Caesarean Delivery and Women's Health: Population-Based Studies

Trends, Offspring Birthweight, Fecundability and Maternal Cardiovascular Disease Mortality

Yeneabeba Tilahun Sima

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2024

UNIVERSITY OF BERGEN

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Date of defense: 22.02.2024

Year: 2024

Title: Caesarean Delivery and Women's Health: Population-Based Studies

Name: Yeneabeba Tilahun Sima

Print: Skipnes Kommunikasjon / University of Bergen

Contents

Scientific environment

The work has been conducted within the ReproEpi - Registrybased reproductive epidemiology research group, at the Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen.

This PhD is part of the HealthierWomen project, funded by the European Research Council. Professor Rolv Skjærven is the principal investigator of the project.

The main supervisor has been Associate Professor Linn Marie Sørbye at the Norwegian Research Centre for Women's Health, Oslo University Hospital, Rikshospitalet, and at the Department of Global Public Health and Primary Care, University of Bergen.

Co-supervisors has been Professor Rolv Skjærven, Associate Professor Liv Grimstvedt Kvalvik and Professor Nils-Halvdan Morken.

UNIVERSITY OF BERGEN
Faculty of Medicine

Acknowledgement

Pursuing a PhD in a new research environment is undeniably exciting. However, embarking on this journey amid the COVID-19 pandemic presented unforeseen challenges. I arrived in Bergen when the nationwide lockdown came into effect, marking an unprecedented start to my academic journey. The first few months were very difficult. I am thankful for the support I received from my supervisors, colleagues, and friends during this extraordinary period.

It brings me great pleasure to thank all people who made valuable contribution to this work.

I would like to thank the European Research Council for financing this project with a three-year fellowship.

I am forever grateful to my main supervisor, Linn Marie Sørbye, for her excellent guidance. Under her supervision, a nurturing and appreciative work environment was cultivated, and this has been an incredible source of motivation for me. Her patience and consistent check-ins provided a solid foundation, while her enthusiasm in research was inspiring. I am thankful for all the valuable lessons she has shared with me. This thesis would not have been possible without her continued support.

I want to express my sincere gratitude to my co-supervisor, Rolv Skjærven, for the opportunity to be part of this project. His extensive knowledge in registry-based epidemiology, creative thinking, curiosity about the unknown, and, most importantly, his ability to infuse joy into research have all been truly inspirational. I am grateful to my co-supervisor, Liv Grimstvedt Kvalvik, for generously sharing her knowledge, offering valuable advice, and providing feedback on my work. Her innovative approaches to tackling complex concepts have been valuable source of learning for me. I am thankful for my co-supervisor, Nils-Halvdan Morken, for his feedback on my work, insightful discussions, and contributions to the thesis writing process.

I would like to thank Kari Klungsøyr for generously sharing her extensive knowledge in perinatal epidemiology and the Medical Birth Registry. I appreciate her valuable contributions to our weekly meetings and publications. I am grateful to Maria Christine

Magnus at the Centre for Fertility and Health, for our collaboration, sharing of her knowledge, and her valuable contribution to Paper III. I would also like to thank Siri Håberg at Centre for Fertility and Health for her assistance in helping me access the Norwegian Mother, Father, Child Cohort data.

I am grateful to Jannicke Igland, Øystein Haaland, and Janne Mannseth for helping me with statistical inquiries and engaging in discussions.

Thank you to my colleague and friend, Prativa Basnet (Prati), who was my companion throughout this journey. I am grateful for the numerous moments we have experienced together. I am thankful for my colleagues at the research group: Sage Wyatt, Aditi Singh, Nadia Arshad, Abdu Seid, Thomas Skogvold and Shwe Sin Win, for the engaging discussions, moments of laughter, and the enjoyable times we have shared over the years.

I am grateful for the Department of Global Public Health and Primary Care at the University of Bergen, which provides a stimulating learning environment. I appreciate the seminars and platforms we had, particularly the Wednesday- and TRACE seminars. I enjoyed the humour and interesting conversations that unfolded during our gatherings. Lastly, I appreciate the help and guidance provided by the administrative staff.

I extend my sincere gratitude to my good friend Baizhen Ciren (Pedron), who have always been there for me. The past few years would have been incredibly challenging without your friendship and encouragement.

I wish to express my heartfelt gratitude to my parents, Tewabech Beyene and Tilahun Sima, for their love and continued support. My gratitude extends to my brothers, who have been my steadfast supporters since the very beginning. Your love and encouragement are deeply cherished, and I am profoundly thankful for each one of you.

Last, but not least, I want to express my gratitude to my husband, Ahmed Duale, whose love, patience, and continued support have been the cornerstone of my journey.

Sammendrag

Bakgrunn

Globalt har det vært en økning i antall fødsler forløst med keisersnitt. Keisersnitt er assosiert med ugunstige utfall både for mor og barn, og det er derfor viktig å studere endring i keisersnitt over tid og eventuelle konsekvensene dette kan ha for kvinnehelsen.

Formål

(I) Undersøke forekomst og tidstrend av keisersnitt blant førstegangsfødende kvinner i relasjon til sosiodemografiske endringer i Norge i perioden 1967-2020.

(II) Evaluere sammenheng mellom endring i fødselsvekt fra første til andre svangerskap og mors risiko for å dø av hjerte-og karsykdom. Videre å undersøke om sammenhengen er forskjellig hos kvinner med spontan- og indusert fødselsstart ved fødsler til termin.

(III) Å undersøke sammenheng mellom tidligere keisersnitt og kvinnens fruktbarhet i neste svangerskap, samt å undersøke den motsatte retningen; om fruktbarhet har sammenheng med keisersnitt.

Metode

(**I**) Vi analyserte 1,067,356 førstegangsfødende kvinner med enkeltfødsel til termin og som fødte sitt barn i hodeleie mellom 1967-2020 i data fra Medisinsk Fødselsregister i Norge (MFR). (**II**) Basert på data fra MFR og Dødsårsaksregisteret, analyserte vi 735,244 kvinner med to påfølgende fødsler til termin i tidsperioden 1967-2020. Fødselsvekt ble delt inn i kvartiler (Q1 til Q4) og er justert for svangerskapsvarighet. (**III**) Ved å koble data fra MFR og Den norske mor, far og barn-undersøkelsen (MoBa) og analyserte 42,379 flergangsfødende kvinner for å studere sammenhengen mellom keisersnitt og senere fruktbarhet. For å evaluere den motsatte sammenhengen, inkluderte vi 74,025 kvinner uten tidligere keisersnitt.

Resultat

(**I**) Forekomst av keisersnitt har økt i Norge mellom 1967-2010, men har stabilisert seg i det siste tiåret. Relativ risiko for keisersnitt vært stabil blant kvinner i alderen 35-39 år i tidsperioden fra 1999 til 2020 sammenlignet med kvinner i alderen 20-24 med spontan fødselstart i perioden 1967-1982. For kvinner over 40 år har relativ risiko for keisersnitt

gått ned både blant kvinner med spontan- (fra 14.2 [95% CI 12.4-16.3] til 6.7, [95% CI 6.2-7.4]) og indusert fødselstart (fra 17.6 [95% CI 14.4-21.4] til 13.4 [95% CI 12.5-14.3]). Risiko for keisersnitt har derimot økt blant kvinner under 35 år i perioden 1999-2020. (**II**) Endring i fødselsvekt fra første til andre svangerskap var assosiert med mors risiko for å dø av hjerte- og karsykdom. Sammenlignet med kvinner som hadde to terminfødsler der begge barna hadde fødselsvekt innenfor kvartilene Q2/Q3, hadde kvinner som fødte barn Q2/Q3 i første fødsel og Q1 i andre fødsel en økt risiko for å dø av hjerte- og karsykdom (HR 1.33 [95% CI 1.18-1.50]). Motsatt observerte vi en lavere risiko for død blant kvinner som endret fødselsvekt til Q4 (HR 0.78 [95% CI 0.67-0.91]) i andre fødsel. Kvinner som endret fødselsvekt fra Q1 i første fødsel til Q4 i andre fødsel, reduserte sin risiko for å dø av hjerte- og karsykdom. (**III**) Kvinner med keisersnitt i sitt forrige svangerskap, hadde lavere fruktbarhets ratio (FR 0.90 [95% CI 0.88 to 0.93]) og forhøyet risiko for infertilitet (RR 1.21 [95% CI 1.10-1.33]) sammenlignet med kvinner som hadde vaginal fødsel i forrige svangerskap. Kvinner som brukte ≥ 12 menstruasjons sykluser før de ble gravide, hadde høyest risiko for keisersnitt (RR 1.55 [95% CI 1.46-1.64]) sammenlignet med kvinner som ble gravide innenfor de første to syklusene.

