotrophoblast expresses ACE2 and spike-priming proteases and may also utilise additional entry factors including DPP4 and CD147[51,56]. Infection appears to trigger a robust innate immune response at the maternal–foetal interface with monocyte–macrophage recruitment and other leukocytes into the intervillous space[51,56]. Complement activation with C4d deposition has been demonstrated and proposed as contributing to trophoblast necrosis and the associated inflammatory response[51,56]. In several case reports, affected placentas show a characteristic triad of chronic histiocytic intervillositis, massive perivillous fibrin deposition and diffuse villous trophoblast necrosis[51,58,59]. This pattern was uncommon before the COVID-19 pandemic[51,58,59].

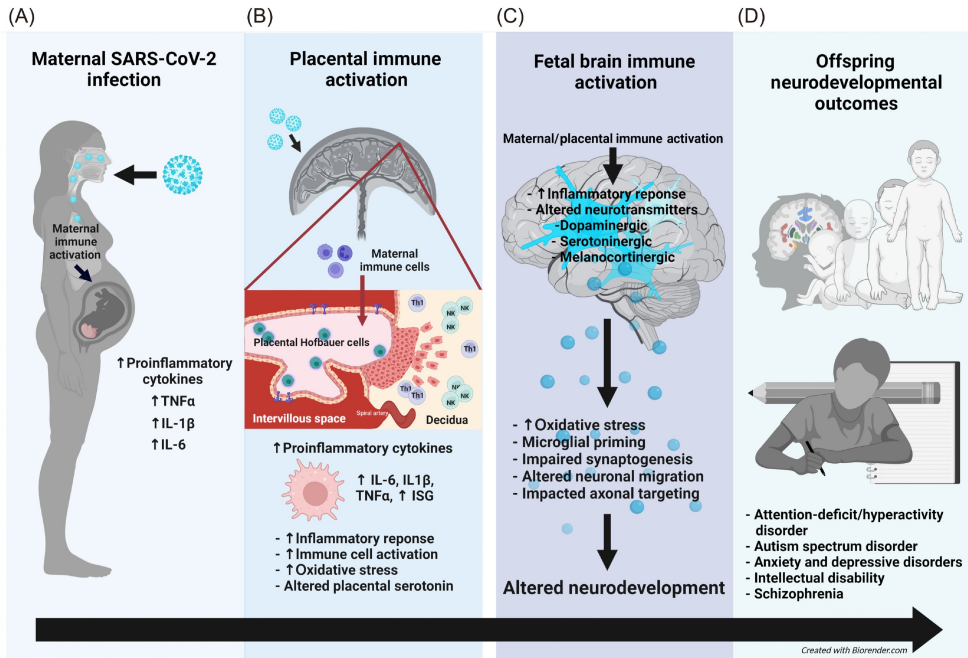


Figure 3. SARS-CoV-2 infection during pregnancy and its potential immune-mediated effects on child neurodevelopment

Maternal immune activation

Importantly, even in the absence of confirmed transplacental transmission, accumulating evidence indicates that SARS-CoV-2 infection in pregnancy can induce maternal and placental immune activation, including activation of

complement pathways[15,50-52,56]. Combined with broader literature linking maternal infection and immune activation to an increased risk neurological diagnoses in the child, including depression, ADHD and autism spectrum disorders (ASD)[14,17,60], this provides a potential pathway to foetal neuroimmune programming and later neurodevelopmental alteration. In fact, maternal immune activation has been proposed as the most common mechanism by which maternal infections affect offspring neurodevelopment[15]. In pregnancy, SARS-CoV-2 infection is associated with a pro-inflammatory maternal profile, particularly elevated interferon-gamma (IFN-γ), interleukin (IL)-1β and IL-6[15]. It also induces up-regulation of interferon-stimulated genes, complement and antigen-presentation pathways in decidua, villous tissue and cord-blood immune cells, even when the placenta itself is PCR-negative[15,52]. Experimental and human data indicate that these immune signals reach the foetal brain, altering neurogenesis, synaptogenesis and synaptic pruning via microglial activation and complement-mediated synapse elimination[15,52]. Such neuroimmune changes have been associated with increased risk of ASD- and ADHD-like phenotypes in the child[15,52] (Figure 3).

Building on these immune-mediated foetal effects, Hill et al. found that higher maternal IL-6 at birth correlated with both maternal illness severity and poorer 12-month communication and problem-solving screening scores in exposed children, suggesting a possible dose–response relationship between cytokine exposure and early developmental delay[50]. Kehdi et al. reported that higher cord-blood IFN-γ and TNF-α were associated with cognitive delays, whereas IL-6, IL-8, IL-17 and IL-1β were linked to motor delays in the first two years of life following antenatal SARS-CoV-2 exposure[61].

Epigenetic mechanisms and magnetic resonance imaging findings

Maternal immune activation is increasingly understood to act through epigenetic mechanisms that embed inflammatory exposures into long-lasting changes in gene expression in brain and immune cells. These mechanisms include DNA methylation, histone modifications and microRNAs[60]. Findings on DNA methylation were mixed: Hill et al. observed associations with genes involved in neurogenesis, synapse organisation, and ASD-related pathways, whereas Kocher et al. found no differences between exposed and unexposed children, but did report methylation changes in pandemic-born children compared to a pre-pandemic cohort[50,62].

Children with antenatal exposure to SARS-CoV-2 showed magnetic resonance imaging findings suggestive of adverse neurodevelopment or ASD, with one study indicating partial mediation of lower Bayley cognition and language scores at two years[63,64]. It is important to note that the studies under this headline included small numbers of SARS-CoV-2–exposed children (n=15–47), which limits definitive conclusions[50,61,63,64].

Potential associations with child neurodevelopment

A primary focus of this thesis is the association between antenatal exposure to maternal SARS-CoV-2 infection and subsequent child neurodevelopment compared with unexposed controls. This has been investigated in several other studies with conflicting results. Some studies with follow-up through the first year of life reported adverse neurodevelopmental outcomes[65-68], while others found no significant association[69-72]. A systematic review and meta-analysis found associations with impairments in hearing, fine motor and problem-solving skills, but these effects appeared to resolve over time[73]. Consistent with this, most studies assessing neurodevelopment beyond one year of age found no significant association[74-76]. It is important to note that most studies used neurodevelopmental screening questionnaires rather than diagnostic tools.

Recently, however, Shook et al. found a higher risk of any International Classification of Diseases (ICD)-coded neurodevelopmental diagnosis at 36 months of age in a retrospective study of 18 943 live births, including 861 children exposed to SARS-CoV-2 in pregnancy[77]. Partially contrasting these findings, Croen et al. found no overall difference in neurodevelopmental diagnoses at 27–48 months in a cohort of 69 987 children, including 2 777 exposed. Still, exposed girls had higher risk of autism-spectrum disorders, while exposed boys had a lower risk of motor impairment[78]. These findings again raise the concern of potential adverse effects on long-term child neurological outcome.

Other pandemic-related influences on child neurodevelopment

Early in the pandemic, it became evident that factors beyond direct exposure to SARS-CoV-2 infection could also influence children's neurodevelopment. Shuffrey et al. did not find an association between maternal SARS-CoV-2 infection in pregnancy and neurodevelopment at six months of age but observed that children born during the pandemic had lower neurodevelopmental screening scores compared to pre-pandemic controls, indicative of poorer neurodevelopmental outcomes[71]. Johnsson et al. confirmed this in a study of over 50 000 children, reporting a small but statistically significant difference in neurodevelopment screening scores that indicated worse outcomes in pandemic-born children[79]. The authors suggested that pandemic-related caregiver psychosocial stress might represent an underlying mechanism, but this was not directly assessed in the studies.

Indeed, high levels of maternal anxiety and depression were reported during the COVID-19 pandemic[80,81]. Furthermore, maternal postpartum depression has been associated with impaired mother–child bonding in this setting[82,83]. Studies conducted before the COVID-19 pandemic have reported associations between maternal postpartum depression and child neurodevelopment[23,24]. Importantly, Göbel et al. showed that impaired parent–child bonding partially mediated this

pathway: higher prenatal depressive symptoms were associated with worse bonding, which in turn was associated with poorer child neurodevelopment[84].

Beyond the broader pandemic-related mental health burden, maternal SARS-CoV-2 infection during pregnancy may itself influence maternal depression. Mental disorders have been associated with greater COVID-19 susceptibility[85], and severe SARS-CoV-2 infection has been associated with an increased risk of subsequent depression in pregnancy[86]. Both virus-induced neurobiological changes and psychological stressors have been proposed as potential mechanisms underlying depression following SARS-CoV-2 infection, but this association has, to my knowledge, not been studied[87].

COVID-19, perinatal care and health-seeking behaviour

Umbilical cord clamping

Due to its health benefits for the newborn, delayed CC is recommended as standard practice for both term and preterm children by most international organisations, including the World Health Organization (WHO), although recommended timing varies from 30 to 300 seconds[88]. In the early phase of the pandemic, concerns about vertical SARS-CoV-2 transmission via placental blood or direct mother–child contact led some guidelines to recommend early CC in mothers with suspected or confirmed SARS-CoV-2 infection[89-91]. These recommendations risked depriving many children of the established benefits of delayed CC[92].

Other perinatal practice

Apart from the potential impact on CC practice, other perinatal practices were also affected by COVID-19. Early in the pandemic, a report from China described Caesarean section rates of 93% in mothers with SARS-CoV-2 infection, with the majority attributed to fear of the effect of COVID-19 on the pregnancy[93]. Silva et al. found a slight increase in Caesarean sections during the pandemic compared with pre-pandemic periods, mainly driven by maternal request[94]. Still, a systematic review found no overall increased risk of Caesarean section during the COVID-19 pandemic[81].

In March 2020, the WHO published clinical guidelines recommending breastfeeding-supportive practices, such as skin-to-skin contact, rooming-in, and direct breastfeeding, for mothers with SARS-CoV-2 infection at birth. Nonetheless, Gribble et al. reviewed 183 guidance documents from 101 countries in November–December 2020 and found that fewer than one quarter recommended these measures for SARS-CoV-2-infected mothers[95]. Restricting these mother–child care practices could potentially have detrimental health consequences for newborns far exceeding those of contracting SARS-CoV-2 infection, particularly in preterm children[96]. Another review found mixed results regarding skin-to-skin practice and rooming-in

after birth in SARS-CoV-2–positive mothers, with some studies reporting decreased rates and others finding no difference compared with uninfected mothers[97]. Furthermore, in a study early in the pandemic, mothers with SARS-CoV-2 infection had longer mother–child separation, which was associated with poorer gross motor neurodevelopmental screening scores at three months. This separation also accounted for most of the indirect effect of maternal infection on gross motor outcome[72].

Impact on health-seeking behaviour

Lockdown measures altered health-seeking behaviour and have been associated with adverse pregnancy and child outcomes. During the first lockdown in Nepal, Kc et al. found that institutional births fell by more than half, while institutional stillbirth and neonatal mortality rates increased[98]. Khalil et al. reported increased stillbirth rates at a UK hospital during the first lockdown, with none attributed to maternal COVID-19. The authors interpreted this as collateral damage of the pandemic response: fewer antenatal visits, delayed presentation with reduced foetal movements, and fear of attending hospital[99]. However, national-level data from England showed no increase in stillbirths during April–June 2020 compared with the prior year, suggesting local patterns in health-seeking behaviour and service organisation rather than a nationwide trend[100]. Overall, increased rates of stillbirth following both pandemic exposure and maternal SARS-CoV-2 infection have been reported in systematic reviews, making it unclear whether, or to what extent, these associations reflect viral infection itself or other pandemic-related effects[81,101].

Taken together, these findings illustrate the multifaceted impact of the COVID-19 pandemic on perinatal care and health-seeking behaviour. They further underscore the difficulty of disentangling effects of maternal SARS-CoV-2 infection from broader 'pandemic pregnancy' exposures.

The Swedish COVID-19 strategy

During the first COVID-19 wave, Sweden adopted a less restrictive strategy than many nations, avoiding nationwide lockdowns. The emphasis was on mitigation to curb spread without halting it entirely: public distancing was advised, but only enforced in venues like bars, restaurants, and gatherings. Nursing home visits were prohibited, preschools and schools for ages up to 16 remained open, whereas upper secondary schools closed briefly for three months. No household or regional quarantines were imposed, and masks were discouraged beyond healthcare settings[102]. In subsequent waves, Sweden aligned more closely with other countries' measures, imposing restaurant and retail restrictions, household quarantine for COVID-19 cases, and facemask mandates on public transport during rush hours[103]

In Sweden, pregnant women, considered a high-risk population, were instructed to undergo testing and notify their midwives of any COVID-19 symptoms. Under Sweden's Communicable Diseases Act, all laboratory-confirmed positive PCR results, and, from early 2021, also antigen tests, were mandatorily reported to the Swedish Register for Mandatory Registration for Notifiable Diseases (SmiNet). Testing capacity expanded swiftly, becoming broadly accessible by June–July 2020, with routine hospital screening implemented at admission from early 2021[104].

Measuring neurodevelopment

Detecting neurodevelopmental delays at an early stage is crucial for initiating timely, appropriate interventions[105]. While comprehensive tools such as the Bayley Scales of Infant and Toddler Development (Bayley) are regarded as gold standards, they are resource-intensive, requiring considerable time and financial investment because administration must be performed by a trained professional. In addition, they require in-person attendance of both child and caregiver, which limits their practicality in low-resource settings, during pandemics, or in studies with large sample sizes[106].

An alternative is to use screening questionnaires to evaluate who needs further assessment, given their low cost, feasibility in large samples, and wide accessibility. Several different screening questionnaires have been developed. The ASQ is a well-known parent-completed screening questionnaire that follows developmental milestones from 1 to 66 months of age and has been shown to have comparatively strong psychometric properties among screening tools[107,108].

The ASQ has been widely used in studies globally in both high-, middle- and low-income settings[106,109], including Sweden and Nepal[42,106,110-112]. It has also been extensively used in studies conducted during the COVID-19 pandemic[73,113]. Psychometric properties of the ASQ vary across studies and age groups. A systematic review and meta-analysis found moderate pooled sensitivity (0.77) and specificity (0.81) for an ASQ cut-off at >2 SD below the mean to detect “any delay” in at least one domain; for severe delay, pooled sensitivity was approximately 0.84 and specificity 0.77, although the certainty of evidence was rated low to very low[106]. The ASQ generally performed less well during the first two years of life, possibly with the exception of gross motor skills[114-116]. When assessed at 24 months of age, both the ASQ and the Bayley Scales showed very low sensitivity but high specificity for predicting cognitive delay at five years, using the Kaufman Brief Intelligence Test as the reference standard[117]. At 36 months, the ASQ had a higher sensitivity of 0.77 and a specificity of 0.68 for predicting an IQ below 85 at 5–6 years on the Wechsler Preschool and Primary Scale of Intelligence[118].

The Nepalese and Swedish context

In 2017, when paper I in this thesis was carried out, Nepal was still classified as a low-income country. The national neonatal and under-five mortality rates were 20.8 and 34.2, respectively[119] (Figure 4-5). In Kathmandu, where the study was performed, institutional birth coverage was high (93.8%). Countrywide antenatal care coverage was estimated at 68% in 2014 (the birth year of the study population) and was likely also higher in our urban study setting[120]. According to the 2011 Nepal census, the literacy rate in Kathmandu was 86.3%[121]. The levels of iron deficiency in infants older than six months were 30% in an urban area[122].

Sweden is a high-income country with one of the lowest neonatal and under-five mortality rates in the world, estimated at approximately 1.4 per 1 000, and 2.5 per 1 000, respectively, in the years 2020-2022[119] (Figure 4-5). Antenatal care is free of charge and covers almost all pregnancies, and more than 99% give birth at a hospital[123]. Iron deficiency rates in infancy were low (around 5%) before the introduction of delayed CC as standard of practice in healthy children and have likely further decreased since then[36,41].

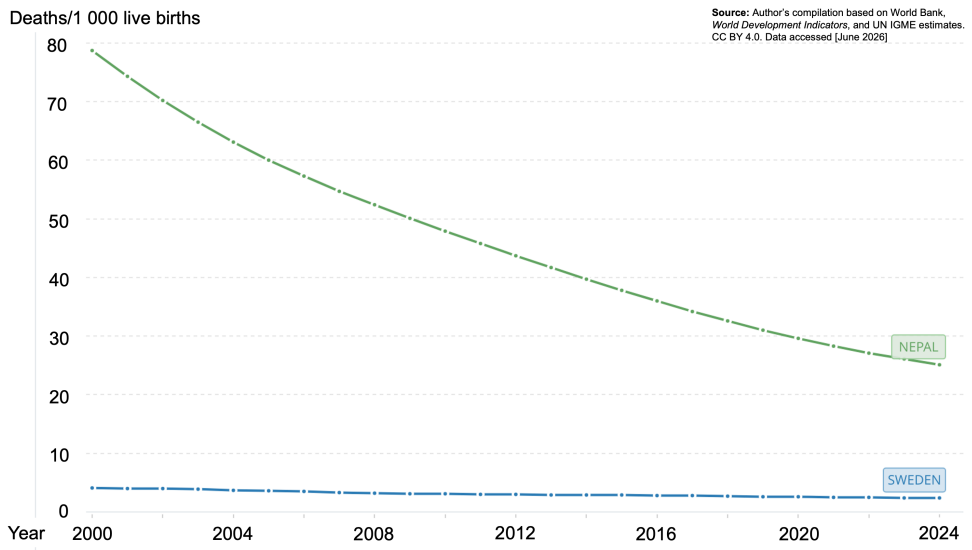


Figure 4. Mortality rate under five years of age (per 1 000 live births) in Nepal and Sweden 2000-2024

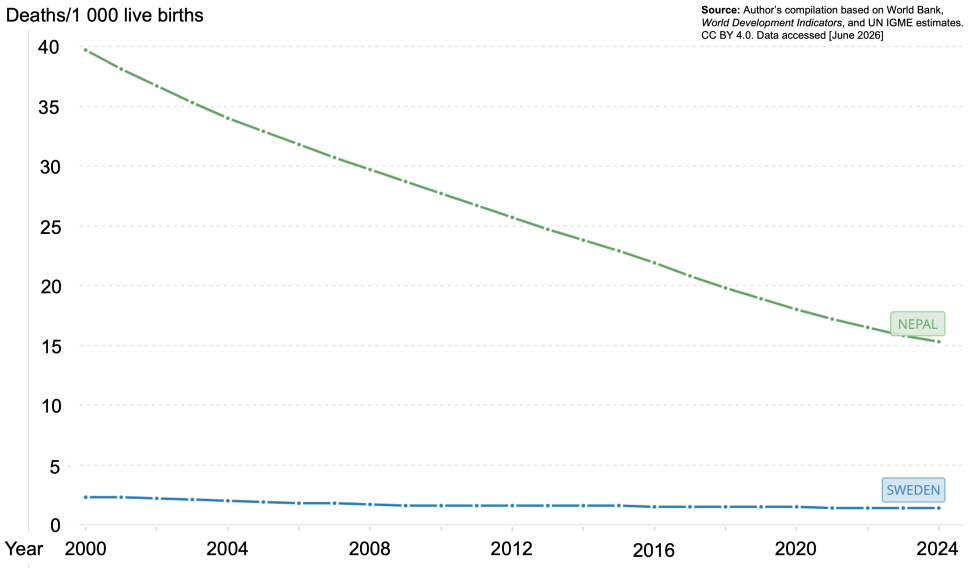


Figure 5. Neonatal mortality rate (per 1 000 live births) in Nepal and Sweden 2000-2024

Rationale

Taken together, the preceding sections outline a common concern: whether perinatal practices and maternal SARS-CoV-2 infection during pregnancy alter early neurodevelopmental trajectories. The central question of this thesis is therefore: How do umbilical CC practices and maternal SARS-CoV-2 infection, in the broader context of the COVID-19 pandemic, affect early child neurodevelopment, and what are the implications for perinatal practice?

Conceptually, the thesis focuses on two main axes that may shape early neurodevelopment. The first axis is umbilical CC practice**,** where delayed CC can increase placental transfusion, improve child iron status, and potentially support neurodevelopment. Conversely, early CC may deprive children of these benefits, particularly in settings with a high burden of iron deficiency. The second axis is maternal SARS-CoV-2 infection and pandemic-related exposures**.** These may influence child neurodevelopment through direct viral effects, placental compromise, immune and epigenetic programming, and indirect pathways such as maternal mental health, bonding, and changes in perinatal care and health-seeking behaviour.

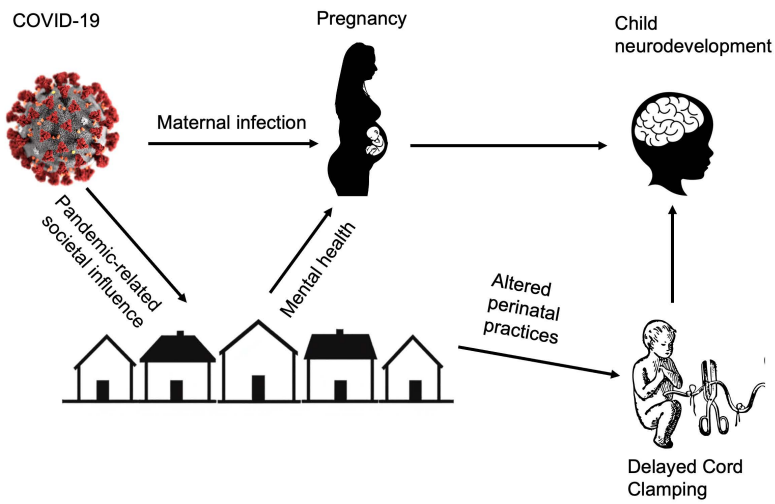


Figure 6. Conceptual model of the thesis: Cord clamping, maternal SARS-CoV-2 infection, and early child neurodevelopment**.**

Within this framework, the four papers address complementary components of the model. A simplified conceptual figure (Figure 6) summarises these relationships:

maternal SARS-CoV-2 infection and pandemic-related factors might influence perinatal practice (including CC) and parental mental health. Early child neurodevelopment, assessed with the ASQ, constitutes the primary outcome. By integrating evidence from a randomised trial, a systematic review and meta-analysis, and prospective register-based cohorts, the thesis seeks to clarify how these pathways influence early neurodevelopment and to inform future clinical and public health recommendations.

When this thesis project was initiated in early 2020, little was known about the impact of delayed CC on child neurodevelopment in a low-income setting with a high prevalence of iron deficiency. In the RCT comparing delayed versus early CC in healthy term children in Nepal, earlier follow-up had shown a reduced risk of iron deficiency from 38.1% to 22.2% at eight months of age, as well as improved ASQ scores at 12 months[37,124]. These findings suggested better neurodevelopment after delayed CC. Paper I of this thesis examined neurodevelopment using the ASQ at 36 months of age in the same trial population to determine whether these early favourable effects persisted over time. To my knowledge, this is currently the longest follow-up study of the effect of delayed CC on child neurodevelopment outside of high-income settings.

During the development of paper I, the sudden emergence of the COVID-19 pandemic fundamentally reshaped societies worldwide, disrupted health systems, placed immense strain on healthcare infrastructure, and changed health-seeking behaviour[98,99,125,126]. It became clear that child neurodevelopment could no longer be studied in isolation from these broader forces. In this rapidly evolving context, the overall aims of the PhD project expanded to also address how the pandemic and maternal SARS-CoV-2 infection might influence CC practice and child neurodevelopment.

Early in the COVID-19 pandemic, concerns about vertical SARS-CoV-2 transmission via placental blood or direct mother–child contact led some guidelines to recommend early CC[89-91]. This created clinical uncertainty and raised concern that many children might be deprived of the established benefits of delayed CC. However, no study had systematically examined CC practices or guideline recommendations, and no robust evidence linked delayed CC to an increased risk of mother-to-child SARS-CoV-2 transmission, leaving important gaps that needed assessment. Paper II was designed to address these gaps through a systematic review and meta-analysis.

When the thesis was outlined, knowledge of how maternal SARS-CoV-2 infection affected mothers and their newborns was limited. Previous case series had reported high maternal and infant mortality and morbidity associated with the coronaviruses causing Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS)[127,128]. An early systematic review suggested that maternal SARS-

CoV-2 infection was associated with maternal morbidity, neonatal death, and possible mother-to-child viral transmission[49]. Together with the established association between maternally induced immune activation and adverse effects on foetal brain development[14,60], these findings raised concerns that maternal SARS-CoV-2 infection during pregnancy could affect long-term neurodevelopmental outcomes in the child. These concerns motivated papers III–IV which examine the association between antenatal maternal SARS-CoV-2 infection and child neurodevelopment. Despite a growing number of studies investigating this association, the evidence remains inconclusive, highlighting the importance of these two studies in addressing this ongoing uncertainty.

In parallel, emerging reports indicated that pandemic-related health concerns, social isolation, and the possibility of mother–child separation at birth could contribute to increased stress and depressive symptoms among pregnant women[89,129]. This could in turn affect mother–child bonding, and potentially child neurodevelopment[130,131]. An early report by Wu et al. associated the pandemic with increased depressive symptoms in pregnant women, but otherwise little was known about this issue[129]. A recent systematic review by Rizzo et al. found that most studies examining the association between antenatal SARS-CoV-2 exposure and child neurodevelopment were limited by insufficient adjustment for maternal psychopathology[73]. Moreover, the mediating role of maternal postpartum depression and mother–child bonding in this association has, to my knowledge, not been investigated during the pandemic. These gaps motivated paper IV, which examined whether maternal postpartum depression and mother–child bonding mediate a potential association between antenatal SARS-CoV-2 exposure and child neurodevelopment.

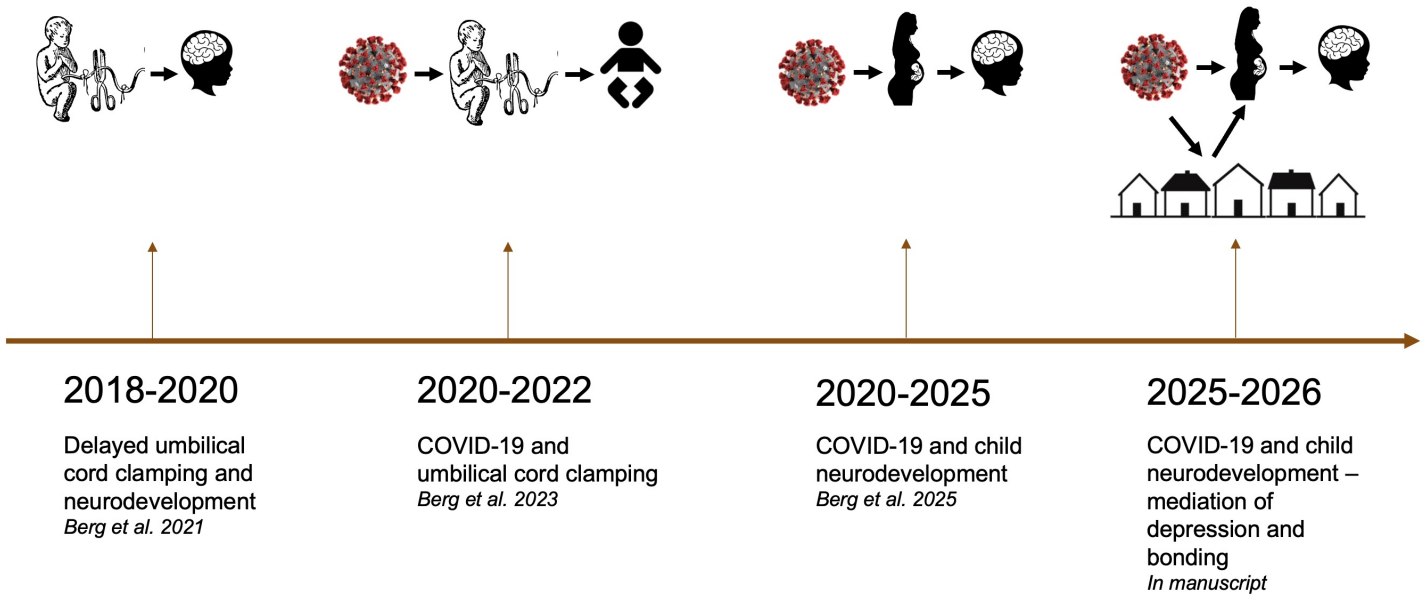


Figure 7. Timeline and progression of the papers included in this thesis

Aims

The overall aim of this thesis was to explore the impact of umbilical CC practices and maternal SARS-CoV-2 infection on early child neurodevelopment, and to examine CC practices in SARS-CoV-2-positive mothers.

Paper I

To assess the effects of delayed CC (≥180 s) compared to early CC (≤60 s) on neurodevelopment using the ASQ at age 36 months.

Paper II

To review CC recommendations and reports of practice as well as to analyse associations between timing of CC and mother-to-child SARS-CoV-2 transmission during the early phases of the pandemic.

Paper III

To investigate the association between antenatal maternal SARS-CoV-2 infection and neurodevelopment using the ASQ in four-month-old infants.

Paper IV

To investigate the association between antenatal maternal SARS-CoV-2 infection and child neurodevelopment using the ASQ at 24 months of age, while accounting for the influence of maternal postpartum depression and mother–child bonding.

Methods

Table 2. Summary of thesis methods

	Paper I	Paper II	Paper III	Paper IV
Design	Single-centre randomised controlled trial	Systematic review and meta-analysis	Prospective multicentre cohort	Prospective multicentre cohort
Population	540 term, healthy Nepalese children; 350 followed at 36 months.	SARS-CoV-2–positive pregnant women and their liveborn children	1 446 Swedish children (exposed vs unexposed to maternal SARS-CoV-2).	745 Swedish Children (exposed vs unexposed to maternal SARS-CoV-2)
Data source	Trial data from one maternity hospital and ASQ phone interviews.	Published studies and official guidelines	COPE cohort, parent-reported ASQ and linked Swedish national health registers	COPE cohort, parent-reported EPDS, PBQ and ASQ and linked Swedish national health registers,
Intervention/ exposure	Early cord clamping (≤60 s) vs delayed clamping (180 s).	Early vs delayed cord clamping practice or recommendations	Maternal SARS-CoV-2 infection during pregnancy (yes/no, severity, trimester of exposure).	Maternal SARS-CoV-2 infection during pregnancy (yes/no, severity).
Outcome	Neuro-development; ASQ total and domain scores at 36 months; "at risk" developmental status.	Child SARS-CoV-2 positivity and timing of transmission; selected care practices (e.g., mode of birth, breastfeeding)	Neuro-development; ASQ total and domain scores at 4 months; below-cutoff proportions.	Neuro-development; ASQ total and domain scores at 24 months; below-cutoff proportions.
Analysis	Intention-to-treat comparisons using t-tests and Fisher's exact tests, multiple regression analysis	Descriptive synthesis and pooled prevalence estimates by clamping category	Group comparisons and multiple regression for mean differences and odds ratios.	Group comparisons and multiple regression for mean differences and odds ratios. SEM, mediation analysis

Abbreviations: ASQ, Ages and Stages Questionnaire; CC, cord clamping; COPE, COVID-19 during Pregnancy and Early Childhood; EPDS, Edinburgh Postnatal Depression Scale; PBQ, Postpartum Bonding Questionnaire; SEM, structural equation modelling; SNQ, Swedish Neonatal Quality Register

The overall aim of this thesis was to evaluate umbilical cord clamping practices and maternal SARS-CoV-2 infection in relation to early child neurodevelopment. Table 2 provides an overview of the design, populations, data sources, exposures, outcomes, and main analyses for papers I–IV.

Design and study populations

Paper I

Paper I uses secondary outcome data from a randomised controlled trial (NCT02222805) in which children born to women allocated to delayed or early CC were compared in a 1:1 ratio[132]. The trial took place in the low-risk birth unit at Paropakar Maternity and Women's Hospital, a public tertiary facility in Kathmandu, Nepal, which had an annual delivery volume of about 20 000 births during the study's inclusion period, 2 October to 21 November 2014.

Eligibility criteria were identical to those for admission to the unit: healthy women (no documented hypertension, infection, diabetes, or other chronic medical illness) with uncomplicated pregnancies, planned vaginal birth, gestational age 34+0–41+6 weeks, and singleton pregnancies. Children with major congenital malformations or syndromes considered likely to influence the outcomes were excluded. A research assistant recruited participants continuously, 24 hours a day on both weekdays and weekends. The treatment allocation was disclosed only when delivery was imminent, as previously described[37]. The team responsible for conducting and administering the ASQ interviews remained blinded to group assignment.

Paper II

Paper II was a preregistered systematic review and meta-analysis (PROSPERO CRD42020199500) conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[133]. Prospective and retrospective cohort studies, case series, case reports, and preprints were eligible if they (1) described CC practice at birth in women diagnosed with COVID-19 during pregnancy, (2) reported outcomes for live-born children at any gestational age, and (3) were published between 1 December 2019 and 20 July 2021. In addition, guidelines issued by governmental agencies, professional societies, or international health organisations that included recommendations on CC in this context during the same period were included. Publications were restricted to English, German, Swedish, French, Italian, Spanish, Portuguese, and Romanian.

Papers III–IV

Papers III–IV were based on a prospective multicentre cohort, the Swedish national study "COVID-19 during pregnancy and early childhood" (COPE, NCT04433364). Twenty-four maternity units and their affiliated neonatal units contributed data. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (https://www.strobe-statement.org).

Women aged 18 years or older who received antenatal care or gave birth at participating hospitals and had live-born children of any gestational age were invited to participate. Recruitment was undertaken by clinical staff during routine antenatal visits.

Variables

Exposure variables

Umbilical cord clamping

Umbilical CC was used as an exposure variable in papers I–II. In paper I, timing of CC was recorded at birth and defined as delayed ≥180 seconds versus early ≤60 seconds. This categorisation was based on an observational study from the same hospital reporting a mean CC time of 61 seconds (SD 33 seconds)[134]. In paper II, CC was regarded as delayed when the cord was clamped ≥30 seconds after birth or, when no specific timing was reported, when CC was explicitly described as "delayed," "deferred," or "late."

Maternal SARS-CoV-2 infection

Maternal SARS-CoV-2 infection during pregnancy was used as an exposure variable in papers II-IV. For paper II, maternal SARS-CoV-2 infection was considered present if the original study stated that the woman had a diagnosis of SARS-CoV-2 infection. For papers III–IV, access to Swedish national health registers enabled a more detailed definition. Maternal infection was defined as either (1) a positive SARS-CoV-2 test result (polymerase chain reaction [PCR] or antigen test) recorded in SmiNet[135] or (2) a relevant diagnostic code in the Swedish version of the International Classification of Diseases, Tenth Revision (ICD-10: U07.1 or U07.2) in the Swedish Pregnancy Register[123], the National Patient Register[136] or the Swedish Intensive Care Register[137]. Almost all SARS-CoV-2 infections were PCR confirmed. The exposure window for maternal infection was identical in papers II–IV: from start of pregnancy up to two days after birth, extended postpartum to capture the shortest reported mean incubation period[138].

In papers III–IV, exposure to severe SARS-CoV-2 infection was analysed. It was defined as hospitalisation or receiving oxygen therapy due to COVID-19, corresponding to a score of three or higher on the WHO seven-point ordinal severity scale[139].

Paper III analysed maternal SARS-CoV-2 infection exposure divided by trimester. Trimesters were defined as follows: first trimester, from conception up to 11 weeks six days; second trimester, from 12 weeks zero days to 27 weeks six days; and third trimester, from 28 weeks zero days onwards.

Swedish national health and quality registers that were linked with the COPE dataset used in papers III–IV

The Swedish Pregnancy Register

This national quality register, established by Sweden's regional healthcare authorities, integrates prospectively collected information from several sources, including the Swedish Maternal Health Care Register, the National Quality Register for Prenatal Diagnosis, and standardised electronic records from antenatal, delivery, and neonatal care. It captures data on over 95% of all births in Sweden and follows pregnancies from the initial antenatal visit through the postpartum follow-up at 8–12 weeks[123]. The register provides detailed information on maternal demographics, medical and reproductive background, antenatal assessments, delivery outcomes, and postpartum follow-up (http://www.graviditetsregistret.se/).

The Swedish Register of Notifiable Infectious Diseases (SmiNet)

COVID-19 is classified as a notifiable disease in Sweden. All confirmed SARS-CoV-2 infections (positive PCR tests and, from 2021, antigen tests) are reported to SmiNet by both the laboratories performing the analyses and the physicians responsible for patient care (https://www.folkhalsomyndigheten.se/smittskydd-beredskap/overvakning-och-rapportering/sminet/)[104,135].

The Swedish Intensive Care Register

This national quality register contains data on intensive care in Sweden[137]. For women requiring ICU admission, information on disease severity and clinical interventions was retrieved from this source (http://www.icuregswe.org/).