Konklusjon

(**I**) Til tross for økende alder blant førstegangsfødende, har antall keisersnitt gått ned blant kvinner ≥ 35 år. Den generelle økningen i keisersnitt ser derfor ikke ut til alene å kunne forklares av økende alder blant førstegangsfødende kvinner. (**II**) Blant kvinner med to terminfødsler, var en nedgang i fødselsvekt fra første til andre fødsel assosiert med økt risiko for å dø av hjerte- og karsykdom; mens en økning i fødselsvekt var assosiert med redusert dødelighet. Stratifiserte analyser for spontan- og indusert fødselsstart viste samme mønster. Informasjon om fødselsvekt (i forhold til svangerskapslengde) fra påfølgende fødsler kan bidra til å fange opp variasjoner i mors langtids risiko for å dø av hjerte- og karsykdom. (**III**) Kvinner med tidligere keisersnitt hadde nedsatt fruktbarhet og forhøyet risiko for infertilitet. Det ble også observert en høyere risiko for keisersnitt blant kvinner med redusert fruktbarhet, noe som kan indikere felles underliggende mekanismer heller enn keisersnittet i seg selv.

Abstract

Background

Caesarean delivery (CD) is increasing globally. Because CD has been linked with adverse outcomes for the mother and the baby, it will be important to study changes in CD rate over time and its consequences on women's health.

Objectives

(I) To examine the trend in CD among nulliparous women, in relation to sociodemographic changes in Norway during 1967-2020.

(II) To evaluate the association between changes in offspring birthweight by gestational age from the first to second pregnancy and maternal cardiovascular disease (CVD) mortality. Further, to assess if the associations vary among spontaneous- and iatrogenic term deliveries.

(III) To examine the bidirectional associations between CD and fecundability.

Methods

(**I**) We analysed 1,067,356 women with their first singleton cephalic term birth between 1967-2020, using data from the Medical Birth Registry of Norway (MBRN). (**II**) Based on data from MBRN and the Cause of Death Registry, we conducted an analysis involving 735,244 women who had their first two term births between 1967 and 2020. Standardized offspring birthweight by gestational age were grouped into quartiles (Q1 to Q4). (**III**) Using linked data from the Norwegian Mother, Father and Child Cohort Study (MoBa) and MBRN, our study included 42,379 women with previous deliveries when assessing the relationship between CD and subsequent fecundability. To evaluate the reverse association, we included 74,025 women without previous CDs.

Results

(**I**) CD rates increased in Norway between 1967-2010, while stabilizing in the last decade. Compared to women aged 20-24 years with spontaneous labour onset between 1967 to 1982, the RR of CD was stable among women aged 35-39 years between 1999-2020. Among women aged ≥40 years, the RR of CD decreased both among women with spontaneous- (from 14.2 [95% CI 12.4-16.3] to 6.7[95% CI 6.2-7.4]), and induced labour onset (from 17.6 [95% CI 14.4-21.4] to 13.4 [95% CI 12.5-14.3]). Conversely,

the risk of CD increased in women aged < 35 years between 1999 and 2020. (**II**) Changes in offspring birthweight by gestational age from first to second pregnancy were associated with maternal CVD mortality. Compared to women who had their first two term births in Q2/3, those who had their first birth in Q2/Q3 and second birth in Q1 exhibited a higher CVD mortality (HR 1.33 [95% CI 1.18-1.50]), whereas the lowest risk was observed among those whose second birth occurred in Q4 (HR 0.78 [95% CI 0.67-0.91]). Similarly, among women who had their first birth in Q1, the increased risk disappeared if the second birth was in Q4. (**III**) Women with previous CD had lower fecundability ratio (FR 0.90 [95% CI 0.88 to 0.93]) and increased infertility risk (RR 1.21 [95% CI 1.10-1.33]) compared to women with prior vaginal delivery. When assessing the reverse correlation, we found that women who did not conceive within 12 or more cycles had a higher risk of CD (RR 1.55 [95% CI 1.46-1.64]) compared to women who conceived within their first two cycles.

Conclusions

(**I**) Despite the ongoing shift with increasing age of nulliparous women, CD declined among women aged ≥ 35 years. The overall rise in CD cannot be merely explained by a shift in the age of nulliparous women. (**II**) In women with two term births, a decrease in birthweight by gestational age from the first to second birth was associated with an increased maternal CVD mortality, while an increase in birthweight by gestational age was associated with decreased mortality. Stratified analyses by spontaneous - and iatrogenic births showed similar pattern. Adding birthweight by gestational age information from subsequent births might capture a heterogeneity in maternal CVD mortality. (**III**) Reduced fecundability and increased risk of infertility were evident among women with a previous CD. A higher risk of CD was observed in those with reduced fecundability, suggesting a bidirectional association between CD and fecundability. Therefore, the reduced fecundability observed following a CD could be explained by some common underlying mechanisms, rather than the CD procedure itself.

List of publications

I. Sima YT, Skjærven R, Kvalvik LG, Morken N-H, Klungsøyr K, Sørbye LM. Caesarean delivery in Norwegian nulliparous women with singleton cephalic term births, 1967–2020: a population-based study. BMC Pregnancy and Childbirth 2022; 22:419.

II. Sima YT, Skjærven R, Kvalvik LG, Morken N-H, Klungsøyr K, Mannseth J, Sørbye LM. Birth Weight in Consecutive Pregnancies and Maternal Cardiovascular Disease Mortality Among Spontaneous and Iatrogenic Term Births: A Population-Based Cohort Study. American Journal of Epidemiology. 2023.

III. Sima YT, Magnus MC, Kvalvik LG, Morken N-H, Klungsøyr K, Skjærven R, Sørbye LM. The relationship between caesarean delivery and fecundability: a population-based cohort study. In Manuscript.

List of abbreviations

BMI: body mass index

CD: caesarean delivery

CI: confidence interval

CTG: cardiotocography

CVD: cardiovascular disease

FR: fecundability ratio

HR: hazard ratio

ICD: International Classification of Diseases

MBRN: Medical Birth Registry of Norway

MoBa: Norwegian Mother, Father, and Child Cohort

NIPH: Norwegian Institute of Public Health

OECD: Organisation for Economic Co-operation and Development

OR: odds ratio

Q: quartiles

RR: relative risk

TTP: time to pregnancy

WHO: World Health Organization

List of figures and tables

Background

There is an ongoing discussion on the role of pregnancy complications on women's long-term health[1]. It is not clear whether pregnancy complications are causally linked to maternal cardiovascular disease (CVD) mortality, or if the complications manifest as signs of underlying subclinical risk factors for CVD[1 2]. An alternative perspective argues that pregnancy complications might be associated with CVD mortality primarily due to their correlation with reduced fertility[3]—a factor that itself has been identified as a marker for future chronic diseases[4]. Hence, pregnancy history and women's reproductive experience have been increasingly identified as a "window of opportunity" for improving long-term chronic disease in women[1]. Insights derived from studies exploring these associations hold the potential to bring a paradigm shift in women's health[5].

Caesarean delivery (CD) is the most frequent operative procedures at Norwegian hospitals performed for women with complicated pregnancies[6]. However, in recent times, its occurrence has extended to uncomplicated pregnancies as well, resulting in an increasing number of women undergoing CD[7]. This thesis seeks to comprehensively assess the possible consequence of CD on women's short and long-term health, while considering women's pregnancy history.

1. Caesarean delivery

This chapter will briefly describe the change in CD rates, and its consequences on maternal health. Summary of the existing classification systems used for monitoring CD rates will also be described.

1.1 Global caesarean delivery trends

Globally, over the past three decades, CD rates have surged, with an average annual growth rate of 4.4%[7]. Between 1990-2014, the highest increases were observed in Latin America and the Caribbean at 19.4%, followed by Asia at 15.1%, and Oceania at 14.1%. Conversely, Africa had the lowest increment at 4.5%, followed by Northern America at

10%, and Europe at 13.8%. The Nordic countries have also experienced an increase in CD rates, though to a lesser extent[8]. The proportions and trends of CD in the Nordic countries are presented in **Figure 1**.The highest increase was observed in Denmark and Norway, while Finland had a moderate increase[9]. The main contributors to this increment were nulliparous women and women with prior CD[8].

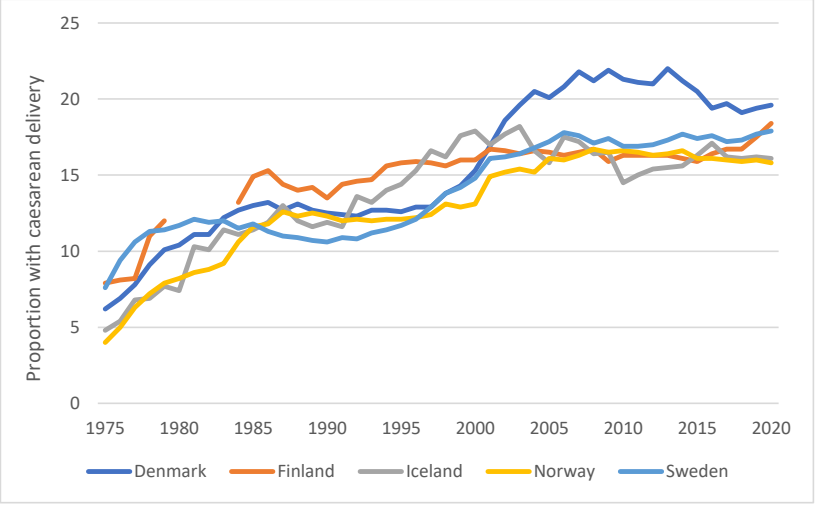

Figure 1. Caesarean delivery in Nordic countries, 1975-2020

Source: Nordic perinatal statistics 2020[9]

CD rates serve as a crucial marker of access to obstetric services[10]. However, there are no universally accepted optimal CD rate at the population level[11]. Previously, the World Health Organization (WHO) recommended that surpassing a CD rate of 10-15% might not be beneficial and could potentially result in increased adverse outcomes for both mothers and infants[12]. However, from 2016 on, WHO has removed the target rate for CD, and instead focused on ensuring a safe and positive experience for all women and their babies[13 14]. In general, there is overuse of CD services in many high- and middle-income countries, while concurrently, there is underutilization in numerous low-income countries, thus exacerbating social inequities in health between nations[7 11 15].

1.2 Consequences of caesarean delivery on women health

When CD is deemed necessary, also called medically indicated, it plays a crucial role for the well-being of both the mother and her baby[7 16]. However, the continuous increase in CD rates in high-income countries lacks evidence of increased effectiveness[16]. In fact, it has been associated with adverse outcomes both for the mother and her baby[16 17]. Immediate complications following a CD include thromboembolism, bleeding, infection, and extended hospital stays[16]. Advances in medicine have reduced occurrences of bad outcomes after CD, may have contributed to more interventions during normal childbirth[18]. However, on average the cost of CD is estimated to be three times that of vaginal delivery[19], posing a huge burden to society.

In the long-term, CD has been linked to increased morbidity both in mothers and children[16 17]. A recent systematic review and meta-analysis[17], which included 79 cohort studies and one randomized controlled trial, revealed a higher risk of placental abnormalities and uterine rupture following CD compared to vaginal delivery, summarized in **Table 1**. Women who underwent CD were more likely to experience miscarriage, ectopic pregnancy, stillbirth, and infertility (reviewed in detail in section 4.3). On the other hand, rates of postpartum haemorrhage, pelvic prolapse and urinary incontinence were reduced.

Table 1. Adverse outcomes in subsequent pregnancies among women with caesarean delivery.

Adverse outcomes	Odds ratio[a] (95% CI)
Placenta previa	1.74 (1.62-1.87)
Placenta accreta	2.95 (1.32-6.60)
Placental abruption	1.38 (1.27-1.49)
Uterine rupture	25.81 (10.96-60.76)
Miscarriage	1.17 (1.03-1.31)
Stillbirth	1.27 (1.15-1.40)
Infertility	1.6 (1.46-1.76)
Urinary incontinence	0.56 (0.47-0.66)
Pelvic prolapse	0.29 (0.17-0.51)
Postpartum haemorrhage	0.72 (0.55-0.95)

[a] Compared to women with previous vaginal delivery. Results adopted from Keag O, Norman J, Stock S. Long-term risks and benefits associated with caesarean delivery for mother, baby, and subsequent pregnancies: Systematic review and meta-analysis. PLoS Med. 2018;15(1)[17].

1.3 Caesarean delivery classification systems

The rising CD rates, along with subsequent morbidities and increased cost, seem to pose considerable challenges for women's health[16]. To propose optimal CD rates, we cannot simply rely on the overall CD rate as it fails to identify groups and factors driving the observed trends[20 21]. Instead a comprehensive evaluation of CD is necessary[21]. This entails monitoring fluctuations in CD rates over time, pinpointing contribution from specific groups, and evaluating quality of healthcare through the surveillance of maternal and perinatal outcomes based on obstetric risks[22].

Torloni and colleagues conducted a systematic review on the existing classification systems that are used to monitor and compare CD rates worldwide[21]. They examined and qualitatively assessed the strengths and limitations of each system by utilizing a framework that has been evaluated and graded by an international team of experts in the field. The framework consisted of seven criteria: simplicity, clarity, inclusiveness, mutual exclusivity of categories, potential for prospective application, reproducibility, and implementation requirements. Each classification system was scored on a scale of 0 (poor), 1 (average), to 2 (good) for each criterion. The authors classified 27 primary classification systems into four distinct groups based on the seven criteria [21]. Indication-based classifications focused on explaining the reasons behind CD, while urgency classifications addressed the timing of CD. Women's group classifications aimed to determine which individuals would undergo CD. The remaining group included systems that aimed to answer all these questions comprehensively. While indication-based classifications were found to be the most used in clinical settings, the women-based classification and particularly the ten-group classification system (**Figure 2**) proposed by Robson was deemed highly suitable for CD rates comparisions[20].

1.1.1 The Robson ten-group classification system

In 2015, WHO endorsed the Robson ten-group classification as a global standard tool for monitoring and comparing CD rates across different time periods and countries[13 22]. This classification system groups women into ten distinct categories based on six parameters: plurality (*singleton or multiple*), foetal presentation (*cephalic, breech,*

transverse/oblique), gestational age (<37 week *or* ≥*37 week*), previous CD (*yes or no*), parity (*nulliparous or parous*), and onset of labour (*spontaneous, induced, or pre-labour CD*)[20]. The tool is easy to use, and the parameters are routinely collected in most healthcare institutions and registries[22]. The system also ensures that each woman is assigned to a single group, with the groups being mutually exclusive and comprehensive. In addition to assessing the changes in CD rates, this classification system is also beneficial in identifying specific indications such as induction, breech presentation and multiple pregnancies[23].

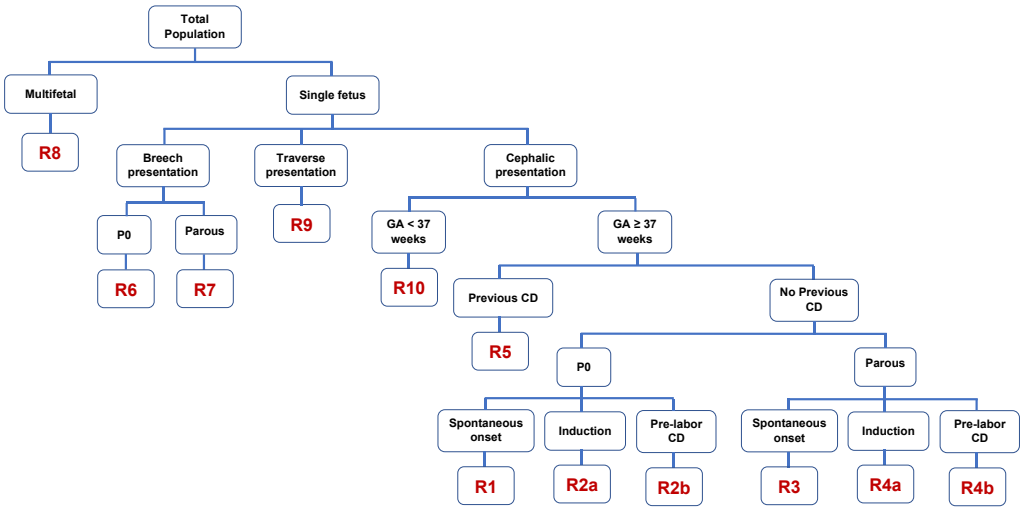

Figure 2. The Robson ten-group classification system[20]

*P0 stands for nulliparous women, GA stands for gestational age, CD stands for caesarean delivery

Despite increasing use of the Robson classification system [8 22 24 25], it is not without limitations[26]. The tool fails to account for other factors influencing CD rates, such as maternal age, body mass index (BMI) and pregnancy complications[23 26 27]. Considering these factors is crucial for monitoring and evaluating changes in CD rates and making meaningful comparisons among institutions or countries[27].

2. Factors influencing caesarean delivery rates

In most high-income countries, there is a growing trend of women choosing to delay childbirth due to various social, economic, and educational reasons[28]. Likewise, advancements in technology have brought about changes in the management of labour and delivery[18]. While numerous factors could potentially influence CD rates, this section will focus on the following four main factors: fertility rate, delayed childbearing, migration and socioeconomic status, and medicalization of childbirth.

2.1 Total fertility rate

Total fertility rate refers to the average number of children a women would have during her lifetime[29]. Fertility rates have decreased in nearly all European countries and currently fall below the replacement rate of 2.1 children, averaging at 1.50 (2021)[30]. These rates vary across countries, with Malta having the lowest rate at 1.13 and France having the highest rate at 1.84 in 2021. In the Nordic countries, Iceland has the highest fertility rate (1.72), followed by Denmark (1.67) and Sweden (1.66)[9].