The National Patient Register

This mandatory national health register includes diagnostic information from both inpatient care and specialised outpatient services[136]. Data on ICD-10 diagnoses during pregnancy were extracted for the study population (https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/patientregistret/).

Outcome variables

Neurodevelopment – the ASQ

Neurodevelopmental status measured with the ASQ served as the primary outcome in papers I and III–IV. The ASQ is a caregiver-completed developmental screening tool that tracks milestones from 1 to 66 months of age. Each questionnaire includes three components: (1) brief questions on background characteristics, (2) thirty items divided into five developmental domains (communication, gross motor, fine motor, problem solving, personal-social), and (3) ten open-ended questions about parental concerns. In every domain, six items are scored "yes," "sometimes," or "not yet," corresponding to ten, five, and 0 points, respectively, for a maximum of 60 points per domain. Higher scores reflect more advanced neurodevelopment. Domain scores are interpreted using established cutoffs that classify children as "low risk" (≤1 standard deviation [SD] below the mean), "monitor" (>1 but ≤ 2 SD below the mean), or "refer" (>2 SD below the mean), according to the ASQ User's Guide [107,140].

This thesis focused on the second, domain-based part of the ASQ, described in the introduction. A total ASQ score was also derived by summing all five domains (i.e. communication, gross motor, fine motor, problem solving, personal-social) to a maximum score of 300. Thresholds for "monitor" and "refer" were set at 1 and 2 SD below the mean, as described above[140]. The English version of the ASQ was translated into Nepali and Swedish and then back-translated into English; translation was performed by a professional translator for paper I and by a native English speaker for papers III–IV. In addition, the official Arabic, English and Somali translations of the ASQ were used in papers III–IV.

Table 3 outlines the ASQ-related outcome definitions used in the different papers. The ASQ User's Guide recommends relying on cutoff scores[107,140], but mean scores are also frequently reported in research[42,50,66,71,76]. For paper IV, an additional outcome, "at least one domain >2 SD below the mean", was included, reflecting both the manual's recommendations[140] and definitions applied in previous work[75,106]. Because validated Nepali and Swedish versions of the ASQ were not available, mean scores from papers I and IV were interpreted using the study sample's own distributions, whereas paper III used reference data from approximately 6 000 four-month-old children participating in the NorthPop study[141].

Table 3. Ages and Stages Questionnaire outcome definitions used in this thesis

Outcome (ASQ score definition)	Analysis (primary/exploratory) by paper		
	Paper I	Paper III	Paper IV
Total mean	Primary	Primary	Primary
Total >1 SD below the mean	Primary	Exploratory	-
Total >2 SD below the mean	-	Secondary	Exploratory
Subdomain mean	Primary	-	Exploratory
Subdomain >1 SD below the mean	Primary	Exploratory	-
Subdomain >2 SD below the mean	-	Secondary	Exploratory
Any subdomain >2 SD below the mean	-	-	Primary

Abbreviations: ASQ, Ages and Stages Questionnaire; SD, standard deviation.

Mother-to-child SARS-CoV-2 transmission

In paper II, neonatal SARS-CoV-2 infection was analysed in the included cohort studies. Neonatal positivity was defined as a positive reverse transcription PCR (RT-PCR) test on nasopharyngeal, blood (neonatal or umbilical cord), placental, amniotic fluid, rectal, or faecal samples within 48 hours after birth, or as positive serology for anti-SARS-CoV-2 immunoglobulin M (IgM). In all included studies, timing of transmission (in utero, intrapartum, or early postpartum) was categorised according to WHO criteria[142].

Background variables

Background variables collected in the different papers are summarised in Table 4.

Table 4. Background variables collected across papers included in this thesis

Domain	Variable	Mother/ child/ system	Paper	Source
Maternal socio-demographics	Maternal age	Mother	I, III–IV	Trial records; SPR
	Maternal country of birth	Mother	III–IV	SPR
	Maternal educational level	Mother	III–IV	SPR
	Parity	Mother	I, III–IV	Trial records; SPR
	Single parent in early pregnancy	Mother	III–IV	SPR
Maternal health & pregnancy	Early-pregnancy BMI	Mother	III–IV	SPR
	Pre-pregnancy comorbidity[a]	Mother	III–IV	SPR
	Smoking in late pregnancy	Mother	III–IV	SPR
	Number of antenatal check-ups	Mother	I	Trial records/medical charts
Birth and neonatal factors	Gestational age at birth	Child	I, III–IV	Trial records; SPR; SNQ
	Birth weight; SGA; LGA	Child	I, III–IV	Trial records; SPR; SNQ
	Mode of birth	Mother /child	II, III–IV	Review extraction; SPR; SNQ
	Apgar score	Child	I, III–IV	Trial records; SPR; SNQ
	Sex of child	Child	I, III–IV	Trial records; SPR; SNQ
	Multiple vs singleton pregnancy	Child	II–IV	Trial records; review extraction; SPR; SNQ
Postnatal care & feeding	Breastfeeding	Child	All	Trial records; SPR; review extraction
	Early skin-to-skin contact, rooming-in practice	System / care	II	Review extraction
	Child feeding habits, 8 & 12 months	Child	I	Trial records
Study/system level	Country/region and income level of study site	System	II	

[a]Pre-pregnancy comorbidity included diabetes, hypertension, cardiovascular disease, kidney disease, and lung disease.

Abbreviations: BMI, body mass index; LGA, Large for gestational age; SGA, small for gestational age; SNQ, Swedish Neonatal Quality Register; SPR, Swedish Pregnancy Register

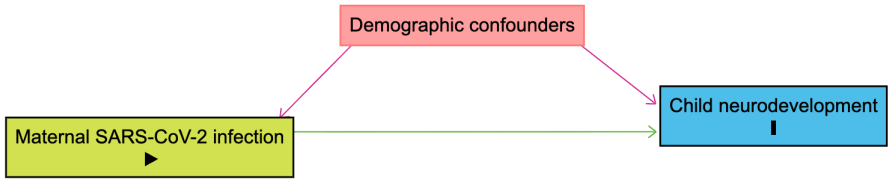


Figure 8a. Demographic confounders

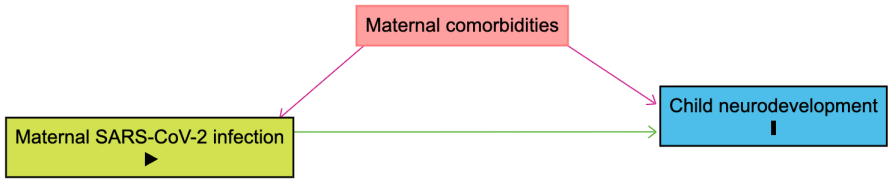


Figure 8b. Maternal comorbidities

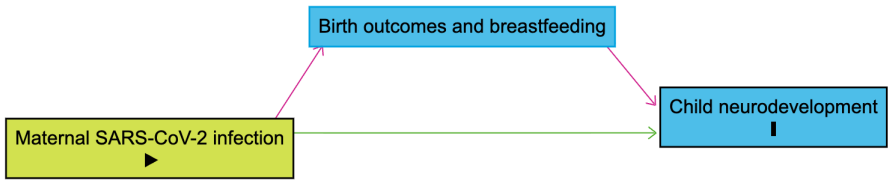


Figure 8c. Birth outcomes and breastfeeding

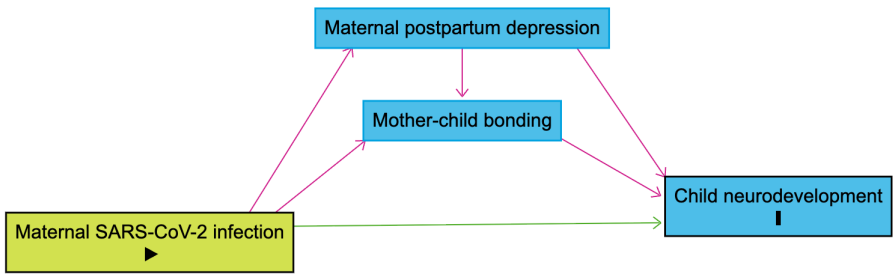


Figure 8d. Maternal postpartum depression and mother–child bonding

Figure 8a-d. Directed acyclic graphs displaying hypothesised pathways between maternal SARS-CoV-2 in pregnancy and child neurodevelopment
Note: Figure 8a – model including mother's age at childbirth, education, country of birth, and parity; Figure 8b – model including early pregnancy body mass index and pre-pregnancy comorbidities; Figure 8c – model including gestational age at birth, Caesarean section, Apgar score <7 at five minutes, breastfeeding at age four weeks, and small for gestational age; Figure 8d – model including maternal postpartum depression and mother–child bonding at 8–12 weeks postpartum

Variables included in regression models

In papers III–IV, Covariates were organised into four conceptual groups: (1) sociodemographic factors, (2) maternal health factors, (3) birth outcomes and early postnatal factors, and (4) maternal postpartum depression and bonding. Covariate selection was done a priori, guided by a structural equation modelling framework informed by directed acyclic graphs, used to distinguish confounders from mediators and effect modifiers (Figures 8a-d). An overview of the evidence on associations between covariates and the exposure (maternal SARS-CoV-2 infection during pregnancy) and outcome (child neurodevelopment assessed with the ASQ) is provided in Table 5 and described in more detail below.

Confounding variables

Maternal sociodemographic factors (age, education, country of birth, and parity) were treated as confounders due to their hypothesised associations with both exposure and outcome. Advanced maternal age has been associated with higher risk of severe SARS-CoV-2 infection[101]. Maternal education predicts later child cognitive development and has been associated with susceptibility to and severity of SARS-CoV-2 infection, with lower education associated with higher risk[143,144]. Lower maternal education may affect the accuracy of ASQ reporting[145], although larger studies suggest the ASQ performs well irrespective of educational level[146,147]. Conversely, higher maternal education has been associated with potential overreporting of child health conditions[148]. Being born outside the country of residence is associated with higher risk and greater severity of SARS-CoV-2 infection in pregnancy[143,149]. Child neurodevelopmental outcomes vary by maternal origin, with some groups showing more favourable and others less favourable outcomes compared with children of mothers born in the country of residence[150]. Parity appears unrelated to infection risk but may influence neurodevelopment, with patterns differing by migration background[151]. One study found that firstborn children had slightly better early cognitive and school readiness skills in more socioeconomically advantaged families, whereas later-born children had similar or better skills in more socioeconomically disadvantaged or language-minority families[151].

Maternal health factors, including early pregnancy body mass index (BMI) and pre-pregnancy comorbidities (any of hypertension, cardiovascular disease, pre-gestational diabetes, lung disease, or kidney disease), were also considered confounders. Higher BMI has been associated with increased risk of SARS-CoV-2 infection in pregnancy and adverse neurodevelopment[101,152,153]. Similarly, comorbidities, particularly diabetes mellitus, have been associated with more severe maternal SARS-CoV-2 infection and increased risk of adverse neurodevelopmental outcomes, although much of the evidence relates to pregnancy-related rather than pre-existing conditions[101,149,154,155].

Table 5. Variables included in regression models in papers III–IV

Variable	Variable type	Role in causal model	Evidence of association with exposure (Maternal SARS-CoV-2 infection)	Evidence of association with outcome (Neurodevelopment)	Paper(s)
Maternal socio-demographics					
Maternal education	Binary	Confounder	Lower education: higher risk of infection and severe disease[143]	Mixed: lower accuracy of reporting with lower educational attainment [145]; potential overdiagnosis with higher educational attainment[148]; no education-related differences[146,147]	III & IV
Mother's country of birth	Categorical	Confounder	Foreign-born status: higher risk of infection and severe disease[143,149]	Associations varied by country of origin[150]	III & IV
Parity	Binary	Confounder	No association[149]	Associations differed by immigrant status: first-born children had more favourable outcomes among non-immigrant mothers, whereas second-born children had more favourable outcomes among immigrant mothers[151].	III & IV
Maternal age	Continuous	Confounder	Age ≥35 years associated with higher risk of severe disease[101,156]	No evidence identified	III & IV
Maternal comorbidities					
BMI ≥30 in early pregnancy	Binary	Confounder	BMI ≥30: higher risk of infection and severe disease[101,153]	BMI ≥30: higher risk of adverse outcome[152]	III
Pre-pregnancy comorbidities[a]	Binary	Confounder	Higher risk of infection and severe disease[101,149,154]	Higher risk of adverse outcome[155]	III
Birth outcomes and breastfeeding					
Gestational age at birth	Continuous	Mediator	Higher risk of preterm birth[101]	Lower gestational age associated with adverse outcome[157]	III

Caesarean section	Binary	Mediator	Higher likelihood[101]	Mixed: poorer outcome in some studies but not in others[158-161]	III
APGAR <7 at 5 min	Binary	Mediator	No association[101,149]	Higher risk of adverse outcome[162]	III
Breastfeeding	Categorical	Mediator	No association[149]	More favourable outcome if breastfed[12]	III
Small for gestational age[b]	Binary	Mediator	Theoretical pathway via placental insufficiency, but no association in Swedish population[149]	Higher risk of adverse outcome[163]	III
Maternal mental health and bonding					
Maternal postpartum depression	Binary and continuous	Mediator	Higher risk following severe infection[86]	Higher risk of adverse outcome[23,24]	IV
Mother–child bonding	Binary and continuous	Mediator	No evidence identified	May mediate the association between maternal postpartum depression and child neurodevelopment (largely prepandemic findings)[84]	IV
Stratification variable/potential effect modifiers					
Child sex	Binary	Stratification variable	NA	Mixed findings[c]	III & IV
Trimester of exposure	Categorical	Stratification variable	NA	Mixed findings[c]	III
Severity of maternal SARS-CoV-2	Categorical	Stratification variable	NA	Mixed findings[c]	III & IV

[a]Pre-pregnancy comorbidities included diabetes, hypertension, cardiovascular disease, kidney disease, and lung disease.
[b]Defined according to Maršál et al[164]
[c]Further discussed in the Discussion section of the thesis
Abbreviations: BMI, body mass index; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGA, small for gestational age

Mediating variables

Birth outcomes and early postnatal factors (gestational age, Caesarean section, Apgar score at five minutes, breastfeeding, and small for gestational age) were considered mediators. Maternal SARS-CoV-2 infection has been associated with an increased risk of preterm birth, and lower gestational age in turn predicts poorer school performance[101,157]. Decreasing Apgar scores at five and ten minutes predict subsequent epilepsy and cerebral palsy[162]. However, current evidence does not indicate an association between maternal SARS-CoV-2 infection and lower Apgar scores[101,149]. SARS-CoV-2-positive mothers had a higher risk of undergoing Caesarean section[101]. While adverse neurodevelopmental outcomes have been reported during the first three years of life following Caesarean section in some studies, a systematic review found inconsistent evidence[158-161]. Breastfeeding is associated with improved neurodevelopment but there was no association between breastfeeding rates and maternal SARS-CoV-2 infection in Sweden[12,149]. Being born small for gestational age is associated with adverse neurodevelopment, but no increased risk has been observed following maternal SARS-CoV-2 infection in the Swedish population[149,163].

Maternal postnatal depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS) 8–12 weeks after birth, with a cutoff of ≥12 used to indicate postnatal depression[165]. Mother–child bonding was measured with the Postpartum Bonding Questionnaire (PBQ); a total score of ≥26 was interpreted as indicating a bonding disturbance[166]. Both variables were considered mediators. The EPDS and PBQ are validated self-reported screening questionnaires with adequate predictive performance[165,166].

Severe maternal SARS-CoV-2 infection has been associated with higher levels of postpartum depression[87]. Postpartum depression was associated with impaired mother–child bonding during the pandemic[83]. Prepandemic findings have linked maternal postpartum depression to child neurodevelopment[23,24]. Finally, mother–child bonding problems mediated an association between increased depressive symptoms and adverse child neurodevelopment[84].

Data collection procedures

Paper I

Timing of CC was recorded at birth by a research assistant. Before use in the trial, the ASQ was piloted on a group of ten children. Because literacy levels are low in Nepal and written ASQ responses were therefore not feasible, two nurses trained in ASQ administration conducted parent interviews by telephone. Baseline

characteristics were obtained from medical records and from clinical assessments of the child at one and six hours after birth. Child feeding practices at eight and 12 months of age were collected through parental interviews.

Paper II

Study eligibility was assessed in two stages by two reviewers working independently: titles and abstracts were screened first, followed by full-text evaluation of potentially relevant records. Disagreements were resolved by a third more senior reviewer. Overlapping study populations and outcomes were checked so that duplicate publications could be identified and excluded.

Two reviewers then independently evaluated the methodological quality of each included study using an adapted Murad et al. tool[167] incorporating items from the JBI Critical Appraisal Checklist[168] (maximum score 7; 0–3 low, 4–5 moderate, 6–7 high quality). Any disagreements were resolved by consensus. Data were extracted by one reviewer with a standardised form piloted on 15 studies and guidelines. Extracted variables covered setting (country, data collection period), design, CC policy and timing, gestational age, mode of birth, plurality, timing and modality of maternal and neonatal SARS-CoV-2 testing, and maternal and neonatal clinical outcomes. For guidelines, CC recommendations and any variation by mode of birth or confirmed/suspected maternal SARS-CoV-2 infection were recorded.

Papers III–IV

Child neurodevelopment, maternal postpartum depression, and mother–child bonding were assessed using web-based versions of the ASQ, EPDS, and PBQ, respectively. The ASQ was available in Swedish, English, Somali, and Arabic. Questionnaires were sent to the birthing mother, but both parents were encouraged to complete them together. To account for preterm birth, the ASQ was distributed at four and 24 months after the expected date of birth rather than the actual birth date. The completion date for the ASQ was then checked against the eligibility window specified in the manual[140]. Background characteristics and covariates were collected from the Swedish Pregnancy Register and the Swedish Neonatal Quality Register (Table 4).

Sample size

In paper I, the sample size calculation was based on the primary outcome of anaemia at eight months of age[132]. For papers III–IV, the achievable sample size was determined by the overarching COPE study[137]. Since outcome distributions were

unknown at the start of the COVID-19 pandemic, sample size estimation for these papers was challenging. To assess feasibility, a calculation was therefore performed using four-month ASQ scores from a previous Swedish cohort[40].

We assumed a two-sided test with a type I error rate (α) of 0.05 and 80% power, corresponding to a type II error rate (β) of 0.20. The original COPE plan was to recruit 200 SARS-CoV-2–exposed and 1 000 unexposed children, which meant an expected exposure prevalence of 17%. A ten-point difference in ASQ total mean score between exposed and unexposed children was considered clinically important. With an assumed standard deviation of 30, this yielded required group sizes of 87 exposed and 421 unexposed children, respectively.