In Norway, fertility rates have declined from nearly 3.0 in the 1960s to 1.64 in the mid-1980s[28] (**Figure 3**). Since then, the rates have remained consistently above 1.80, with a stable rate of 1.86 children from 2000 to 2013[28]. This stable trend can be attributed, in part, to the presence of generous social welfare, which allows women to have family without compromising their education and career[31], and a prevalent culture of cohabitation among couples[28]. However, there has been a gradual decrease in fertility rates in the last decade, with the latest rate being 1.46 (2021)[32]. Factors such as delayed age at first birth and a reduction in the number of three births have been identified as significant contributors to this trend[28].

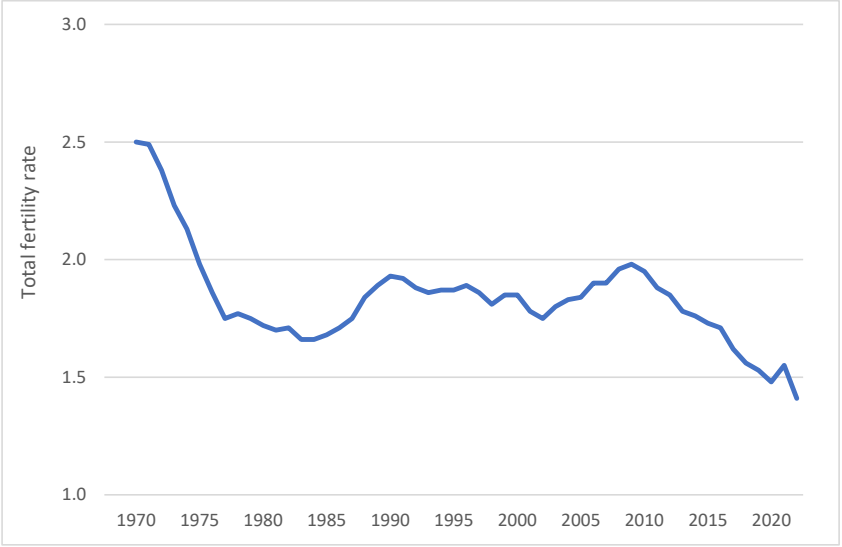

Figure 3. Total fertility rate for women, Norway, 1970-2020

Source: Statistics Norway (ssb.no) [32]

2.2 Delayed childbearing

According to a recent report from the Organisation for Economic Co-operation and Development (OECD, 2023), the average age at which women give birth has reached 30 years and above in the OECD countries (consisting of 15 high-income countries) [33]. In the Nordic countries, the mean age of women giving birth ranged from 30.0 to 31.4 years, while for nulliparous women, it ranged from 28.0 to 29.8 years[9]. Iceland had the lowest proportion of women giving birth ≥35 years (19.6%), while Finland had the highest proportion (24.8%)[9] (**Figure 4**).

Good access to contraceptives[34] and availability of assisted reproduction technologies[35] may contribute to this trend by possibly delaying pregnancy, while legal access to abortion services could reduce the rates of unintended pregnancies[36]. Overall coverage of contraceptives is high in European countries, with an average of 90% of women in fertile age, and even higher among northern European countries [34].

Delayed childbearing has been identified as a factor explaining the rise in CD[37]. A systematic review of 21 observational studies involving women with singleton pregnancies reported an increase in the risk of CD by maternal age, with women ≥35 years having a CD risk ranging from 1.4 to 2.8, both in nulliparous and multiparous women, compared to women <35 years [37]. In nulliparous women in the UK, the risk of CD increased linearly[38 39], with every 5-year increment correlated with a 20% increase in CD risk[40]. In the Nordic countries, nulliparous women particularly those who underwent induction, had a 3-5-fold surge in CD risk for every 5-year increase in maternal age[41]. This elevated risk could be attributed to factors like the aging myometrium[38 39] as well as a decreased number of receptors in the uterus[42]. Higher maternal age is also linked with higher incidence of dystocia, foetal distress and malpresentation [39 43 44 45].

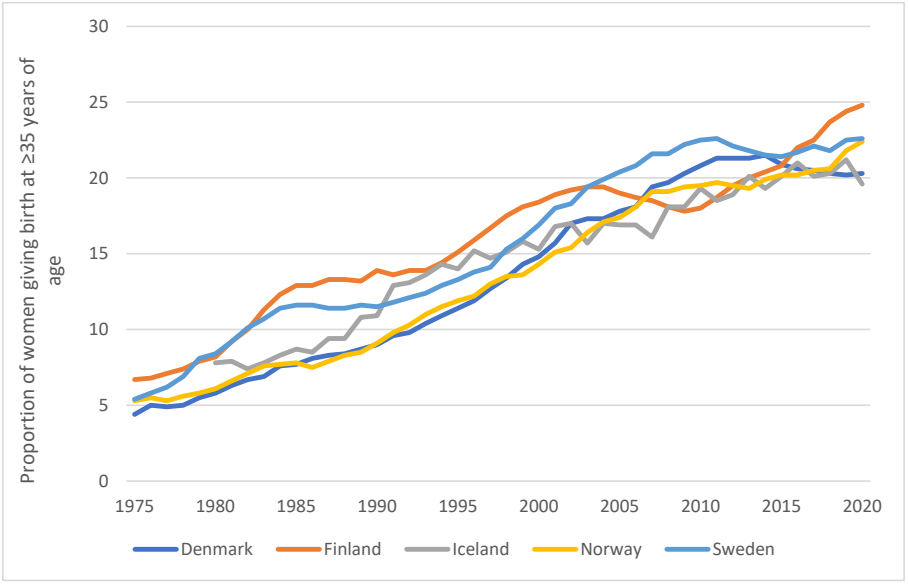

Figure 4. Proportion of women giving birth at the age ≥ 35 years in the Nordic countries, 1975-2020

Source: Nordic perinatal statistics 2020[9]

In addition to affecting uterine contractility, advanced maternal age (≥ 35 years) has been linked with increased risk of pregnancy complications such as hypertensive disorders[46-48], diabetes[46-48], preterm delivery[49], obesity[50] and growth restriction[44 46 48], all of which have been correlated with increased risk of CD[41-43 51 52].

2.3 Migration and socioeconomic status

The increasing immigration to Norway is resulting in a higher proportion of immigrant women giving birth in Norway[32]. Studies from different countries in Europe have reported higher CD rates in immigrant women[53]. The increased CD risk in this group could be attributed to higher frequencies of risk factors like diabetes mellitus[54 55] and obesity[56]. Non-medical factors such as cultural differences and language barriers have also been identified to contribute to a higher risk of CD in immigrant women[55 57 58]. In Norway, immigrant women exhibit a higher occurrence of CD, particularly emergency CDs[59 60].

In Norway, a woman's risk of undergoing a CD is associated with her socioeconomic status[55]. This association is explained by differences in the occurrence of both obstetric and medical indications for CD among various socioeconomic groups[55]. Women with lower education, a proxy for low socioeconomic status, were found to have an increased risk of CD[55 61]. The risk of diabetes mellitus and small for gestational age babies were higher among low educated women[55].

2.4 Medicalization of childbirth

Today's society tends to be more risk averse, and a similar trend has been observed in modern obstetrics[62]. The utilization of interventions during childbirth has surged to unprecedented levels in many high-income coutries[11 18]. With the improvement of maternal and perinatal outcomes, public expectations regarding childbirth might have shifted compared to times when adverse outcomes were more common[62]. This trend may be further driven by heightened litigation and the privatization of health systems[63]. As a result, obstetric interventions during labour have become customary practices even

among uncomplicated deliveries, as observed in most high-resource settings[52]. Moreover, there have been shifts in the perspectives of women and healthcare providers concerning the birthing experience[18 45 64]. All these evolving dynamics collectively have the capacity to influence CD rates[18].

2.4.1 Advancement in technology

Norway has noticed a steady rise in labour interventions[6 65]. The introduction of electronic foetal monitoring (CTG) and ultrasound in the early- and late 1970s, respectively, could have contributed to a higher frequency of obstetric interventions including CD[45] (**Figure 5**). While CTG has proven to be helpful in identifying foetuses at risk of hypoxia during labour, the false positive rates have been linked to elevated risk of CD among low-risk women[52 66]. In response to these concerns, CTG is no longer recommended for routinely administered to low-risk women in Norway, while it remains a standard procedure for all women during labour and delivery in Sweden and Finland[66]. Gestational age estimation using ultrasound during second trimester has been offered to the general population at no cost from 1984 onwards[45]. Since the implementation of ultrasound, there has been a decrease in the occurrence of post-term pregnancies[67]. The change in the reporting format of the Medical Birth Registry of Norway (December 1998)[68] and change in management of term pregnancies with breech presentation (2000)[69] might also influence CD rates.

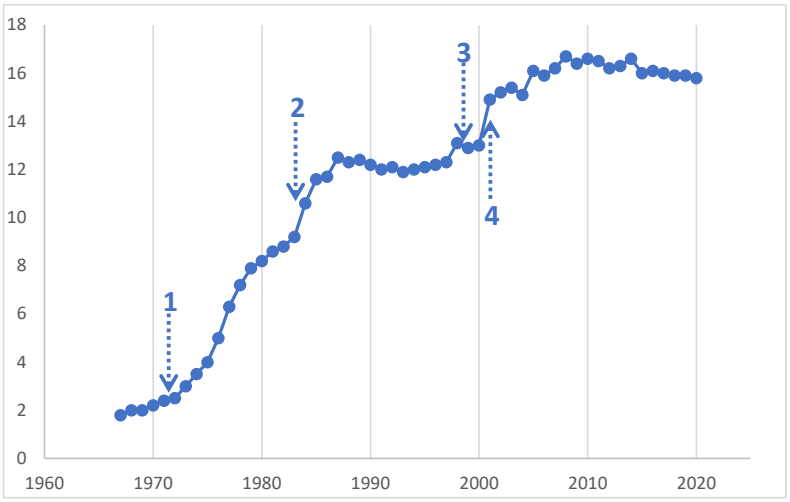

Figure 5: The percentage of caesarean delivery rate by year of delivery, Medical Birth Registry of Norway, 1967-2020

1: Introduction of cardiotocography[45] (early 1970s), 2: Gestational age estimation using ultrasound during 2nd trimester became available to the general population[45] (starting in 1984), 3: Change in the reporting formats in the Medical Birth Registry of Norway[68] (December 1998), 4: Term breech Trial [69] (2000)

Source: Statistics Norway (ssb.no) [32]

2.4.2 Obstetric recommendations and interventions

Over the years, changes in obstetric guidelines and recommendations have had the potential to influence the prevalence of CD rates[45]. One important change in obstetric practice involved the management of breech presentations. A pivotal multi-centre randomized study conducted in 2000 sparked a change in obstetric practice, favouring planned CD for term pregnancies with breech presentation[69]. Additionally, there has been a growing trend towards more proactive management of post-term pregnancies (≥42 weeks)[70]. While a recent Cochrane review reported lower risk of CD for pregnancies induced from 41 weeks onward [70], recent studies from settings with low perinatal mortality have presented conflicting results[65]. Specifically, studies from Norway[65] and Denmark[71] have reported an increased risk of CD with induction from 41

weeks, while no difference was observed in another study from Sweden[72] and the Netherlands[73]. Since 2011, the Norwegian Directorate of Health recommend induction all pregnancies no later than 42 weeks[74].

Induction rates among term pregnancies (37-41$^{+6\ days}$ weeks) have also been on the rise across most high-resource settings[75 76]. In the United States, approximately one-third of pregnant women opt for induction[75], while in Europe, around 60% of countries have reported induction rates exceeding 20%[76]. While inducing labour may prove advantageous in preventing adverse outcomes for both mothers and infants in complicated pregnancies[77], it is also associated with risk of uterine hyperstimulation, which may lead to foetal distress and, in rare instances, uterine rupture[70]. Several studies have additionally highlighted an increased likelihood of CD following induction[41 71 78-80]. However, Stock et al.(2012) reported unaltered CD rates among induced births [81], while others have observed reduced CD rates following induction[82-87].

In Norway, there has been a rise in induction rates of all births, reaching 26% in 2019[65], and approximately one tenth of inductions were carried out without medical indications[88]. Failed induction and prolonged first stage of labour accounted for nearly half of the CDs performed among induced nulliparous women[89]. Although there was a wide variation in induction methods across hospitals in Norway[89], there has been a general trend towards increased use of vaginal misoprostol and cervical balloon, alongside a decrease in the utilization of dinoprostone[90]. However, changes in induction methods have not shown influence on CD rates[90].

The National Guidelines, made by the Norwegian Society of Gynaecology and Obstetrics, concerning induction, particularly in the management of post-term pregnancies, have undergone multiple revisions[74]. Before 2010, pregnant women in gestational week 42$^{+0\ days}$ to 42$^{+2\ days}$ were evaluated, and induction was recommended if women were deemed high-risk pregnancy[65]. If not, women were advised to undergo expectant management until week 43$^{+0\ days}$. In 2010, the guidelines were updated to include the evaluation of pregnant women within gestational weeks 41$^{+2\ days}$ to 42$^{+0\ days}$. If danger signs were present, induction was advised; otherwise, women were encouraged

to wait for spontaneous labour onset until gestational weeks $42^{+0\ days}$ to $42^{+2\ days}$. Since 2014, pregnant women have been evaluated for induction no later than gestational weeks $41^{+2\ days}$ to $41^{+4\ days}$. Additionally, due to the trend in induction and the need to evaluate adverse perinatal outcomes, the proportion of induced women was incorporated into the national quality indicator in 2016[74].

2.4.3 Women and healthcare provider preference

In Norway, there has been an increasing involvement and inclusion of women in decision making regarding the mode of delivery[91]. This could partly have contributed to an increase in CD[92]. In general, a smaller proportion of women seem to express preference for CD[93], ranging from 7.6-15% of women in Europe[94]. Fear of birth, concerns about physical harm, prior CD and negative prior birth experiences were main reasons for preferring CD[61 95 94 96]. A previous Norwegian study reported that around 10% of women indicated preference for CD[61]. This preference seems to be more common among women ≥35 years, women with low education, and those who used assisted reproduction. Aasheim et al. (2013) also reported that older women were more likely to express preference for CD due to concerns about the baby's well-being and potential complications[97].

The perspectives of healthcare professionals regarding childbirth are also likely to influence women's choice of delivery[63]. Today, there seem to be a greater receptiveness and positivity among professionals toward interventions during childbirth, contrasting with practices observed in earlier periods[45 98]. In Canada, there has been an increasing acceptance of labour interventions, particularly among younger physicians[99]. A similar trend has been observed in Norway, where female physicians demonstrate higher rates of performing CD compared to their male counterparts[100]. Additionally, there seem to be a growing willingness to accommodate maternal requests for CD[63]. Among obstetricians from eight European countries, concerns regarding patient autonomy and fear of litigation were reported as the primary reasons for accommodating maternal requests for CD [63].

2.4.4 Obstetric care in Norway

In Norway all women have free access to antenatal- and obstetric care and almost all deliveries occur in public hospitals[6]. Approximately 50,000 births are annually distributed in the 48 birth units, and differentiated into three levels of obstetric care[101]. Level 3 consists of midwifery-led units that primarily serve low-risk women. Level 2 is situated in smaller hospitals with birth units equipped to provide obstetric and aesthetic services. Conversely, Level 1 comprises specialized birth units that offer advanced obstetric, paediatric, and anaesthetic services, including neonatal intensive care units.

Norway has one of the lowest CD rates among high-income nations[8], and several factors may contribute to this achievement. Firstly, the country has adopted National Obstetric Guidelines since 1995[102]. These guidelines ensure consistency in antenatal and obstetric care across various healthcare institutions[103], which could potentially reduce unnecessary CD rates[104]. A standardized antenatal care program is accessible and recommended for all pregnant women[105]. Secondly, Norway benefits from a system of multi-professional teamwork within obstetric care[106]. When women arrive at the labour ward, an assessment is conducted by the midwife to determine their risk level (low or high risk)[101]. For low-risk women, intermittent foetal auscultation is used to monitor progress of labour[6]. In most cases, women will have a spontaneous delivery[107]. However, if signs of potential complications emerge during delivery, the woman's risk status will be changed to high-risk, leading to the involvement of attending obstetricians[101]. Such close collaboration and well-accepted division of responsibilities could possibly lead to fewer interventions[104]. And there are no incentives for clinicians to perform CDs[106]. Additionally, the healthcare system encourage women to attempt vaginal birth after a previous CD[106], with Norway having higher vaginal birth after a previous CD than other countries[108].

3. Obstetric interventions, offspring birthweight and maternal cardiovascular disease mortality

The main aim of obstetrics is to ensure health of both the mother and the baby[109]. Among women with spontaneous onset, initiation of labour occurs without external intervention. In women with pregnancy complications or in women with chronic conditions, clinicians may need to intervene and initiate labour by either induction or planned CD. Such interventions halt pregnancies before their natural completion, potentially affecting newborn's birthweight and gestational age[110]. This chapter describes the existing evidence on the link between obstetric intervention, offspring birthweight and maternal CVD mortality.

CVD is the leading cause of death worldwide[111]. It encompasses various conditions affecting the heart and blood vessels, including ischemic heart disease, cerebrovascular disease, hypertensive disorders, rheumatic disease, pulmonary heart disease, and diseases of the arteries, veins, and lymphatic system[112]. Among these, ischemic heart disease and cerebrovascular disease contribute to four out of every five CVD-related deaths[112]. Risk factors that have been identified to influence CVD onset and progression include lifestyle-, socioeconomic-, and environmental factors[112].

Since the 1970's, high-income countries have observed a decrease in CVD mortality[113]. This positive trend has been largely attributed to changes in modifiable risk factors such as reduced tobacco smoking and alcohol consumption, effective management, and advancements in medical care[113 114]. However, a recent study utilizing data from the WHO mortality database, encompassing 23 high-income countries including Norway, has uncovered a notable deceleration in this declining trend[113]. Both prevalence of CVD and risk factor scores have been found to be increasing among young people[114 115], especially women[115].