Statistical analysis

Descriptive statistics and univariable group comparisons (all papers)

Across all papers, continuous variables were summarised as means and standard deviations for normally distributed data and as medians and ranges for skewed data. Categorical variables were presented as counts and percentages. For comparisons of baseline characteristics between groups, unpaired Student's t tests, Mann–Whitney U tests, and chi-square or Fisher's exact tests were applied as appropriate. In paper I, Student's t tests and Fisher's exact tests were also used to evaluate the effect of delayed versus early CC on neurodevelopmental outcomes (ASQ).

Regression analysis (papers I, III–IV)

Regression modelling was applied in papers I and III–IV to examine associations between exposures and neurodevelopmental outcomes (ASQ). In paper I, multiple regression analyses were adjusted for covariates selected based on (1) imbalanced baseline characteristics or (2) significant correlations between baseline variables and outcomes.

In papers III–IV, the associations between maternal SARS-CoV-2 infection and neurodevelopmental outcomes were analysed using simple and multiple regression models. Linear regression was used for continuous outcomes and logistic regression for categorical outcomes, with covariates selected a priori from the literature.

In paper III, three models were specified. Model 1 adjusted for child age at ASQ completion and demographic factors: maternal age, educational attainment, country of birth, and parity. Model 2 additionally included maternal health-related factors: body mass index in early pregnancy and pre-pregnancy comorbidity (any of hypertension, cardiovascular disease, pre-gestational diabetes, lung disease, or kidney disease). Model 3, an exploratory model, further adjusted for birth outcomes and breastfeeding: gestational age, Apgar score, small for gestational age, Caesarean

section, and breastfeeding. In paper IV, two models were used: a minimally adjusted model including only child age at ASQ completion and a fully adjusted model adding demographic confounders identical to model 1 in paper III.

In papers I, III–IV, analyses were stratified by child sex. Paper III also included stratification by trimester and severity of maternal SARS-CoV-2 infection. Because no convincing trimester-specific effects were observed at four months, and similar null findings were reported elsewhere[70,71,75,76,169], trimester-specific analyses were not repeated in paper IV. Stratification by infection severity was retained because a potential association was observed in the four-month data and this association was considered biologically plausible based on available evidence[50].

Mediation analysis (paper IV)

In paper IV, mediation analyses were performed within a structural equation modelling (SEM) framework to explore whether postpartum depressive symptoms, measured with the EPDS at 8–12 weeks postpartum, and mother–child bonding, measured with the PBQ at the same time point, might represent potential pathways linking antenatal SARS-CoV-2 exposure to child neurodevelopment at 24 months. Continuous outcomes were analysed using linear SEM with robust maximum likelihood estimation and full information maximum likelihood for missing data, whereas binary outcomes were analysed using probit-link SEM with weighted least squares mean and variance adjusted estimation. In both models, direct, indirect (including serial), and total effects were estimated after adjustment for mother's age at childbirth, educational attainment, parity, and country of birth.

Other and exploratory analyses

In paper I, Spearman's rank correlation was used to examine the association between ASQ cutoff scores (>1 SD below the mean) at 12 and 36 months. In papers III–IV, several prespecified analyses were designated exploratory because of the large number of comparisons. In paper III, ASQ cut-offs >2 SD below the mean were considered primary outcomes, whereas cut-offs >1 SD below the mean were treated as exploratory. The third regression model (model 3) including birth outcomes and breastfeeding was also regarded as exploratory, as were stratified analyses by severity and trimester of maternal infection and child sex. In paper IV, all ASQ subscale outcomes were treated as exploratory, whereas stratification by child sex and severity of maternal infection was considered part of the primary analytic plan, informed by findings from paper III and previous studies (Table 5). No analyses were designated as exploratory in paper I.

Handling of missing data and sensitivity analyses (papers I, III–IV)

In paper I, both per-protocol and intention-to-treat analyses were conducted because of protocol deviations in the delayed CC group. In papers I and III–IV, baseline characteristics were compared between participants lost to follow-up and those

included in the analyses. In paper IV, additional dropout analyses were undertaken because of a high attrition rate: (1) background characteristics were compared between all mothers who completed the ASQ at four months only and those who completed the 24-month ASQ; (2) ASQ results at four months (total mean score and the presence of a score >2 SD below the mean in at least one domain) were compared between all respondents and those who also returned the 24-month questionnaire; and (3) EPDS and PBQ scores were compared between women included in the mediation analyses and all eligible respondents. In papers III–IV, a "missing" category was created for covariates with more than 2% missingness.

Software and general approach

The data were analysed using SPSS (version 25 for paper I, version 27 for paper II, and version 29 for paper III; IBM Corp., Armonk, NY, USA). For paper IV, RStudio version 2025.09.2+418 using the lavaan package (version 0.6.20) for SEM (Posit Software, PBC, Boston, MA, USA) was used. Covidence Systematic Review Software was used for screening in paper II (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Significance was set at $p < 0.05$. A statistician (PI) was consulted during the planning of the statistical analyses for papers III–IV.

Ethical considerations

The studies included in this thesis involve pregnant women, newborns, and young children, all of whom are vulnerable and require particular protection in research. Research involving newborns and young children requires particularly careful ethical consideration, mainly because the participants themselves cannot provide informed consent. In accordance with the Declaration of Helsinki[170] and CIOMS guidelines[171], the overarching principle has been to ensure that any additional burden or risk is carefully justified and that research involving children was conducted only when the questions could not be answered in adults. Given the context of a global pandemic, the benefit–risk assessment necessarily placed weight on the potential to generate knowledge that could protect pregnant women and children, while still prioritising participants' welfare. For papers I, III–IV, data were stored securely and handled in a way that protected participant confidentiality, and results were reported only at group level.

In papers I, III–IV, recruitment occurred in a care context, where patients and relatives may experience a dependency on their clinicians. To mitigate this, information was given both orally and in writing, voluntariness was strongly emphasised, and it was clearly stated that declining participation or later withdrawal would not affect current or future care. Nevertheless, some women and partners, particularly those with limited trust in authorities or language barriers, may still have

doubted that care was truly unaffected, and this residual risk of subtle pressure must be acknowledged.

Papers III–IV were part of the multicentre COPE cohort, in which efforts were made to improve inclusion of under-represented groups through translation of study information and questionnaires into English, Arabic and Somali and recruitment across several Swedish maternity units. Despite this, foreign-born mothers and those with a lower educational level were less likely to be included and more likely to be lost to follow-up, which is ethically problematic because these groups carry higher risks related to COVID-19 and perinatal outcomes[143]. This underrepresentation affects both scientific validity and justice, since those most affected by the pandemic may be least reflected in the resulting evidence. Future studies should therefore further strengthen targeted outreach and community collaboration to improve inclusion.

Participation in the COPE study entailed repeated web-based questionnaires, each requiring 5–30 minutes to complete. This cumulative workload risks favouring continued participation among more resourceful families and may contribute to selection bias. At the same time, it was one of the few feasible ways to obtain large-scale longitudinal data on parental mental health and child development during the ongoing pandemic. We also judged that the expected knowledge gain for present and future families justified the workload put on families.

In papers III–IV, a limitation is that parents with cognitive impairments, limited literacy, or greater need for support to understand written information were not explicitly addressed in the inclusion criteria or consent procedures. In practice, the requirement to read and complete web-based instruments likely excluded some of these individuals. Even if this group of parents is likely to be relatively small in Sweden, it raises concerns about both fairness and the representativeness of the findings. In paper I, ASQ assessments were done by telephone interviews due to low literacy levels in Nepal.

Filling in the ASQ may also trigger parental worry about the child's neurodevelopment. In papers III–IV, parents who became concerned were advised to contact child health services, which is appropriate in principle but in practice sometimes meant that clinicians unfamiliar with ASQ were asked to interpret scores, potentially creating uncertainty for both parents and staff. Given limited resources and the urgent need for data, it was not feasible to build a parallel clinical follow-up system, and this trade-off was accepted. Still, with more time and resources, additional training or information for child health service staff would have been desirable.

Paper I was a randomised trial in Nepal comparing early (≤60 s) and delayed (≥180 s) CC in generally healthy term children. The early CC group reflected standard practice determined from a previous observational study[134]. At the time of the original trial, delayed CC had already shown clear benefits for infant iron status with

few reported adverse effects, which motivated the study intervention. The neurodevelopmental follow-up reported in this thesis did not involve invasive procedures such as blood sampling.

Paper II, a systematic review and meta-analysis, did not involve new individual-level data and therefore did not require formal ethical approval. However, it carried significant ethical responsibility because its conclusions could influence CC practice worldwide at a time of uncertainty. Early in the pandemic, precautionary concerns may have favoured early CC despite a lack of evidence that delayed CC increased mother-to-child SARS-CoV-2 transmission, thereby potentially depriving children of a well-established beneficial practice. In this context, we considered it an ethical obligation to conduct a methodologically rigorous review and to publish reassuring or "null" findings showing similar neonatal SARS-CoV-2 positivity after early and delayed CC, in order to support continuation of delayed CC where safe.

All components of this thesis underwent ethics review where applicable. Paper I was approved by the Institutional Review Board of Paropakar Maternity and Women's Hospital and the Ethical Review Board of the Nepal Health Research Council (reg. no. 2014-1403). The COPE study, forming the basis for papers III–IV, was approved by the Swedish Ethical Review Authority (2020-02189, with amendments 2020-02848, 2020-05016, 2020-06696, 2021-00870, 2022-00260-02, and 2022-01231-02).

Declaration of AI use

Generative AI tools (Perplexity AI, 2025-26, and ChatGPT, OpenAI, 2025-26) were used during the thesis writing process to support language editing, drafting of phrasing, exploration of alternative ways of structuring the thesis, and refinement of academic expression. These were used as assistive writing tools. All substantive content, interpretation, and final wording were independently reviewed, revised, and approved by the author, who retains full responsibility for the thesis content.

Results

Table 6. Results overview

Paper	Design	Number analysed	Main exposure	Main outcome
I	Randomised controlled trial (Nepal)	350	Cord clamping (early vs delayed)	No overall difference in neurodevelopment at age 36 months
II	Systematic review/meta-analysis	1476	Cord clamping (early vs delayed)/	Similar neonatal SARS-CoV-2 positivity rates
III	Prospective cohort (Sweden)	1446	Maternal SARS-CoV-2	No overall association with neurodevelopment at age four months
IV	Prospective cohort (Sweden)	745	Maternal SARS-CoV-2	No overall association with neurodevelopment at age 24 months

Effects of CC on child neurodevelopment (paper I)

ASQ outcomes at 36 months after early versus delayed CC

Paper I evaluated the effects of delayed CC (≥180 s) compared to early CC (≤60 s) on neurodevelopment using the ASQ at age 36 months. Between 2 October and 21 November 2014, 540 term children were enrolled at Paropakar Maternity and Women's Hospital, Kathmandu, Nepal. They were randomised equally to early or delayed cord clamping (n = 270 per group). Of these, 350 children (64.8%) were analysed at 36 months **(**Figure 9**)**.

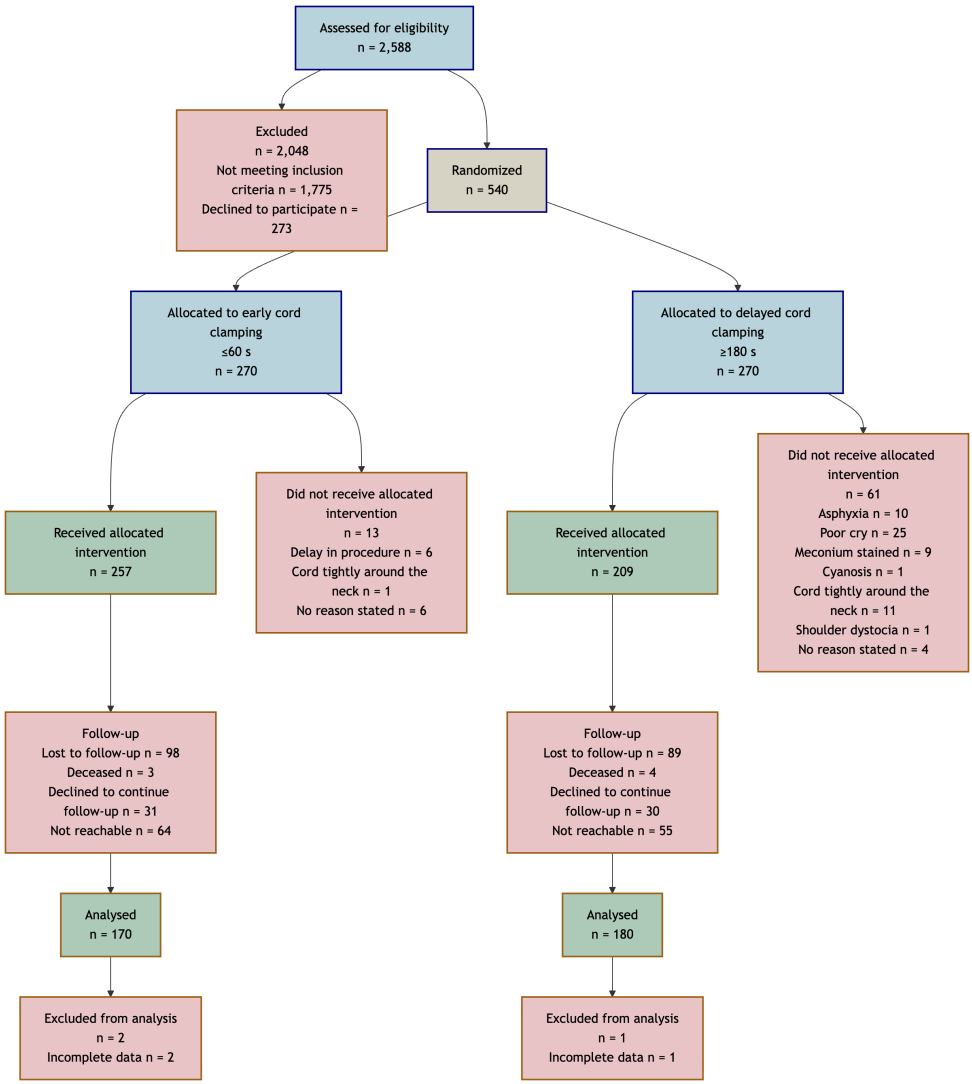


Figure 9. Flowchart of paper I
Abbreviations: n, number;

Baseline characteristics of mothers and children are shown in Table 7. The groups were comparable at baseline, with no clinically relevant differences between the early and delayed CC groups. Mean time to CC was 35.4 seconds (SD 20.0) in the early group and 157.9 seconds (SD 72.1) in the delayed group. Protocol violations occurred in seven participants (4.1%) in the early group and 42 participants (23.3%) in the delayed group.

Table 7. Baseline maternal and child characteristics by intervention in paper I

	Umbilical cord clamping group			
	Early CC (≤ 60 s, n=170)[a]		Delayed CC (≥180 s, n=180)[a]	
	Mean (SD)	Participants (n)	Mean (SD)	Participants (n)
Mother				
Age at childbirth, years	24.6 (4.5)	170	23.9 (3.8)	180
Parity (including study child)	1.7 (0.9)	170	1.7 (0.9)	180
Child				
Gestational age, weeks[b]	39.0 (1.2)	170	39.3 (1.1)	180
Birth weight, g	3056 (445)	170	3027 (414)	180
Apgar score, 1 min[c]	6 (1-7)	170	6 (1-7)	178
Apgar score, 5 min[c]	8 (2-9)	170	8 (2-9)	178
Time to cord clamping, s	35.4 (20.0)	170	157.9 (72.1)	180

[a] Protocol violation: seven (4.1%) in the early group and 42 (23.3%) in the delayed group.
[b] Difference was 0.3 weeks (p=0.006). *p* value by Student's t-test.
[c] Results presented as median (minimum-maximum).
Abbreviations: CC, cord clamping; n, number; SD, standard deviation.

ASQ total and domain scores did not differ significantly between the early and delayed CC groups at 36 months of age in the per-protocol analysis (Figure 10). Intention-to-treat analysis was also performed due to protocol violations in the delayed CC group, where clamping occurred earlier than intended, with similarly non-significant findings. In sex-stratified analyses, fewer girls in the delayed CC group were classified as at risk (>1 SD below the mean) for gross motor delay: 6 (6.3%) in the delayed CC group versus 14 (18.9%) in the early CC group (p = 0.02). No such difference was observed among boys.

Exploratory analyses

Cutoff scores >1 the below mean at 36 months did not correlate with those from the 12-month follow-up for ASQ total score or in any subdomain. Neither was there a difference in ASQ scores at 36 months of age between children with and without iron deficiency anaemia at age eight months.

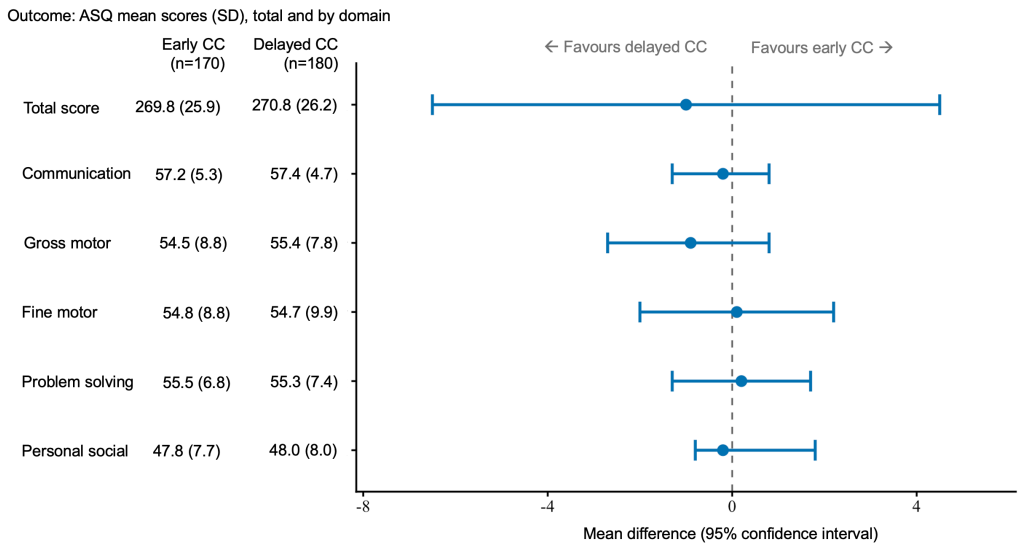


Figure 10. Ages and Stages Questionnaire (ASQ) mean scores at three years: Delayed vs early cord clamping (CC)
Note: Delayed CC (≥180 seconds) vs early CC (≤60 seconds), by Student's t-test

The COVID-19 pandemic and CC practice (paper II)

Paper II systematically reviewed CC recommendations and reported practice and analysed associations between CC timing and mother-to-child SARS-CoV-2 transmission during the early phases of the pandemic.