3.1 Pregnancy and maternal cardiovascular disease mortality

CVD accounts for approximately one-third of all female deaths[116]. However, the prediction and management of CVD in women have not received the same level of attention as in men[116]. The existing knowledge about CVD predominantly stems from studies conducted on men, with limited inclusion of women in clinical trials[1]. Notably, the manifestation of CVD seems to differ between genders[117], with coronary heart disease typically appearing 7-10 years later in women compared to men[118]. Consequently, women seem to be underdiagnosed and less likely to be recognized as being at risk for CVD compared to their male counterparts[116 118]. This highlights the need for increased attention and research focused on understanding and addressing the unique aspects of CVD in women[1].

Women's response to physiological changes during pregnancy may be used to assess early signs into future risk of CVD[119]. During pregnancy, a women's organ system undergoes changes, primarily driven by hormonal activity originating from the placenta[119 120]. The placenta produces corticotropin-releasing hormone, which stimulates the release of adrenocorticotropic hormone from the pituitary gland, subsequently leading to cortisol production from the adrenal glands[120]. These hormonal cascades results in a physiological state of hypercortisolism[119]. Additionally, there is a temporary phase of insulin resistance, resulting in transient hyperglycaemia, hyperinsulinemia, and a hypercoagulable state[120]. The maternal cardiovascular system also undergoes a series of changes that begin in early pregnancy and peak during the second and early third trimesters[120]. Peripheral vasodilation begins as early as the fifth week of pregnancy, causing a gradual decrease in vascular resistance that levels off in the middle of the second trimester. To counteract this, the maternal heart increases its stroke volume, reaching its peak by early third trimester. Simultaneously, the heart rate increases steadily throughout pregnancy, reaching maximum in the third trimester. Both responses serve as a test for maternal carbohydrate and lipid metabolism, as well as vascular function[119].

Pregnancy complications have been linked to increased risk of maternal CVD mortality[1 2]. Women with history of complications, such as preeclampsia, preterm, diabetes

mellitus, stillbirth, and low offspring birthweight face increased risk of CVD mortality, ranging from 1.5 to 2.7-fold[2]. Hence, Sattar and Greer proposed that pregnancy could serve as a cardiac "stress" test and that these complications could potentially signal future CVD risk [121]. Others studies emphasize that pregnancy complications are linked to reduced fecundability/infertility[3], which is in turn associated with increased risk of future chronic diseases[4] including CVD[122 123].

3.2 Offspring birthweight and maternal cardiovascular mortality

Following studies by Barker and collaborators [124], numerous studies have investigated the association between birthweight and the risk of CVD in adults[125]. There has been less attention towards the link between maternal pregnancy outcomes and her long-term health, leaving women's pregnancy history as an "underused opportunity" to examine the long-term risk of maternal CVD[1].

Giving birth to a low birthweight infant (< 2500 grams) has been identified as an indicator of maternal CVD mortality[1 2 126]. While variations in offspring birthweight can stem from a mix of genetic and environmental factors[127], most cases of low birthweight are primarily attributed to preterm birth or hypertensive disorders like chronic hypertension, gestational hypertension and preeclampsia [128-130], which are independent risk factors for CVD[2]. Previous studies that explored the associations between offspring birthweight and maternal CVD mortality were mostly focused on preterm births[1 2] (**Table 2**). Women with preterm births have a 1.9 to 3-fold increased hazard of dying from CVD [128 131-134]. Despite the increased CVD risk faced by these women, preterm births account for a minority of total births, approximately 10% in the US, 9% in Europe, and close to 6% in Norway[135]. The association between offspring birthweight and maternal CVD mortality have not been thoroughly investigated within the term birth population, which comprises most women giving birth. A recent Norwegian study revealed that women who delivered in the early term period (37-38 weeks) had a 41% increased CVD mortality compared to those delivering between weeks 39 and 41[136].

This observation implies that even within the term period, there is heterogeneity in the risk of CVD mortality, which has been less closely studied.

Furthermore, most studies seem to concentrate on women's first birth or assess the associations with any single birth, disregarding the importance of a woman's complete reproductive history[128 137-139]. This is an important limitation as the majority of women in Norway have more than one births[137]. Also, focusing on women's first birth do not allow us to distinguish between those who stop reproducing after one pregnancy, who typically carry a higher risk of mortality, and women who continue to subsequent births[137 140]. Moreover, both recurrence and order of pregnancy complications has been shown to affect maternal CVD mortality[136]. Therefore, the partial inclusion of reproductive information runs the risk of concealing the heterogeneity within different groups of women[137].

Table 2. Studies assessing offspring birthweight and maternal cardiovascular disease mortality

Study	Country	Exposure	Outcome	Follow up time (years)	Total sample	Included
Davey Smith 1997[141]	Scotland	BW	CVD death	29	794	Any birth
Davey Smith 2000[142]	Finland	BW	CVD death	34	3706	Any birth
Davey Smith 2000[143]	UK	BW	CVD death	10	44813	First birth only
Davey Smith 2001[144]	Scotland	BW	CHD event	17	129920	First birth only
Davey Smith 2005[145]	Sweden	BWG	CVD death	20	783814	Any birth
Wikström AK 2005[146]	Sweden	BWG	CHD event/death	15	403550	First two births
Friedlander 2007[147]	Israel	BW	CHD death	34	37718	Any birth
Bonamy 2011[132]	Sweden	BWG	CVD event/death	11.8	923686	First birth only
Lykke 2010[133]	Denmark	BWG	CVD death	14.6	782287	First birth only
Rich-Edwards 2015[136]	Norway	BWG	CVD death	25	688662	First two births
Morken 2018[131]	Norway	BWG	CVD death	25	711726	First birth only

BW: absolute birthweight, BWG: birthweight adjusted for gestational age, CVD: cardiovascular disease, CHD: coronary heart disease

3.3 Obstetric interventions and offspring birthweight

The increasing use of obstetric interventions might affect birthweight and gestational age distribution among newborns[110]. When evaluating maternal CVD mortality in relation to offspring birthweight, it will be essential to consider birthweight in the context of gestational age, rather than relying solely on absolute birthweight[148]. This methodology can offer greater insight into the factors affecting birthweight and CVD mortality[148]. In pregnancies with spontaneous onset, labour starts naturally, allowing us to assess the mother's inherent physiological capacity. However, in cases of iatrogenic births, pregnancies are terminated before reaching their natural endpoint. Differentiation between spontaneous and iatrogenic births is essential for gaining insights into the mechanisms contributing to maternal susceptibility to CVD[131 149].

Studies have indicated a higher CVD mortality among women who undergo medically initiated deliveries than those with a spontaneous onset of labour[149 150]. However, these studies focused on only women with preterm deliveries. Except for Rich-Edwards et al. (2015)[136], no study has explored this difference among term deliveries.

4. Caesarean delivery, time to pregnancy and fecundability

Understanding the impact of CD on women's subsequent reproduction is of importance, given the rise in global CD rates[7] and the ongoing trend of delayed childbearing[33]. This chapter will briefly describe the normal physiology of conception and focus on the use of time to pregnancy (TTP) as a measure of women's fecundability. Additionally, an overview of the current knowledge regarding the correlation between CD and fecundability will be provided.

Epidemiologists tend to use various terminologies to describe women’s ability to be pregnant following sexual intercourse, leading to discrepancies in the use of terms across the literature[151]. In this thesis, fecundity is defined as a measure of women’s ability to conceive, while fertility is used as a measure of the capacity to have births[152]. Fecundability measures the likelihood of achieving conception in a given menstrual

cycle among couples that are engaged in regular intercourse and not utilizing contraceptives[151] [152]. Thus it measures the duration from conception to pregnancy detection[153].

4.1 Conception and pregnancy

Every month, when women in their reproductive age experience ovulation, a mature egg is released into the fallopian tube[154]. This process is regulated by gonadotropin hormones, specifically follicular stimulation hormone and luteinizing hormone. If a woman engages in sexual intercourse around this time, there is a possibility of pregnancy. It is generally assumed that the best time for conception is during the middle of the menstrual cycle, specifically five days leading up to ovulation and the day of ovulation itself[153].

In the event of fertilization, the genetic material from the sperm and egg combines, giving rise to a zygote[153]. This zygote then embarks on a journey through the oviduct towards the uterus, typically spanning a duration of 6-12 days[155]. Throughout this period, continuous cell division takes place, facilitating the development of the zygote. Upon reaching the uterus, the zygote-derived trophoblasts attach the fertilized egg to the endometrium, without provoking an immune response from the mother's body[153]. Additionally, the trophoblasts release the hormone human chorionic gonadotropin, which aids in the production of progesterone, a crucial hormone for maintaining pregnancy. From this phase on, it is possible to detect the hormone both in the maternal serum and urine, making it the most commonly way to screen for pregnancy [153].

The majority of conceptions do not lead to successful pregnancies, with a significant number of losses occurring before pregnancy is even detected or before a missed period[156]. According to Chard et al.(1999), up to 60% of losses happen during the preclinical phase, which includes the process of implantation and early pregnancy, mainly due to chromosomal abnormalities [157]. The remaining 10% of losses occur after pregnancy has been detected and are commonly known as miscarriages[157]. Consequently, even under optimal conditions, the conception rate per menstrual cycle is approximately 30%[156].

4.2 Time to pregnancy

Although the majority of couples are able to conceive relatively quickly, approximately 10-15% of couples experience difficulties in achieving pregnancy within a 12-month timeframe[158], a condition referred to as infertility[151]. Certain clinical conditions, including polycystic ovarian syndrome, endometriosis, fibroids, and pelvic inflammatory disease, have been identified as causes of infertility in women[153]. In 5-15% of cases, no specific causes can be identified, while in some instances, changing partners can affect the fertility outcome[153].

One commonly utilized epidemiological measure for studying women's fertility is the assessment of fecundability[159]. By examining the TTP, we can indirectly observe the duration, in terms of the number of menstrual cycles, it takes for a couple to successfully conceive. This indirect approach is adopted because directly measuring the probability of conception can be challenging. A longer TTP indicates lower fecundability and possibility of early loss[159].

TTP data can be obtained through both prospective and retrospective approaches[159]. In prospective data collection, researchers closely monitor couples who are actively attempting to conceive and observe the occurrence of pregnancy[159]. Typically, these studies involve couples who planned to have a baby and have discontinued the use of contraceptives[160]. This study design is considered ideal for collecting TTP data since both the TTP and other relevant information are collected prospectively, minimizing the risk of recall bias[159 161]. However, prospective studies can be expensive and demanding, posing challenges in recruiting a large number of participating couples[159]. Additionally, potential selection biases may arise, especially since such studies are likely to exclude populations where unplanned pregnancies are more common[161].

As a result, retrospective studies are commonly employed in epidemiology due to their cost-effectiveness and utilization of readily available information[153]. In retrospective studies, TTP data is gathered by asking couples to recall the duration it took them to conceive[159]. Although this approach has its limitations, it allows for larger sample sizes

and provides population-level estimates due to the increased number of participants[159] [161].

4.3 Caesarean delivery and fecundability

Numerous studies have explored the relationship between CD and subsequent fecundability. Similarly, other studies have focused on fecundability and the risk of CD.

4.3.1 Caesarean delivery and subsequent fecundability

Several studies have suggested fewer pregnancies among women with a previous CD, while some studies have found no such change[162] [163] [164]. Two recent systematic reviews reported a 10% lower risk of subsequent pregnancy and longer inter-pregnancy interval among women with a previous CD[164] [163]. A more recent meta-analysis of 11 studies revealed that the odds of experiencing infertility were higher after CD compared to vaginal delivery, with an odds ratio (OR) of 1.60 (95% CI 1.45-1.76)[17].

The degree to which the decline in fertility is attributed to the CD procedure remains unclear. Various factors, including indications for CD, women's intention, infertility concerns and parity, have the potential to influence the association[164]. Most of the studies assessing fertility following CD have relied on the interpregnancy or birth interval (**Table 3**). While interval provides valuable insights into reproductive patterns, it fails to consider essential elements such as pregnancy intention[165]. Intention can be influenced by a diverse range of factors, including desired family size, maternal prior health, and previous pregnancy and birth experiences[163] [164]. Further, some studies fail to consider important factors such as access to infertility treatment, contraception use, or important lifestyle risk factors such as smoking and BMI[163] [166]. Such limitations are particularly evident in studies based on datasets collected before 2000[163]. Furthermore, the practice of CD has undergone changes over the years[7]. Thus, findings from earlier studies may not fully reflect the current circumstances[163] [164].

Table 3. Summary of cohort studies assessing the link between caesarean delivery and subsequent fertility

Study	Design	Setting	Country	Period	Total sample	Measurement used	Estimate
Hemminik 1985[167]	Retrospective	Population	USA	1982	4420	BI	OR
Hall 1989[168]	Retrospective	Population	UK	1964-1983	22948	PI	OR
Hemminik 1996[162]	Retrospective	Population	Finland	1987-1989	73104	BI	OR
Murphy 2002[165]	Prospective	Population	UK	1991-1992	14541	TTP	OR
Mollison 2005[169]	Retrospective	Population	UK	1980-1997	25377	PI	HR
Smith 2006[170]	Retrospective	Population	UK	1980-1999	109991	PI	RR
Tollanes 2007[166]	Retrospective	Population	Norway	1967-1996	596341	BI	RR
Eijsink 2008[171]	Retrospective	Hospital	Netherlands	1998-2002	5515	PI	T-test
Kjerulff 2013[172]	Retrospective	Population	USA	2000-2008	52498	BI	RR
Gurol-Urganci 2014[173]	Retrospective	Population	UK	2000-2013	1047644	PI	HR
Fussing-Clausen 2014[174]	Retrospective	Population	Denmark	1987-2009	642052	BI	HR
O'Neill 2014[175]	Retrospective	Population	Denmark	1982-2010	832996	BI	HR
Ever 2014[176]	Prospective	Hospital	USA	2008-2013	982	TTP	OR
Elvander 2015[177]	Retrospective	Population	Sweden	1992-2010	771690	PI	HR
Radin 2016[178]	Retrospective	Population	Denmark	2007-2012	5046	TTP	FR
Kjerulff 2020[179]	Retrospective	Population	USA	2009-2011	2423	TTP	HR

BI: birth interval, HR: hazard ratio, OR: odds ratio, PI: pregnancy interval, RR: relative risk, TTP: time to pregnancy

4.3.2 Fecundability and Caesarean delivery

Women experiencing lower fecundability/infertility are at an increased risk of encountering adverse pregnancy complications, including preterm birth[180], preeclampsia[181], low birthweight (<2500 grams)[180 182], perinatal deaths[183], and congenital anomalies[184]. Additionally, women with lower fecundability/infertility face an increased risk of obstetric interventions[180 182 183], including induction of labour and operative vaginal deliveries. Similarly, the risk of CD is higher in these women[165 180 182 183], ranging from 1.20 to 2.4 times. The increased CD risk seem to persist despite adjustments made for various confounding factors including sociodemographic, lifestyle, and infertility treatment[46 165 180 182].

Beyond the immediate pregnancy related concerns, women with reduced fecundability/ infertility have also found to be at an elevated risk of developing chronic diseases such as CVD[122 123] and various types of cancers[185]. These implications highlight the importance of identifying infertility as a potential indicator of poor future health in women[4].

Rational for the thesis

The rising global rates of CD may have consequences for women's short and long-term health[16 17]. Further, the occurrence of a CD is not random; instead, it is more common in women with underlying chronic conditions and pregnancy complications[163 164]. Therefore, when studying the consequences of CD, it is vital to distinguish between the effects of the medical indications for CD and the physical outcomes resulting from the CD procedure[166]. Such study can benefit from using linked registry-based data that includes the mother's previous and subsequent pregnancy history, thereby providing a more comprehensive picture[186].

There is a gap in knowledge when it comes to the potential negative consequences of the CD procedure on women's subsequent health[17]. Most studies only consider information from the index pregnancy and therefore fail to include information from subsequent pregnancies, while other studies have too short follow up[17 163 164]. Also, previous studies evaluating consequences of CD report findings for all women, and not specific to the population of lower risk women, making it difficult to differentiate between the effect of CD and the medical indications for CD[16 162].

Paper I

In the Nordic countries, nulliparous women have been identified as one of the key groups contributing to the recent rise in CD rates[8]. The outcome of first pregnancy has been found to affect subsequent pregnancies, including CD recurrence rates[17]. In Norway, more than half of women who had CD in their first pregnancy also had a CD in their second pregnancy[187]. Thus, in countries where the majority of women have two

or more births, closely monitoring CD rates in nulliparous women becomes crucial as this is the start of their reproduction career[188].

To gain a comprehensive understanding of the factors influencing CD rates and to develop targeted strategies to address any concerning trends, it is essential to utilize a standardized tool that has already been developed to facilitate easy comparisons within countries and institutions[22]. In doing this, we should also take into account important social and obstetric factors that may explain variations in CD rates[27].

⟹ Thus, we need to assess the changes in CD rates among nulliparous women over the last five decades in relation to sociodemographic changes happening in Norway.

Paper II

Pregnancy history can serve as a valuable tool to identify women at high risk for CVD and facilitate early interventions for those who could benefit the most[1 2]. Women giving birth to an offspring with low birthweight has been found to have higher risk of dying from CVD[1 2 126]. However, most studies have focused solely on women's first/any birth without considering information from subsequent births[128 137 189]. Also, these studies commonly rely on absolute birthweights, without considering gestational age[131]. Using only absolute offspring birthweight information becomes particularly challenging in the context of the ongoing increase in obstetric interventions, which may result in more babies being born earlier[110]. Moreover, the variation in CVD mortality among women giving birth within the term period has not been thoroughly explored.