Guideline recommendations versus reported practice

Cord clamping practices were reported in 48 included clinical studies (six prospective cohorts, nine retrospective cohorts, 29 case reports, and four case series) involving 1 476 children born to SARS-CoV-2-positive mothers (Figure 11). Forty national or international guidelines giving CC recommendations in SARS-CoV-2-positive mothers were also included. Methodological quality was low in four studies (0–3), moderate in 21 (4–5), and high in 23 (6–7; median 6).

Delayed CC was recommended in 70% of guidelines (28/40). In the cohort studies, early CC practice predominated (34.6%) over delayed CC (17.8%) despite guideline recommendations. Distribution of included studies and guidelines by geography and World Bank country income classification is shown in Figure 12a-b. Delayed CC was recommended in 83% of HICs guidelines (19/23) versus 50% of LMICs

guidelines (4/8). Similarly, studies from HICs more often reported delayed CC as standard practice (6/23, 26%) than those from LMICs (3/25, 12%).

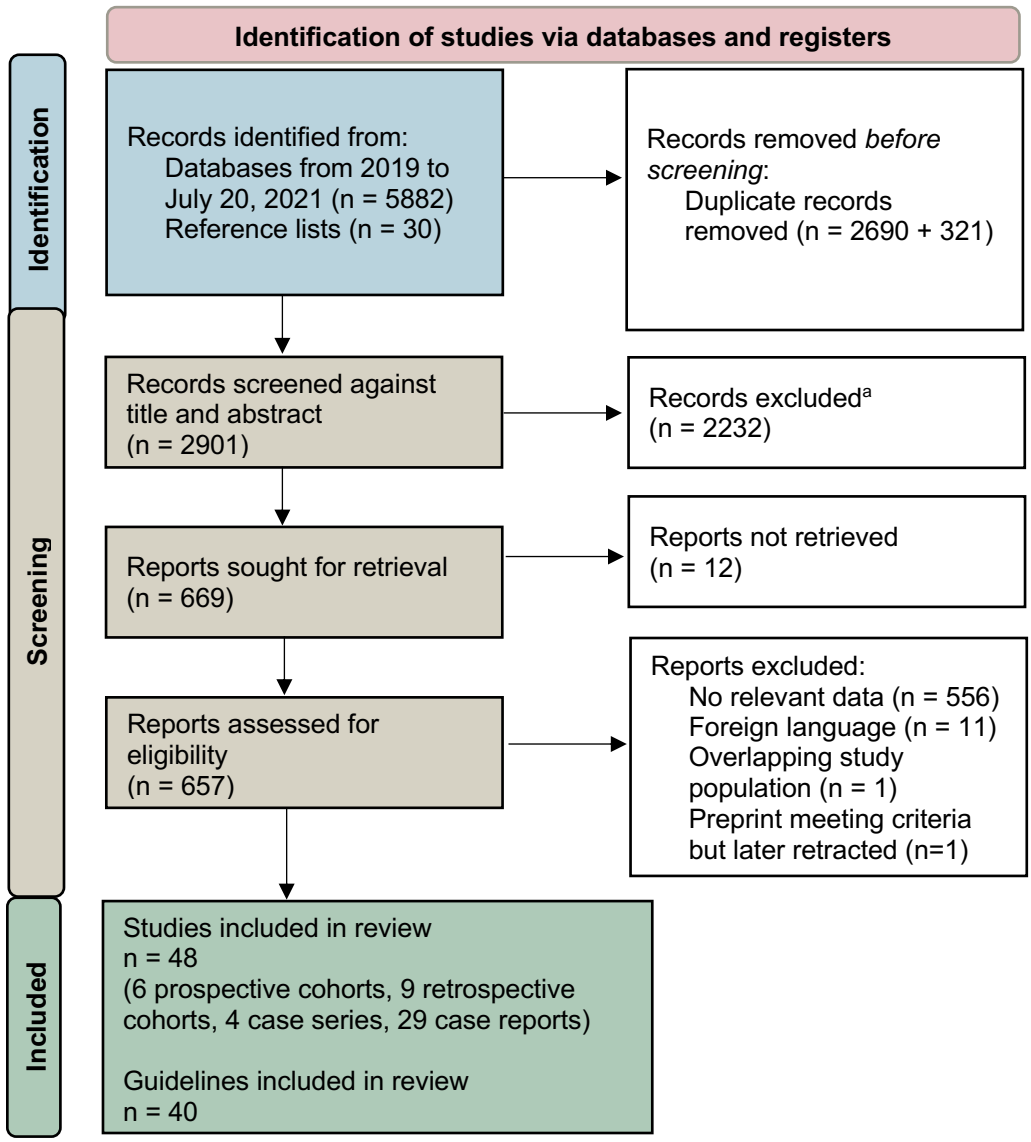


Figure 11. PRISMA flow diagram of paper II

[a]Automation tools were not used for data screening.Timing of CC and mother-to-child SARS-CoV-2 transmission

Figure 12a. Geographic variation in cord clamping (CC) practices reported in studies conducted during the SARS-CoV-2 pandemic

Note: Proportion of studies recommending delayed, early, or mixed/no specific CC (%); n = number of studies. Distribution of studies according to World Health Organization region.

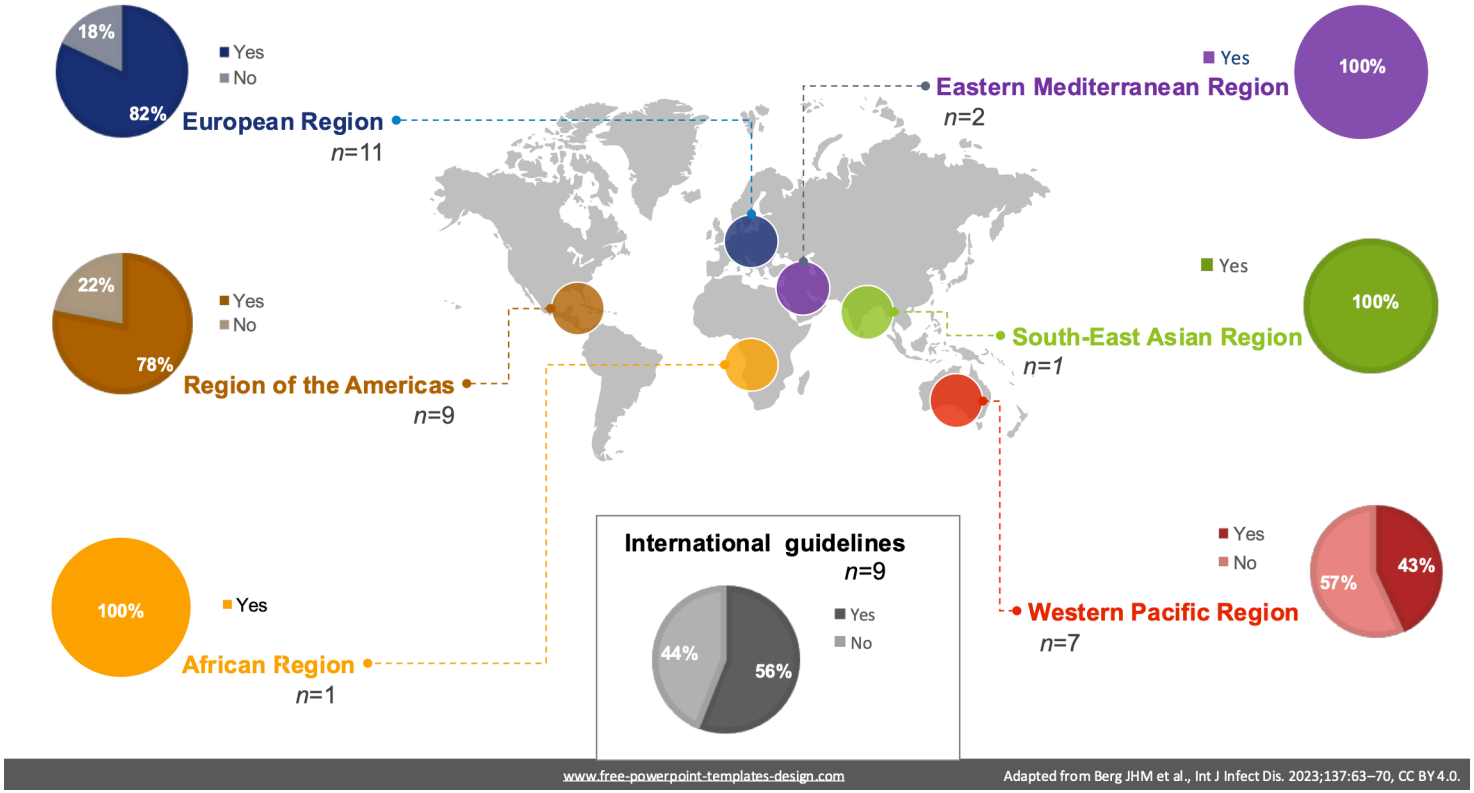


Figure 12b. Geographic variation in recommendations for cord clamping among mothers with suspected or confirmed SARS-CoV-2 infection

Note: Proportion of guidelines recommending delayed cord clamping (%); n = number of guidelines. Distribution of guidelines according to World Health Organization region.

Timing of CC and mother-to-child SARS-CoV-2 transmission

In cohort studies where both CC timing and neonatal SARS-CoV-2 status were available, positivity rates were low and comparable between delayed (1.2%) and early (1.3%) clamping. In all studies, among classifiable infected children (per WHO criteria), 93% were classified as potential intrauterine transmissions. None were intrapartum cases following delayed CC (Figure 13).

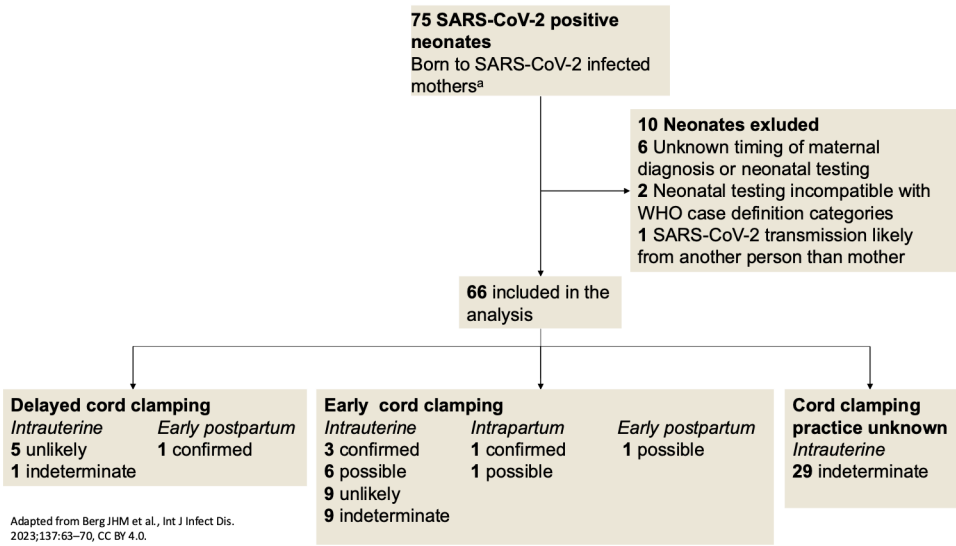


Figure 13. Mother-to-child SARS-CoV-2 transmission classified according to the World Health Organization definition, by umbilical cord clamping (CC) practice.
Maternal infection during pregnancy or up to 2 days postpartum. In Kulkarni et al.[172], maternal PCR was negative at birth and day five, but serology was positive at day ten. The study was included due to positive placental RT-PCR at birth. Transmission was classified as one indeterminate intrauterine case.

Sub-analyses

Pooled outcomes for birth mode, skin-to-skin contact, rooming-in, breastfeeding, and preterm birth were compared in studies where delayed or early CC was encouraged or performed. Studies in which delayed CC was encouraged or performed reported lower proportions of Caesarean sections and preterm births, and higher proportions of skin-to-skin contact, rooming-in, and breastfeeding (Table 8).

Table 8. Pooled birth outcomes according to cord clamping practice among women with SARS-CoV-2 infection in pregnancy

Outcome, No./total No. (%)	Studies (n)	Delayed cord clamping (Encouraged or performed)	Early cord clamping (Encouraged or performed)	Mixed recommendation or cord clamping practice not specified
Caesarean section	46	95/431 (29.0)	230/433 (53.1)	20/45 (44.4)
Vaginal birth	46	279/431 (64.7)	165/433 (38.1)	23/45 (51.1)
Instrumental birth	35	23/252 (9.1)	34/274 (12.4)	1/13 (7.7)
Skin-to-skin contact	39	197/328 (60.1)	108/457 (23.6)	14/22 (63.6)
Rooming in	31	82/156 (52.6)	0/176 (0.0)	27/45 (60.0)
Breastfeeding, any	35	287/352 (81.5)	179/401 (44.6)	24/36 (66.7)
Preterm birth	43	67/877 (7.6)	68/317 (21.5)	10/45 (22.2)

[a]Analysed in all included studies, prospective and retrospective cohort studies, case series and case reports.

Abbreviations: n, number

Associations between SARS-CoV-2 and neurodevelopment (papers III–IV)

Papers III–IV investigated the association between antenatal maternal SARS-CoV-2 infection and neurodevelopment using the ASQ at four and 24 months of age.

Of the 2 449 children included at baseline, 1 446 (555 exposed, 891 unexposed to maternal SARS-CoV-2 infection during pregnancy) provided valid ASQ data at four months (mean age 4.06 ± 0.30 months, prematurity-adjusted). At 24 months, 745 children (295 exposed, 450 unexposed) contributed data (mean age 24.0 ± 0.32 months, Figure 14).

Table 9 presents demographic and health characteristics of exposed and unexposed children at the four- and 24-month follow-ups, respectively. Compared with uninfected mothers, mothers with SARS-CoV-2 infection during pregnancy were characterised by lower educational level, greater parity, a lower proportion of births in Nordic countries, and a higher prevalence of obesity. At four and 24 months, respectively, education >12 years was 85.8% versus 78.2% and 89.3% versus 84.0%, multiparity 48.5% versus 54.2% and 47.9% versus 54.8%, births in Nordic countries 93.3% versus 89.9% and 94.9% versus 92.9%, and BMI ≥30 14.3% versus 20.0% and 13.5% versus 21.7%. Child outcomes did not differ between groups, except for a higher proportion of boys in the SARS-CoV-2-exposed group at the 24-month follow-up compared with the unexposed group, 55.3% versus 48.0%. Among participants in the 24-month follow-up, there were no differences in EPDS

or PBQ scores, and fewer than ten mothers had a PBQ score of 40 or higher, indicating severe bonding problems.

Table 9. Health and demographic profiles of included mothers and children who completed the Ages and Stages Questionnaire at four- and 24 months

Characteristics	Maternal SARS-CoV-2 status during pregnancy			
	Four-month follow-up		24-month follow-up	
	Negative	Positive	Negative	Positive
Mother	n=891	n=555	n=447	n=295
Age at childbirth, years, Mean (SD)	32.7 (4.0)	32.2 (4.0)	32.8 (3.9)	32.3 (4.1)
Missing data	10	0	2	0
Education >12 y, No. (%)	626 (85.8)	366 (78.2)	335 (89.3)	210 (84.0)
Missing data	161	87	72	44
Multiparous, No. (%)	427 (48.5)	301 (54.2)	213 (47.9)	161 (54.8)
Missing data	10	0	2	0
Country of birth, No. (%)				
Nordic	789 (93.3)	473 (89.9)	406 (94.9)	261 (92.9)
Non-Nordic Europe	30 (3.5)	21 (4.0)	15 (3.5)	11 (3.9)
Other	27 (3.2)	32 (6.1)	7 (1.7)	9 (3.2)
Missing data	45	29	19	13
Pre-pregnancy comorbidity, No. (%)[a]	99 (11.7)	59 (11.1)	62 (13.9)	35 (11.9)
Missing data	48	24	13	8
BMI at start of pregnancy				
Mean (SD)	25.1 (4.9)	25.9 (5.3)	25.2 (4.8)	26.1 (5.5)
BMI ≥30, No. (%)	121 (14.3)	106 (20.0)	59 (13.5)	62 (21.7)
Missing data	41	24	9	8
Mode of birth, No. (%)				
Vaginal, non-instrumental	688 (78.1)	431 (77.7)	356 (79.1)	223 (75.6)
Vaginal, Instrumental	56 (6.4)	37 (6.7)	30 (6.7)	16 (6.4)
CS	137 (15.6)	87 (15.7)	61 (13.7)	56 (19.0)
Emergency CS rate, No. (% of all CS)	*98 (71.5)*	*51 (58.6)*	*43 (70.4)*	*34 (60.7)*
Missing data	10	0	2	0
Breastfeeding at 4 weeks, No. (%)				
No	72 (9.2)	53 (11.2)	38 (9.3)	24 (9.4)
Partly	117 (14.9)	61 (12.9)	52 (12.7)	31 (12.2)
Exclusively	596 (75.9)	359 (75.9)	319 (78.0)	200 (78.4)
Missing data	106	82	38	39
Breastfeeding at 4 months, No. (%)				
No	44 (6.0)	33 (6.7)	24 (6.3)	15 (5.7)
Previously, but not anymore	101 (13.8)	63 (12.9)	40 (10.4)	29 (11.1)
Yes	585 (80.1)	394 (80.4)	320 (83.3)	217 (83.1)
Missing data	161	65	66	34

Table 9 (continued)	**Four-month follow-up**		**24-month follow-up**	
Mother	**Negative**	**Positive**	**Negative**	**Positive**
PPD (EPDS score), 8 wks				
Mean (SD)	-	-	6.3 (4.7)	6.5 (4.9)
Score ≥12, No (%)	-	-	57 (13.4)	42 (15.3)
Missing data	-	-	23	20
Bonding (PBQ score), 8 wks	-	-		
Mean (SD)	-	-	10.3 (7.8)	10.2 (4.75)
No (%)	-	-		
≥26	-	-	22 (5.3)	11 (4.0)
Missing data	-	-	28	20
COVID-19 severity No. (%)				
Mild	-	530 (95.5)		282 (95.9)
Severe		25 (4.5)		12 (4.1)
SARS-CoV-2 infection by trimester				
Trimester 1	-	63 (11.4)		43 (14.6)
Trimester 2	-	278 (50.1)		137 (46.6)
Trimester 3	-	214 (38.6)		114 (38.8)
Child	n=891	n=555	n=450	n=295
Sex, No. (%)				
Female	433 (49.1)	264 (47.7)	233 (52.0)	131 (44.4)
Male	448 (50.9)	289 (52.3)	215 (48.0)	163 (55.3)
Unknown/Missing data	10	2	<5 (<0.5%)	<5 (<0.5%)
Gestational age, weeks				
Mean (SD)	39.8 (1.6)	39.7(1.8)	39.7(1.7)	39.8 (1.7)
No. (%)				
<37	44 (4.9)	23 (4.1)	24 (5.3)	13 (4.4)
≥37	847 (95.1)	532 (95.9)	426 (94.7)	282 (95.6)
Missing data	0	0	0	0
Birthweight g, mean (SD)	3612 (515.3)	3569 (543.1)	3600 (525)	3615 (526)
Large for gestational age, No. (%)[b]	49 (5.5)	31 (5.6)	28 (6.3)	12 (4.1)
Small for gestational age, No. (%)[b]	23 (2.6)	11 (2.0)	10 (2.3)	4 (1.4)
Missing data	11	1	3	0
Apgar score, median (min-max)				
1 min	9 (0-10)	9 (1-10)	9 (0-10)	9 (1-10)
5 min	10 (3-10)	10 (5-10)	10 (3-10)	10 (6-10)
10 min	10 (7-10)	10 (6-10)	10 (7-10)	10 (6-10)
Apgar score <7 at 5 min, No. (%)	7 (0.8)	7 (1.3)	5 (1.1)	3 (1.0)
Missing data	20	5	8	4
Age at completion of ASQ, m, mean (SD)	4.05 (0.3)	4.08 (0.3)	24.0 (0.3)	24.0 (0.4)

[a]Pre-pregnancy comorbidity included diabetes, hypertension, cardiovascular disease, kidney disease, and lung disease; [b]According to Maršál et al[164]

Abbreviations: ASQ, Ages and Stages Questionnaire; BMI, body mass index; CS, Caesarean section; EPDS, Edinburgh Postnatal Depression Scale; No., number; PBQ, Postpartum Bonding Questionnaire; PPD, postnatal depression; SD, standard deviation; y, years; wks, weeks; SGA, small for gestational age

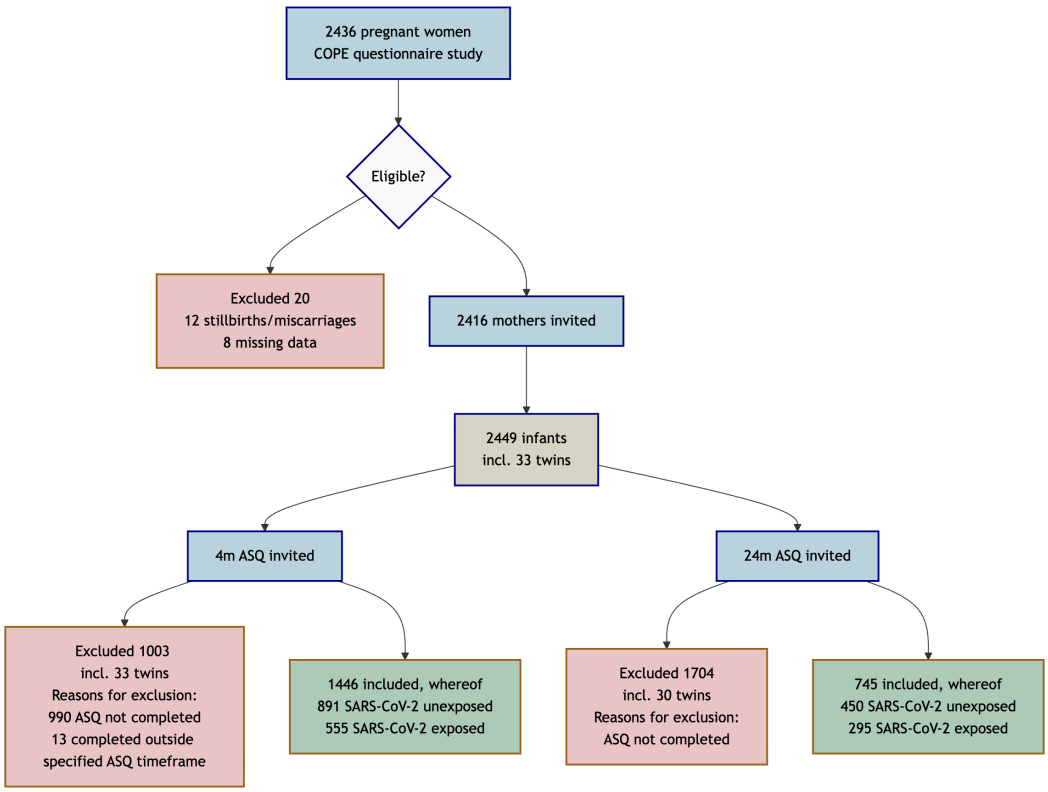


Figure 14. Flowchart of papers III–IV
Abbreviations: ASQ, Ages and Stages Questionnaire; m, months

ASQ scores after antenatal SARS-CoV-2 exposure

Multiple linear and logistic regression analyses, adjusted for demographics (maternal age, education, country of birth, parity and child's age at ASQ completion), revealed no differences in mean ASQ total scores between exposed and unexposed children at four months (aMD 2.70, 95% CI −0.44 to 5.84, p=0.09) or 24 months (aMD −1.11, 95% CI −5.99 to 3.76, p=0.66, Figure 15). Proportions with scores >2 SD below the mean in ≥1 domain were comparable at 24 months (17.7% exposed versus 18.0% unexposed; aOR 1.06, 95% CI 0.71 to 1.57, p=0.77).

At four months, exposed children had lower odds of fine motor scores >2 SD below the mean (4.0% versus 6.6%; aOR 0.55, 95% CI 0.33 to 0.92, p=0.02). There were no differences in cutoff scores in the other ASQ domains. No domain-specific differences were observed at 24 months.

At four months, further adjustment for maternal comorbidities (early-pregnancy BMI and pre-pregnancy diabetes, hypertension, cardiovascular, kidney, or lung disease) and birth outcomes (gestational age, Apgar score <7 at five minutes, mode of delivery, small-for-gestational-age status, and breastfeeding at four weeks) was performed. The association between antenatal SARS-CoV-2 exposure and ASQ scores was essentially unchanged after these further adjustments.

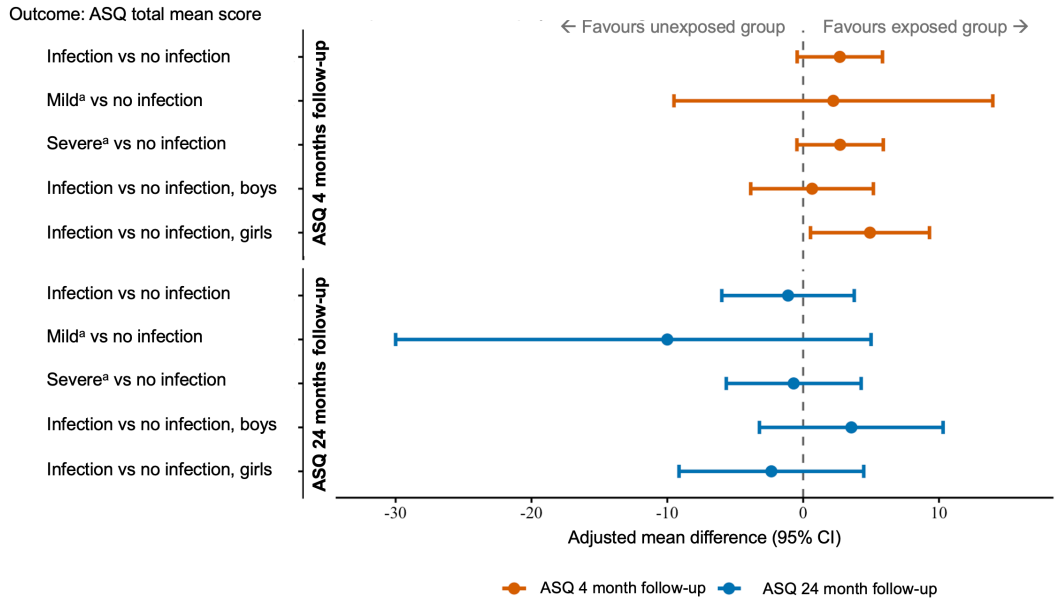


Figure 15. Ages and Stages Questionnaire (ASQ) mean scores by antenatal SARS-CoV-2 exposure. Four and 24-month follow-ups

Note: Multiple linear regression analysis adjusted for maternal age, educational level, maternal country of birth, parity, child's age at ASQ assessment BMI in early pregnancy and prepregnancy comorbidity (any of hypertension; cardiovascular disease; pre-gestational diabetes; lung disease; and kidney disease)

[a]Mild/asymptomatic vs. severe maternal infection was defined as a positive SARS-CoV-2 test with vs. without inpatient care

Abbreviations: ASQ, Ages and Stages Questionnaire; CI, confidence interval.

Subgroup analyses by SARS-CoV-2 severity, sex, and trimester

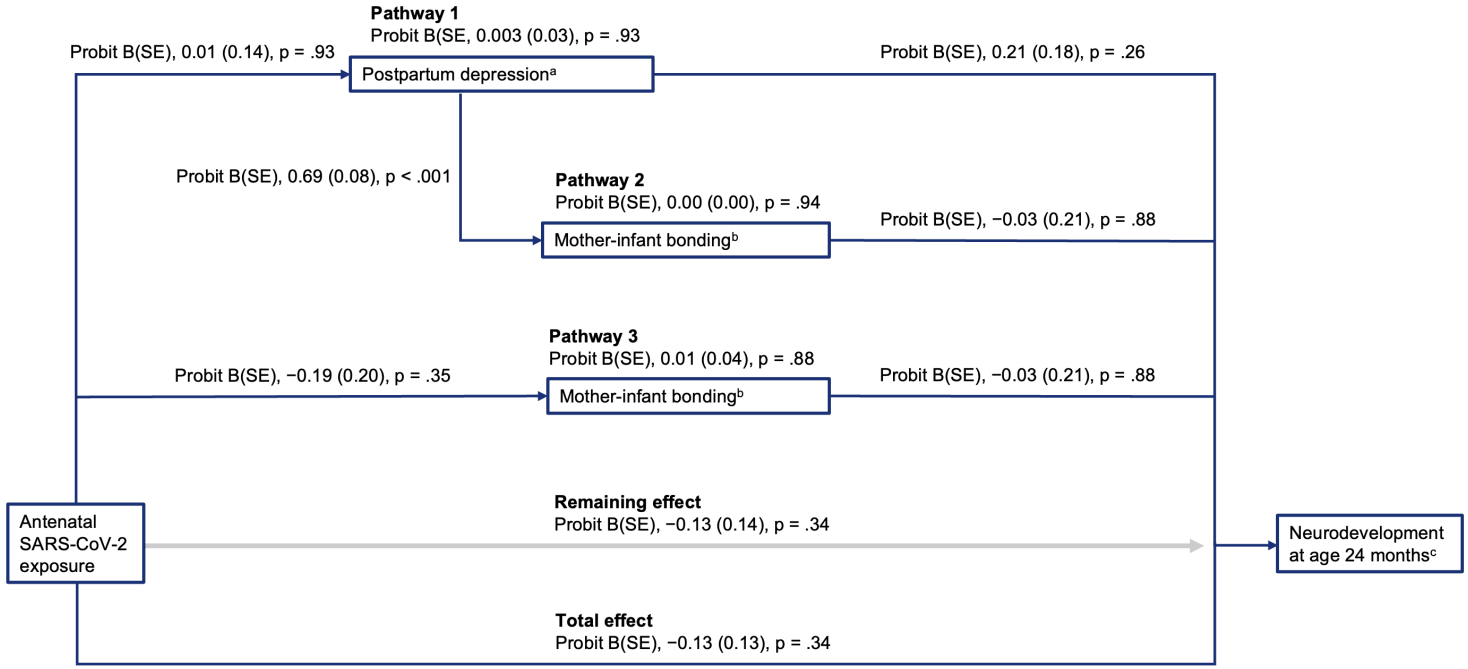
There was no association between exposure and ASQ total mean scores at four months regardless of maternal SARS-CoV-2 infection severity (Figure 15). In exploratory analyses, children exposed to severe maternal SARS-CoV-2 had higher odds of having ASQ total cutoff scores >2 SD below the mean (16.0% versus 6.1%; aOR 3.57, 95% CI 1.14–11.24, p=0.03) and gross motor scores below the cutoff (24.0% versus 7.1%; aOR 3.82, 95% CI 1.42–10.27, p=0.008). At 24 months, no associations between exposure and neurodevelopment were observed. These

analyses were limited by the small number of children with severe exposure, particularly at 24 months (n=25 at four months and n=12 at 24 months).

Stratified analyses by trimester of exposure were conducted only at four months of age and showed results similar to those of the unstratified analysis. Stratification by child sex was performed at four and 24 months of age. At four months, higher mean ASQ total scores were observed in exposed girls compared to unexposed girls (aMD 4.50, 95% CI 0.11 to 8.89, p=0.04). No difference was observed between boys (aMD 0.88, 95% CI -3.65 to 5.41, p=0.70). At 24 months, no significant differences were found in total or domain scores between exposed and unexposed children within either sex.

Mediation analyses for depression and bonding

In paper IV, the mediating effects of maternal postpartum depression and mother–child bonding on the potential association between SARS-CoV-2 exposure and child neurodevelopment were explored. Adjusted mediation models at 24 months showed no significant total, direct, or indirect association between antenatal SARS-CoV-2 exposure and impaired ASQ outcomes (a score >2 SD below the mean in ≥1 ASQ subdomain). Postpartum depressive symptoms (EPDS) and mother–child bonding (PBQ) at 8–12 weeks had no mediating effect on this association. Mediation results were unchanged with continuous ASQ total scores as the outcome. However, higher EPDS and PBQ scores were associated with lower ASQ total scores, and EPDS was strongly related to PBQ (Figure 16a–b).

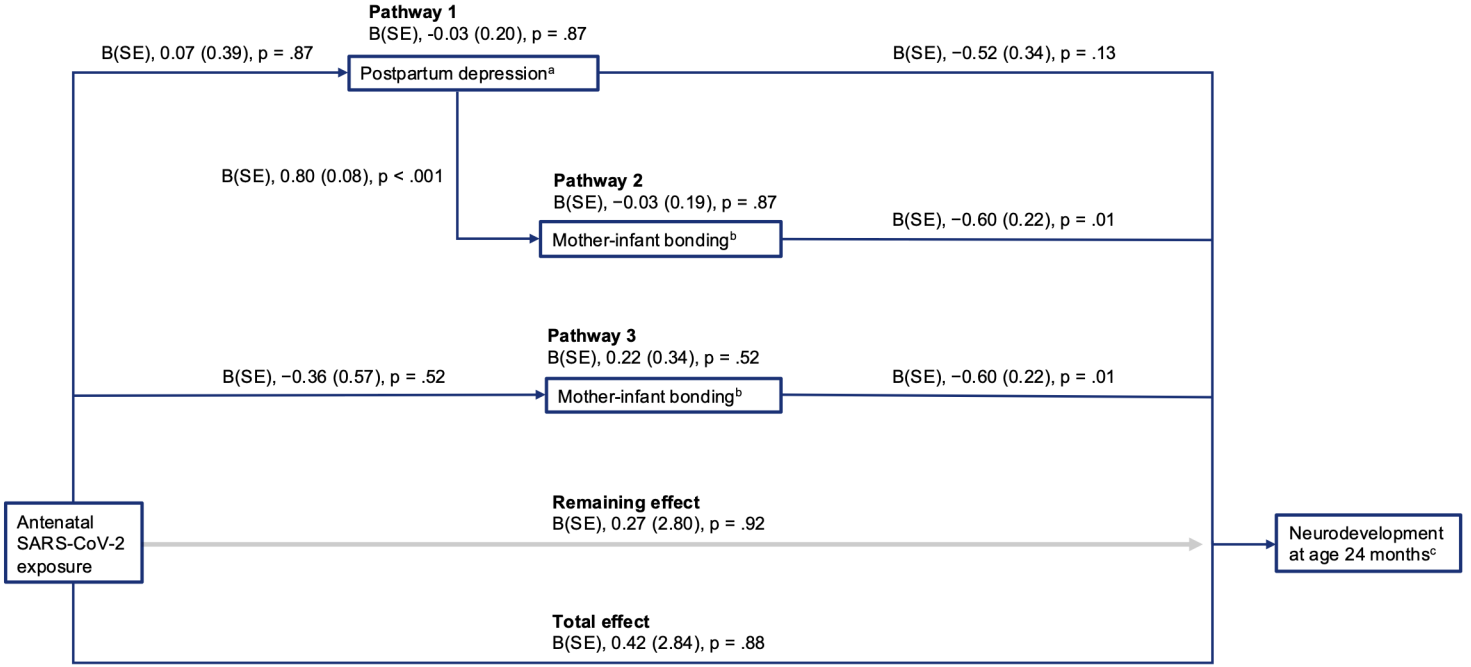


Pathway 1 - SARS-CoV-2 exposure in pregnancy → Maternal depression 8 weeks postpartum → Child neurodevelopment at age 24 months
Pathway 2 - SARS-CoV-2 exposure in pregnancy → Maternal depression 8 weeks postpartum → Mother-infant bonding 8 weeks postpartum → Child neurodevelopment at age 24 months
Pathway 3 - SARS-CoV-2 exposure in pregnancy → Mother-infant bonding 8 weeks postpartum → Child neurodevelopment at age 24 months

Figure 16a. Hypothesised pathways in the association between maternal SARS-CoV-2 infection in pregnancy and child neurodevelopment at 24 months of age.

Note: Probit mediation analysis adjusted for maternal age, educational level, maternal country of birth, parity, and child age at ASQ assessment. Missing values for educational level and maternal country of birth were included as separate categories.

[a]Edinburgh Postnatal Depression Scale; [b]Postpartum Bonding Questionnaire; [c]Ages and Stages Questionnaire, third edition.



Pathway 1 - SARS-CoV-2 exposure in pregnancy → Maternal depression 8 weeks postpartum → Child neurodevelopment at age 24 months
Pathway 2 - SARS-CoV-2 exposure in pregnancy → Maternal depression 8 weeks postpartum → Mother-infant bonding 8 weeks postpartum → Child neurodevelopment at age 24 months
Pathway 3 - SARS-CoV-2 exposure in pregnancy → Mother-infant bonding 8 weeks postpartum → Child neurodevelopment at age 24 months

Figure 16b. Hypothesised pathways in the association between maternal SARS-CoV-2 infection in pregnancy and child neurodevelopment at 24 months of age.
Note: Linear mediation analysis adjusted for maternal age, educational level, maternal country of birth, parity, and child age at ASQ assessment. Missing values for educational level and maternal country of birth were included as separate categories.
[a]Edinburgh Postnatal Depression Scale; [b]Postpartum Bonding Questionnaire; [c]Ages and Stages Questionnaire, third edition.

Assessment of representativeness

Dropout analyses were undertaken due to attrition in papers I, III–IV.

In paper I, baseline characteristics were compared between 36-month ASQ completers and those lost to follow-up. Mothers completing the ASQ were older than those lost to follow-up (mean 24.2 versus 22.4 years). Nevertheless, maternal age did not correlate with ASQ scores, and there were no other differences in gestational age, child sex, Apgar scores, birth weight, or CC time.

In papers III–IV, several dropout analyses were conducted to assess representativeness and potential attrition bias. At both four- and 24 months, maternal SARS-CoV-2 positivity rates were similar among mothers included in the analysis and those lost to follow-up. Mothers included in the analysis were, nevertheless, somewhat more socioeconomically advantaged, as reflected by higher educational attainment and a greater proportion born in Nordic countries (at four months: 82.8% versus 66.9% with >12 years of education; 92.0% versus 81.7% Nordic origin; Table 10**)**. In addition, at four months, responders were more often primiparous, more frequently exclusively breastfed at four weeks postpartum, and had children with slightly higher Apgar scores (Apgar <7 at five minutes: 1.0% versus 1.9%; Table 10). Likewise, at 24 months mothers included in the analysis more often had Nordic origin and higher educational attainment, and they more often exclusively breastfed at four weeks postpartum (87.0% versus 71.7% education; 94.1% versus 85.1% Nordic origin; 77.8% versus 69.5% exclusive breastfeeding; Table 11).

When mothers included in the 24-month follow-up were compared with those included only in the four-month follow-up, the groups were similar on all characteristics except for higher educational attainment in the 24-month group (87.0% versus 82.8% with >12 years of education). Importantly, four-month ASQ total scores were equivalent between children with four-month-only data and those with both four- and 24-month data (257.1 versus 255.6, mean difference 1.48, 95% CI -1.6 to 4.5, $p = 0.34$). This indicates that the 24-month sample remained broadly representative of the larger four-month cohort.

Table 10. Comparison of health and demographic profiles: mothers included in four-month analysis vs dropouts (paper III)

Characteristics	ASQ four months completed	ASQ four months not completed
Mother	n=1 446	n= 970
SARS-CoV-2 positive (%)	555 (38.4)	343 (35.4)
Age at childbirth, mean (SD) y	32.5 (4.0)	32.1 (4.5)
Missing data	10	6
Education >12 y No. (%)	992 (82.8)	529 (66.9)
Missing data	248	202
Multiparous, No. (%)	728 (50.7)	557 (56.4)
Missing data	10	6
Country of birth, No. (%)		
Nordic	1262 (92.0)	761 (81.7)
Non-Nordic Europe	51 (3.7)	61 (6.6)
Other	59 (4.3)	109 (11.7)
Missing data	74	62
Pre-pregnancy comorbidity, No. (%)[a]	158 (11.5)	110 (11.6)
Missing data	72	43
BMI at start of pregnancy, ≥30. No (%)	227(16.4)	160(16.9)
Missing data	65	47
Caesarean, No. (%)	224 (15.6)	199 (20.1)
Missing data	10	6
Breastfeeding at 4 weeks, No. (%)		
No	125 (9.9)	130 (16.6)
Partly	178 (14.1)	132 (16.9)
Exclusively	955 (75.9)	520 (66.5)
Missing data	188	210
Child	n=1446	n=1003
Gestational age, Mean (SD)	39.7 (1.7)	39.5 (1.8)
Missing data	10	6
SGA (birthweight < −2 SD), No. (%)[b]	34 (2.4)	29 (3.0)
Missing data	12	7
Apgar score <7 at 5 min, No. (%)	14 (1.0)	19 (1.9)
Missing data	25	15

[a]Pre-pregnancy comorbidity included diabetes, hypertension, cardiovascular disease, kidney disease, and lung disease; [b]According to Maršál et al[164]

Abbreviations: ASQ, Ages and Stages Questionnaire; BMI, body mass index; min, minutes; No., number; SD, standard deviation; SGA, small for gestational age; y, years.

Table 11. Comparison of health and demographic profiles: mothers included in 24-month analysis vs dropouts (paper IV)

Characteristics	ASQ 24 months completed	ASQ 24 months not completed
Mother	n=742	n= 1 674
SARS-CoV-2 positive (%)	295 (39.6)	615 (36.2)
Age at childbirth, mean (SD) years	32.6 (4.0)	32.3 (4.3)
Missing data	2	13
Education >12 y No. (%)	547 (87.0)	978 (71.7)
Missing data	116	334
Multiparous, No. (%)	377 (50.7)	906 (53.9)
Missing data	2	13
Country of birth, No. (%)		
Nordic	671 (94.1)	1357 (85.1)
Non-Nordic Europe	26 (3.6)	85 (5.3)
Other	16 (2.3)	153 (9.6)
Missing data	32	104
Pre-pregnancy comorbidity, No. (%)[a]	99 (13.7)	169 (10.6)
Missing data	20	94
BMI at start of pregnancy, ≥30. No (%)	123 (16.9)	264 (16.5)
Missing data	17	95
Caesarean section, No. (%)	117 (15.7)	304 (18.0)
Missing data	2	13
Breastfeeding at 4 weeks, No. (%)		
No	65 (9.7)	191 (13.9)
Partly	83 (12.4)	229 (16.6)
Exclusively	520 (77.8)	958 (69.5)
Missing data	77	320
Postpartum depression (EPDS), No (%)	101 (14.4)	107 (14.1)
Missing data	43	940
Mother–child bonding disorder (PBQ), No (%)	33 (4.7)	27 (3.6)
Missing data	48	947
Child	n=745	n=1692
Gestational age, Mean (SD)	39.7 (1.7)	39.6 (1.7)
Missing data	0	0
SGA (birthweight < −2 SD), No. (%)[b]	14 (1.9)	48 (2.9)
Missing data	19	22
Apgar score <7 at 5 min, No. (%)	8 (1.1)	26 (1.6)
Missing data	12	28

[a]Pre-pregnancy comorbidity included diabetes, hypertension, cardiovascular disease, kidney disease, and lung disease; [b]According to Maršál et al[164]

Abbreviations: ASQ, Ages and Stages Questionnaire; BMI, body mass index; EPDS, Edinburgh Postnatal Depression Scale; min, minutes; No., number; PBQ, Postpartum Bonding Questionnaire; SD, standard deviation; SGA, small for gestational age; y, years.

Discussion

The overall aim of this thesis was to explore the neurodevelopmental impact of two key perinatal exposures: (1) delayed versus early umbilical CC at birth and (2) maternal SARS-CoV-2 infection during pregnancy. Furthermore, the thesis examined CC practice in SARS-CoV-2-positive mothers. Taken together, the four papers examine both an active intervention and an environmental exposure and use the ASQ as a common neurodevelopmental outcome measure across different contexts, ages, and study designs.

Delayed CC did not affect overall neurodevelopment at 36 months of age, and antenatal exposure to maternal SARS-CoV-2 infection was not associated with overall child neurodevelopment during the first 24 months of life. Our systematic review showed low, similar neonatal SARS-CoV-2 positivity rates regardless of CC timing, supporting its safety in SARS-CoV-2-positive mothers. Still, it revealed a discrepancy: two-thirds of guidelines recommended delayed CC, while early CC was reported approximately twice as often as delayed CC.

These findings are significant given the high prevalence of both exposures, affecting millions of pregnant women and newborns worldwide. Their relevance is further underscored by the limited evidence on long-term neurodevelopmental effects of delayed CC and the novelty of the now endemic SARS-CoV-2. Paper IV uniquely explored whether maternal postpartum depression and mother–child bonding acted as mediators in the potential association between SARS-CoV-2 exposure and child neurodevelopment. As the only systematic review comparing CC practices in relation to guideline recommendations in SARS-CoV-2 infected mothers, paper II gives insight into the healthcare response in the early COVID-19 pandemic, with implications for current care and future pandemics.

Effects of CC on child neurodevelopment (paper I)

Paper I is, to my knowledge, the only study to examine the effect of delayed CC on child neurodevelopment with follow-up beyond one year in a low-income setting. We found no effect of delayed CC on child neurodevelopment at 36 months of age using the ASQ. This was unexpected, as previous findings from the same cohort showed that delayed CC reduced iron deficiency at eight months and was associated

with a lower risk of adverse neurodevelopmental outcomes at 12 months across several ASQ domains[37,124]. Based on these early benefits, we anticipated a corresponding advantage in later neurodevelopment.

Other studies have similarly demonstrated haematological and physiological benefits of delayed CC. Compared with early CC, delayed CC has been associated with increased neonatal blood volume at birth[31,32]. Higher haemoglobin concentrations and improved iron stores during infancy have also been reported across multiple cohorts [36,37,173]. Given the essential role of iron in brain development and the high prevalence of iron deficiency in infancy, these effects provide a biologically plausible pathway for subsequent neurodevelopmental gains[35]. In addition, delayed CC has been associated with improved transitional circulation at birth[35] and, in preterm children, with increased survival[45,174], both of which may have further advantages for later neurodevelopment.

Later child neurodevelopmental outcomes have primarily been studied in high-income settings, with mixed findings. Mercer et al. reported improved myelination at four- and 12 months following delayed compared with early CC, although without corresponding differences in neurodevelopmental screening[38,39]. In a Swedish randomised cohort with follow-up extending to ten years, delayed CC reduced iron deficiency at four months but not at 12 months[36,41]. While no differences in neurodevelopment were observed during infancy, improved fine motor and personal–social skills were reported at four years[40-42]. No association with ADHD symptoms was found at ten years, although this analysis was limited by substantial loss to follow-up[43]. One possible explanation for these age-dependent discrepancies is that the manifestations of iron deficiency may vary over time as children develop and acquire new skills[175,176].

Other explanations may also account for the absence of an overall effect on neurodevelopment at 36 months in paper I in this thesis. Any benefits of improved iron status may have been attenuated over time or counterbalanced by other biological or environmental factors. A commonly discussed concern related to delayed CC is an increased risk of neonatal jaundice requiring phototherapy, which, if severe, could potentially have adverse neurodevelopmental consequences[177]. Even so, recent evidence does not support this concern, and we observed no increased incidence in our cohort, making this an unlikely explanation[35,178]. It is also possible that actual neurodevelopmental differences at 36 months were too subtle to be detected using the ASQ, which is primarily a screening tool. Finally, the neurodevelopmental consequences of iron deficiency may become more apparent at later developmental stages, underscoring the importance of repeated assessments over longer follow-up periods[179].

The COVID-19 pandemic and CC practice (paper II)

The COVID-19 pandemic created a natural experiment that made it possible to study how clinical practice responded under conditions of uncertainty. Early in the pandemic, some guidelines began to recommend early CC in SARS-CoV-2-positive mothers, often citing concern about vertical transmission as the reason[89,180-182]. Our systematic review uniquely provided a more objective assessment of this issue. We found low rates of neonatal SARS-CoV-2 positivity after birth regardless of CC timing and in line with rates reported by others[55]. There was no evidence that mother-to-child transmission differed by CC timing. These findings argue against a clinically meaningful increase in vertical transmission risk associated with delayed CC, which has important implications for clinical practice. The increasing availability of vaccines against SARS-CoV-2 has likely further decreased risk of intrapartum infection since antibodies are transferred to the child[183].

The discrepancy between guideline recommendations favouring delayed CC and the frequent use of early CC reported in most studies is problematic. If these reports reflect actual practice, many children have been deprived of the benefits of delayed CC. Furthermore, higher proportions of preterm births were reported in studies where early CC was encouraged or performed, and early CC was more frequently recommended in LMICs than in HICs. This could be of particular concern, as large systematic reviews have linked delayed CC to reduced mortality in preterm children[45,174], and children in low-resource settings may have even greater benefit from this practice[184].

In our review, studies recommending early CC also reported lower rates of skin-to-skin contact, breastfeeding, and rooming-in, and higher Caesarean section rates. Such co-occurring care practices may have exacerbated adverse effects, particularly for low-birthweight children in low- and lower-middle-income countries where continuous skin-to-skin contact has been linked to improved survival[160,185-189].

Taken together, our findings support practicing delayed CC in SARS-CoV-2-positive mothers. They also suggest that concerns about vertical transmission may have led to a scientifically unwarranted perception of risk, as well as rigidity in the implementation of clinical practice, despite changing guideline recommendations. This may have affected the health and development of children born during the pandemic, and it highlights the importance of learning from this experience when preparing for future epidemics and pandemics.

Associations between SARS-CoV-2 and neurodevelopment (papers III–IV)

In papers III–IV, antenatal exposure to maternal SARS-CoV-2 infection was not associated with overall adverse neurodevelopment at four or 24 months of age measured with the ASQ. These findings are consistent with most cohort studies using neurodevelopmental screening instruments, which have similarly reported no association between antenatal SARS-CoV-2 exposure and overall neurodevelopmental impairment or autism within the first 30 months of life[69-71,74-76,190]. Rizzo et al. summarised the evidence in a systematic review and meta-analysis, and reported early impairments in hearing, fine motor skills, and problem-solving, although these appeared to resolve over time[73]. In contrast, our results in paper III, which included one of the largest cohort of children with antenatal SARS-CoV-2 exposure, suggested better fine motor function in exposed children. Because our study was published after the review, it was not included. Had it been available, it may have partly attenuated the previously observed association and provided additional reassurance for affected families.

In contrast to our findings, a retrospective cohort found increased risk of ICD code-based neurodevelopmental diagnoses in children exposed to maternal SARS-CoV-2 infection at 12 and 36 months of age[67,77], but not at 18 months[191]. The cohort included more than 18 000 children, of whom 861 were exposed. In contrast, in another ICD code-based cohort including 69 987 children (of whom 2 777 were exposed), Croen et al. found no association with overall neurodevelopmental diagnoses at age 27–48 months. Still, there were sex-specific associations in opposite directions: compared to unexposed controls, there was an increased risk of autism in exposed girls and a lower risk of motor delay in exposed boys[78]. The findings from Croen et al. need careful interpretation as the analyses were not adjusted for multiple testing and most autism diagnoses are made at a later age[192]. In both cohorts, outcomes derived from ICD-coded diagnoses may be vulnerable to misclassification and ascertainment bias[193].

Neurodevelopmental assessment by a health professional using a systematic, standardised tool can provide more precise estimates of developmental risk. A few cohorts have used the Bayley Scales, often regarded as a reference standard. While these cohorts have reported a potentially high risk of developmental delay in children antenatally exposed to SARS-CoV-2[61,64,194,195], the findings are difficult to interpret. Conclusions are limited by small sample sizes (n=15–33 in either exposure or control groups)[61,64,195] and by reliance on pre-pandemic[64,194] or absent control groups[61]. This introduces a risk of residual confounding from broader pandemic-related influences on child neurodevelopment.

Overall, our findings are consistent with the increasing body of evidence mostly suggesting little or no effect of antenatal SARS-CoV-2 exposure on child neurodevelopment. Nevertheless, conclusions remain limited by the relatively short follow-up in most studies (mainly three years or less).

Subgroup analyses

In paper III, exposure to severe maternal SARS-CoV-2 infection was associated with ASQ scores below cutoff at four months indicating potential adverse neurodevelopmental outcomes. There was no association at the 24-month follow-up in paper IV. The null 24-month result is difficult to interpret because attrition reduced the severe-exposure subgroup to 12 children, resulting in very low power. While the association at four months requires cautious interpretation due to multiple testing, it is notable since severe COVID-19 triggers a stronger maternal inflammatory response, which one study associated with poorer child neurodevelopment[50]. Other studies examining antenatal exposure to severe SARS-CoV-2 reported mixed findings and were, like our work, constrained by small sample sizes (n=4-54), limiting the ability to draw definitive conclusions [71,194,196].

In paper III, antenatal maternal SARS-CoV-2 infection was not associated with adverse child neurodevelopment at four months of age, regardless of trimester of exposure. As this finding was in line with most previous studies[69-71,75,76,196], we did not examine trimester-specific associations at 24 months. While two recent reports have raised the possibility of trimester-dependent effects, the pattern has been inconsistent. One study indicated greater risk following early-pregnancy exposure, whereas the other found higher risk with late-pregnancy exposure[77,78]. Taken together, the current evidence does not indicate a robust trimester-related association, in line with our results.

Pandemic-related effects

While antenatal exposure to SARS-CoV-2 may adversely affect child neurodevelopment, it remains unclear whether this reflects the virus itself or pandemic-related conditions. Several studies have reported poorer neurodevelopmental outcomes in children born during the pandemic than in prepandemic controls.[62,63,71,79,113,197]. Potential pandemic-related influences on child neurodevelopment that have been proposed include caregiver stress, parental depression, socioeconomic adversity, and mother–child separation at birth[198,199]. Although prepandemic evidence suggests that these exposures may affect child neurodevelopment, they remain underexplored in the context of the COVID-19 pandemic.[198]. Furthermore, many studies examining the association between

maternal SARS-CoV-2 infection and child neurodevelopment have not adjusted for these factors[73]. Maternal mental health, in particular, has frequently been omitted from such analyses [73].

Paper IV uniquely assessed postpartum depression and mother–child bonding as mediators of the potential association between antenatal maternal SARS-CoV-2 infection and child neurodevelopment, finding no mediating effect. Even so, scores indicating lower bonding quality was associated with adverse neurodevelopment. This aligns with a mainly prepandemic study showing that bonding mediated the association between depression and child neurodevelopment[84]. Our latter finding still require confirmation in studies primarily designed to examine the association.

Sex-specific associations (papers I, III–IV)

Sex-specific effects of antenatal SARS-CoV-2 exposure on child neurodevelopment have been suggested in recent cohort studies. Shook et al. reported an increased risk of neurodevelopmental diagnoses in male offspring, interpreted as reflecting greater male susceptibility to maternal immune activation[77]. Croen et al. instead observed elevated autism risk only in girls, also attributing this to sex differences in maternal cytokines and placental interferon signalling[78]. The findings of the latter study contrasted with our findings in paper III where exposed females had better overall neurodevelopmental screening scores. Taken together with human and animal work, most evidence still supports male brains as more vulnerable to immune activation in general and antenatal SARS-CoV-2 exposure in particular[200-202]. In line with the results of papers III–IV, however, current human neurodevelopmental outcome studies do not consistently demonstrate sex-specific adverse effects after antenatal SARS-CoV-2 exposure.[70,71,75,76,196]. Overall, these studies provide no convincing evidence of sex-specific negative neurodevelopmental effects of maternal SARS-CoV-2 infection.

In paper I, fewer girls undergoing delayed CC were at risk of delayed gross motor development. This contrasts with previous studies on CC in term and preterm children reporting either a protective effect in boys[42,46] or no sex-specific differences[38,39,43]. Boys have lower iron stores at birth and in infancy, making them more susceptible to iron deficiency anaemia[27,203], which could explain a stronger protective effect of delayed CC in this group. Conversely, in a cohort of 4 579 children, ferritin levels <12 ng/L were associated with impaired neurodevelopment in girls but not in boys[204]. This suggests that girls with iron deficiency may be more vulnerable to neurodevelopmental impairment and may therefore benefit more from delayed CC.

Overall, sex-specific neurodevelopmental trajectories may produce age-dependent sex differences in domains such as motor skills[205,206], suggesting that discrepancies

between the findings in our papers and those from other studies are not necessarily conflicting. The sex-specific findings of this thesis may also be due to chance, as they were unadjusted for multiple testing.

Strengths and limitations

The methodological limitations of this thesis can be discussed in view of four aspects: generalisability, pandemic evolution, outcome measure and subgroup analyses.

Generalisability

Paper I: Delayed CC and neurodevelopment

Strengths include the RCT design, which provides strong support for causal inference. The clearly defined CC intervention and blinding of outcome assessors further strengthened internal validity. The high institutional birth coverage (93.8%) supports the representativeness of the study population, and the high prevalence of iron deficiency increases the likelihood of detecting neurodevelopmental effects of delayed CC mediated through improved iron stores. It further supports the relevance of the findings for comparable low- and middle-income settings. Nevertheless, the inclusion of only healthy term-born children limits generalisability to higher-risk births.

Limitations include attrition at follow-up. Although baseline characteristics were broadly similar, attrition bias cannot be ruled out. In addition, there was a high rate of protocol deviations in the delayed CC group, primarily due to clinical complications necessitating immediate resuscitation at birth. Such bias may have attenuated a true association between delayed CC and neurodevelopment. Still, excluding protocol deviations did not alter the findings. As only healthy term children were included, the results may not apply to preterm or high-risk neonates, and it may partially explain the relatively high ASQ scores observed compared with other studies in Nepal. The generalisability of the findings to high-income settings, where baseline iron deficiency is less prevalent, is also limited.

Paper II: Delayed CC, SARS-CoV-2 Transmission, and Pandemic CC Practice

Our systematic approach to data identification and selection reduced the risk of missing relevant studies. Application of the WHO case-definition framework to classify timing of mother-to-child transmission added further precision. Nevertheless, inclusion of more languages, particularly Chinese-language

publications from the early pandemic, might have captured additional important studies.

The generalisability of the review's findings was constrained by the characteristics of the included literature. More than 90% of included studies originated from high- or upper-middle-income countries, and no studies were identified from the African region. The implications for low-resource settings where the benefits of delayed CC may be greatest therefore remain uncertain. COVID-19 lockdowns have also been associated with dramatic reductions in institutional births in Nepal[98]. Because the studies included in our review were limited to hospital-based practices, the findings may not be generalisable to the broader population in comparable low-income settings. CC practice was unspecified for many births, and exact timing was reported in only two studies, precluding analysis of a dose-response relationship between CC time and transmission risk. Contacting authors of the studies might have provided more precise data.

Papers III–IV: Maternal SARS-CoV-2 infection and neurodevelopment

The large sample size and prospective multicentre design support the representativeness of the findings for a Swedish context. Linkage to national quality registers, including SmiNet, enabled comprehensive ascertainment of both exposure and confounders across the entire pregnancy and neonatal period. The repeated neurodevelopmental screenings were another strength. Basing exposure on laboratory-confirmed testing reduced misclassification and strengthened exposure certainty compared to studies relying on self-report or serology[69,75]. Pregnant women were classified as a high-risk group and tested more frequently than the general population, further reducing the risk of missed asymptomatic infections.

Generalisability was limited by progressive attrition. In both papers III–IV, mothers included in the analyses were more often Nordic-born, highly educated, and more likely to breastfeed than those lost to follow-up. Even at recruitment, breastfeeding rates and education level appeared higher in our cohort compared to a nearly population-based Swedish register study[149]. Similar studies from other countries have likewise tended to recruit participants with higher educational attainment than national averages[69,74,75]. This suggests a consistent overrepresentation of socioeconomically advantaged participants across studies. As these factors are associated with favourable neurodevelopment, true differences between exposed and unexposed groups may have been attenuated. Compared to uninfected mothers, SARS-CoV-2-infected mothers had a higher prevalence of obesity and lower educational attainment which would be expected to bias towards worse neurodevelopmental outcomes in the exposed group. Attrition might have been reduced by actively re-contacting study participants.

Still, in both papers SARS-CoV-2 infection rates were similar between completers and non-completers, reducing the risk of differential attrition by exposure. Four-

month ASQ scores also did not differ between those assessed only at four months and those followed to 24 months. ogether with similar baseline characteristics among four- and 24-month completers, this suggests that the 24-month sample was broadly representative of the four-month cohort. Even if we adjusted for multiple confounders, residual selection bias cannot be excluded.

Timing of CC was not measured in the COPE study, which is a limitation given evidence from our systematic review of increased early CC among SARS-CoV-2–positive mothers globally. Including data on CC timing would have strengthened the study. However, Sweden adopted delayed CC as standard practice in this group at an early stage[207]. This makes substantial differential CC practice less likely, although comparable CC timing cannot be confirmed because it was not measured

Pandemic evolution – viral strains and healthcare response

By starting recruitment early in the pandemic, papers III–IV likely captured a high proportion of primary SARS-CoV-2 infections before widespread vaccination and viral evolution altered the exposure landscape. However, the epidemiology of SARS-CoV-2 changed substantially during the relatively long recruitment period of the study, with increasing vaccination coverage, shifts in variant virulence and, as exemplified in paper II, evolving birth practice recommendations. This may complicate separation of the effects of infection per se from those related to the evolving healthcare response. Stratifying by the period of SARS-CoV-2 strain predominance and adjusting for SARS-CoV-2 vaccination could have reduced this bias. Even so, Jaswa et al. found no association between COVID-19 vaccination in pregnancy and neurodevelopmental screening scores[208]. Furthermore, offspring exposed to breakthrough infection after vaccination had similar neurodevelopmental screening scores to those exposed to primary infection[75]. This suggests that maternal vaccination status did not appear to modify child neurodevelopment. While adverse maternal outcomes and stillbirths have been suggested to be more common during the Delta strain predominance period[74], limited evidence does not indicate differences in offspring neurodevelopment by SARS-CoV-2 variant. The RECOVER Pregnancy cohort, which stratified by period of Omicron predominance, found no variant-specific differences[69]. No differences in ASQ scores were observed between children exposed and unexposed to maternal SARS-CoV-2 infection in a study conducted predominantly in the pre-Delta period[75]. Favre et al. similarly reported null findings in a cohort recruited exclusively during the Delta and Omicron periods[209].

Outcome measurement - the Ages and Stages Questionnaire

The ASQ, used in papers I, III–IV, is a standardised neurodevelopmental screening tool used across diverse cultures, languages, and settings, including Sweden and

Nepal[42,106,110-112], and has been widely used in comparable pandemic-era studies[73,113]. Although not formally validated in Sweden or Nepal, it has been extensively validated globally, including in similar contexts[116,210,211].

As a parent-reported screening tool, the ASQ is not equivalent to a formal diagnostic assessment and may be influenced by parental perceptions and mental health[212,213]. The latter is particularly relevant given the pandemic's negative impact on maternal mental health. However, in paper IV, postnatal depression and mother–child bonding did not differ between SARS-CoV-2–positive and –negative mothers, nor did they mediate the association with neurodevelopment at 24 months, although bonding was independently associated with ASQ total scores.

Concerns have been raised about the sensitivity of the ASQ for detecting adverse neurodevelopmental outcomes, particularly when categorical cutoffs are used rather than continuous scores[212]. In our studies, findings were largely consistent for both categorical and continuous ASQ measures, with neither approach indicating an overall association. A relatively recent meta-analysis found that the ASQ demonstrated moderate sensitivity and specificity for detecting developmental delay when established cutoff scores were applied[106]. Using a gold-standard tool administered by a trained health professional, such as the Bayley Scales, might have provided higher sensitivity. Even so, a study comparing the 24-month ASQ and Bayley Scales with respect to predicting cognitive delay at five years reported similarly low sensitivity but high specificity for both instruments[117]. In a separate study, the ASQ at 36 months performed substantially better in predicting IQ below 85 at 5–6 years than was reported for the ASQ at 24 months in the aforementioned study. This suggests that the child's age at measurement may be more important than the specific tool used[118].

In paper I, the ASQ was administered via telephone by trained nurses, which may have introduced social desirability bias, potentially explaining the relatively high scores observed compared with similar settings[112,214]. Theoretically, this could have attenuated a true group difference. Previous studies have demonstrated moderate to excellent concordance between telephone-administered and self-administered ASQ, suggesting that any such bias is likely to be limited[215]. An alternative method would be to use a trained examiner-administered ASQ assessment, which has been used previously in Nepal and North India[111,214]. Whereas some ASQ items were culturally adapted in a study in North India, no such adaptations were made in our study, which may have reduced measurement accuracy[214].

Subgroup analyses

Subgroup analyses in papers I, III–IV, including analyses by sex, SARS-CoV-2 infection severity, and gestational trimester of SARS-CoV-2 exposure, were all conducted in samples with limited statistical power and without correction for

multiple testing. As this increases the risk of both false-positive and false-negative findings, they should be interpreted as hypothesis-generating and require confirmation in studies specifically designed and powered to address these questions.

Conclusions

This thesis examined (1) the neurodevelopmental effects of delayed versus early umbilical CC and (2) the association between maternal SARS-CoV-2 infection during pregnancy and child neurodevelopment. It further investigated how the COVID-19 pandemic influenced CC practice.

We found no difference in neurodevelopment measured with the ASQ at 36 months between children undergoing delayed and early CC. Even so, consistent protection against iron deficiency, the absence of adverse effects, and emerging evidence of neurodevelopmental benefits in previous studies support delayed CC for at least three minutes in term children.

Delayed CC did not seem to increase the risk of neonatal SARS-CoV-2 infection in our systematic review, supporting its safety in women with confirmed or suspected infection. Notably, although most guidelines recommended delayed CC, early CC was more frequently reported in the included studies. This discrepancy may reflect an unwarranted concern about mother-to-child SARS-CoV-2 transmission, potentially depriving children of the benefits of delayed CC and underscoring the need to align practice with evolving evidence.

Antenatal exposure to SARS-CoV-2 was not associated with overall adverse neurodevelopment measured with the ASQ, suggesting no certain clinically important negative effects on child neurodevelopment during the first 24 months of life. Severe maternal SARS-CoV-2 infection was associated with adverse neurodevelopment at four months but not at 24 months in exploratory analyses, warranting confirmation in larger studies. These findings are reassuring for both families and healthcare providers. It is important that they are communicated clearly, as parental reassurance may reduce stress and support parents' capacity to promote their children's neurodevelopment[216,217]. Clinically, these results support continued use of standard neonatal and follow-up practices (including promotion of delayed CC when clinically feasible) rather than routine alteration of care on the basis of antenatal SARS-CoV-2 exposure alone.

As a whole, the conclusions of this thesis should be interpreted with caution given the relatively short follow-up period and high attrition rate in papers I, III–IV. It should again be emphasised that the ASQ is a neurodevelopmental screening tool and should not be misinterpreted as diagnostic.

Future scope

SARS-CoV-2 has transitioned from a pandemic to an endemic phase, with increased population immunity, likely reduced virulence, and less draconic infection control measures. This may further attenuate any potential adverse effects of SARS-CoV-2 exposure on child neurodevelopment, raising questions about the generalisability of our findings to children with antenatal exposure who are born today. Nevertheless, millions of children were born during the pandemic, and they will represent a substantial part of society for the next 70 years. Therefore, it is important to continue following this group.

To assess the full neurodevelopmental impact of CC timing and antenatal SARS-CoV-2 exposure, longer follow-up is needed. A full understanding of how COVID-19 and the pandemic have affected children's neurodevelopment requires consideration of both the direct effects of infection and the broader societal influences. The latter include socioeconomic conditions, parental mental health, and healthcare practices such as mother–child separation or separation of the mother from her partner at birth.

Subgroup associations may exist, particularly in relation to the potential impact of severe maternal SARS-CoV-2 infection on child neurodevelopment. This question will likely be best addressed through meta-analyses, given the limited number of severe cases in individual studies.

Especially regarding the association between SARS-CoV-2 exposure and child neurodevelopment, most studies have relied on parent-completed screening tools (such as the ASQ), or on ICD-coded neurodevelopmental diagnoses. Since these approaches both have limitations, golden-standard assessments such as the Bayley Scales or the WPPSI would be preferable. However, the cost and resource demands of adequately powered studies involving hundreds of participants may limit feasibility, making screening questionnaires and ICD codes a reasonable complementary approach for future studies with longer follow-up.

Most studies on antenatal SARS-CoV-2 and neurodevelopment, including ours, have been conducted in high-income settings. It is also important to examine lower-income settings, while accounting for pandemic-related factors that may have had a greater adverse impact on neurodevelopment.

Although the WHO has ended the emergency phase of the COVID-19 pandemic, it has been estimated that there is a 50% chance of another pandemic causing more than 25 million deaths within the next 25 years[125]. The findings of this thesis highlight two key aspects for future response efforts: first, striking a balance between infection control and the preservation of neurodevelopment-promoting, family-friendly health practices; and second, ensuring timely data collection to inform and support clinical practice.

The near-population-based Swedish national quality registers are well suited to collecting health outcomes in large populations, enabling rapid answers to safety questions, including at the subgroup level. They also reduce the risk of socioeconomic selection bias, thereby decreasing the likelihood that socioeconomically disadvantaged groups are underrepresented. For studies of CC, the inclusion of time to CC in the Swedish Neonatal Quality Register is a particular strength, and further development of the Child Health Services register could provide timely data on neurodevelopmental screening outcomes. The national registers will also allow for assessment of longer-term neurodevelopmental effects of antenatal SARS-CoV-2 exposure, as school grades and diagnostic codes are incorporated.

Populärvetenskaplig sammanfattning

Under de första åren i livet utvecklas barnets hjärna snabbt. Det som händer under graviditet, förlossning och den tidiga småbarnstiden kan därför få avgörande betydelse för barnets senare hälsa och utveckling. I min avhandling har jag undersökt tre frågor som är viktiga för både barnhälsa och klinisk praxis: (1) om senarelagd avklämning av navelsträngen vid födseln, s.k. ”sen avnavling”, påverkar barnets psykomotoriska utveckling vid tre års ålder, (2) hur avnavling hanterades under pandemin, och (3) om COVID-19 under graviditet kan ha betydelse för barnets utveckling de första två åren.

I den första delstudien följde vi barn i Nepal och jämförde tidig med sen avnavling. Tidig avnavling definierades som inom en minut, medan sen avnavling definierades som tre minuter eller längre efter födseln. Resultaten visade ingen tydlig skillnad i den övergripande psykomotoriska utvecklingsscreeningen vid tre års ålder mellan grupperna. Samtidigt sågs en möjlig ökad risk för försening i grovmotorisk utveckling hos flickor som genomgått tidig avnavling. Det senare fyndet bör tolkas försiktigt eftersom det kan bero på slumpen. Det är dock fortfarande ett intressant fynd eftersom sen avnavling ger barnet mer blod från placentan, vilket ökar järndepåerna under livets första månader. Bättre järnstatus är i sin tur viktig för hjärnans utveckling. Detta eftersom järn behövs för myelinisering, synapsbildning och utveckling av de signalsubstanssystem som stödjer motorik och kognition. Det är alltså rimligt att tänka sig att sen avnavling kan ha en långtgående positiv inverkan på barnets utveckling. Sådana positiva utvecklingseffekter har också påvisats i andra studier.

Den andra delstudien handlade om hur avnavling hanterades under COVID-19 pandemin. I början av pandemin fanns stor rädsla för smittoöverföring från mor till barn, vilket ledde till att vissa riktlinjer rekommenderade tidig- istället för sen avnavling. Vår genomgång visade dock att sen avnavling inte ökade risken för överföring av COVID-19 från mor till nyfödd. Resultaten talar därför för att sen avnavling fortsatt bör rekommenderas även när modern har COVID-19, eftersom denna praxis är kopplad till flera fördelar för barnet. Förutom de tidigare nämnda positiva effekterna för hjärnans utveckling bidrar sen avnavling även till bättre omställning av blodcirkulationen direkt efter födseln och minskad dödlighet hos för tidigt födda barn.

I de tredje och fjärde delstudierna undersökte vi om barn vars mödrar haft COVID-19 under graviditeten hade sämre psykomotorisk utveckling vid fyra- respektive 24 månaders ålder. Inte heller här såg vi några tydliga skillnader i den övergripande psykomotoriska utvecklingen mellan COVID-19 exponerade och oexponerade barn vid någon av dessa tidpunkter. I vissa analyser fanns signaler om att svårare sjukdom hos modern kunde vara kopplad till sämre resultat, men detta var inte ett genomgående fynd.

Sammantaget visar avhandlingen att sen avnavling verkar vara en säker och fortsatt värdefull rutin, även om mamman har COVID-19, och att COVID-19 under graviditeten inte tycks vara kopplad till en generell försämring av barnets psykomotoriska utveckling de första två åren i livet. Resultaten bidrar till kunskap som kan stödja tryggare och mer evidensbaserad perinatal vård.

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