⟹ Therefore, there is a need to evaluate maternal CVD mortality using standardized offspring birthweight information from subsequent births among women with term births. Additionally, we need to explore the role of obstetric interventions within the term period.

Paper III

Studies have linked CD with women's subsequent reduced fecundability/infertility[17 162-164]. Many of these studies use pregnancy interval as a key measure to assess subsequent reproduction. However, relying solely on interval presents challenges in differentiating whether longer or shorter intervals are due to difficulties in conceiving or intentional decisions made by individuals[165]. Moreover, it has been noted that CD is more prevalent among women with reduced fecundability/infertility issues[165 181-183].

⟹ Thus, it is important to assess the bidirectional relationship between CD and reduced fecundability/infertility.

Aims of the study

The aim of this thesis is to examine the trends in CD and its subsequent consequences, especially concerning women's fecundability and long-term CVD mortality. To achieve this, we linked data from women's first and subsequent births, with the mother serving as the unit of analysis. The main objective is to address the knowledge gap on the impact of CD on women's health, while accounting for women's pregnancy history.

Specific objectives

1. Paper I: to examine the trend in CD among nulliparous women, in relation to sociodemographic changes in the Norwegian society, 1967-2020.

2. Paper II: to investigate the relationship between changes in offspring birthweight by gestational age from the first to second pregnancy and maternal CVD mortality among women with their first two term births. We also aimed to assess potential differences between spontaneous and iatrogenic onset deliveries.

3. Paper III: to examine the bidirectional association between CD and fecundability.

Material and methods

Study designs

All three studies were based on data from population-based historical cohorts[190]. Data on both the exposure and outcome of the three papers were collected prospectively. Maternal unique national identification numbers were used when linking the different sources[186]. The mother was the unit of analysis in *Paper I* and *II*, while in *Paper III* the pregnancy was the unit of analysis.

Data sources

1. **Medical Birth Registry of Norway (MBRN)**

MBRN is a population-based registry that collects data on all births in Norway through mandatory notification[68 191]. The registry has included live- and stillbirths from 16 weeks of gestation since 1967. Information on the health of pregnant women before and during pregnancy is recorded on standardized antenatal form by attending general practitioners or midwives during antenatal visits. After childbirth, the attending health professionals transfer the recorded data from the antenatal records to the MBRN forms. Additional information from hospital records, such as complications during delivery, and perinatal outcomes, is also incorporated into the MBRN forms. During discharge, this form is sent to the MBRN for coding.

Until December 1998, information was recorded as free text and coded using International Classification of Disease (ICD) code 8 (1967-1998)[68]. However, new notification forms were introduced thereafter, which included a combination of check boxes and free text that was coded using ICD-10. These forms also enabled the collection of new information including gestational age estimation using ultrasound, smoking and medication use during pregnancy. Additionally, new notification forms from neonatal intensive care units were introduced, making it mandatory to record all infants transferred to such units after birth, as well as terminations of pregnancy (>12 weeks) due to congenital anomalies or diseases. Electronic notification forms were subsequently introduced during 2005/2006, and the collection of maternal height and

weight started at the same time. However, it was not fully implemented across all units until 2014[192]. Several validation studies have been undertaken to assess the accuracy and reliability of this registry[193-204].

Maternal unique national identification numbers were used to link all births to their mothers, providing sibship files with the mother as the unit of analysis[186].

2. Statistics Norway

Statistics Norway took on the role of overseeing the Cause of Death Registry from 1925 onward[32]. By utilizing the unique national identification number and linking birth records with the population registry and cause of death registry, they offer insights into the dynamics of the Norwegian society. After 2000, the National Institute of Public Health (NIPH) took over the duty of handling the data processing, eventually assuming full control of the comprehensive death registration process.

National Education Database

The National Education Database capture the highest level of education completed by the mothers and are regularly updated. Educational levels in the database are based on the Norwegian Standard Classification of Education[205].

3. Cause of Death Registry

The Cause of Death Registry is a population-based registry, where causes of mortality are coded using ICD-7 (1967-68), ICD-8 (1969-1986), ICD-9 (1986-1995), and ICD-10 (from 1996 on)[206]. Death certificates comprise information on the immediate/intermediate, underlying and contributing causes of death. Prior to 2005, NIPH processed death certificates manually[206]. After 2005, computer programs have automatically identified the underlying cause of death in Norway. The registry included around 98% of all deaths[206] and has undergone several quality checks [207-209].

4. Norwegian Mother, Father and Child Cohort Study (MoBa)

MoBa is a pregnancy cohort conducted by the NIPH, targeting all women giving birth in Norway [210 211]. Among the total 52 delivery units with more than 100 births annually at the time of inclusion, 50 participated. The main objective of this cohort was to identify

the causes and mechanisms behind diseases among children and their parents. Pregnant women were recruited throughout Norway from 1999 to 2008[211]. Invitations to participate in the study were sent along with ultrasound scanning appointments, which are usually scheduled between the 17th and 18th weeks of pregnancy. Ultrasound screening is provided free of charge, and approximately 98% of women attend[212]. Of the invited pregnancies, 41% of women consented to participate[213]. All questionnaires were in Norwegian, and participants returned the completed questionnaires by mail[211].

A total of 95,200 women and 114,500 children participated in the study, with some women participating with more than one pregnancy[213]. The data used in this study was based on self-reported responses to questionnaire, completed during 15-18 weeks of gestation. For our analysis, we utilized Version 12 of the quality-assured data files.

Study population

In *Paper I*, we enrolled women registered with their first pregnancy and who delivered offspring weighing at least 500 grams or with a gestational age of 22 weeks or more, between 1967 and 2020 (**Figure 6**). We excluded women with gestational age >46 weeks, infants with Z-scores (standardized birthweight by gestational age) <-5 or >5, and missing information on any of the six criteria used in the Robson classification tool[20]. To focus on women with lower obstetric risk, we excluded those with breech- and transverse presentation and women with preterm delivery. Ultimately, our study included 1,067,356 women with first singleton cephalic term births.

In *Paper II*, our study included women with their first two singleton births, with the first birth happening between 1967-2013 (**Figure 7**). We excluded women with missing information on gestational age and birthweight, Z scores <-5 or >5, women with a preterm delivery in their first or second pregnancy. Our final study sample included 735,244 women who had their first two singleton term births between 1967 and 2020.

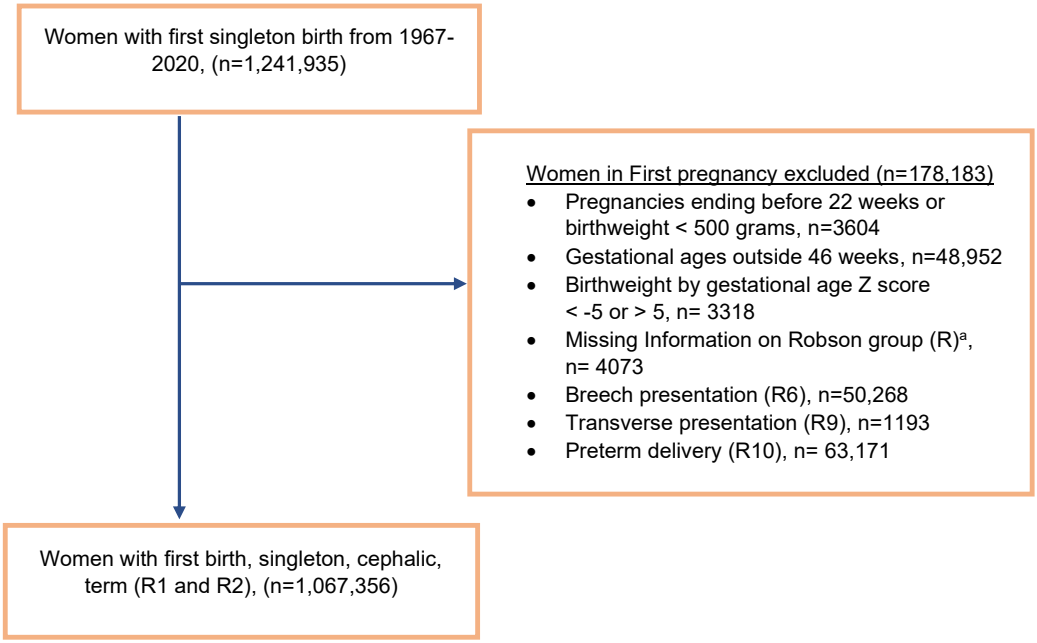

Figure 6. Flowchart of study population in *Paper I*

[a] stands for Robson group classification that stratifies women based on plurality, foetal presentation, gestational age, previous CD, parity, and onset of labour[20].

In *Paper III,* women who responded to Questionnaire 1 of the MoBa were included in this study. Among these participants, we confined to participants who planned their pregnancies, and provided information on TTP. The final dataset consisted of 80,120 planned pregnancies with complete information on TTP (see **Figure 8**).

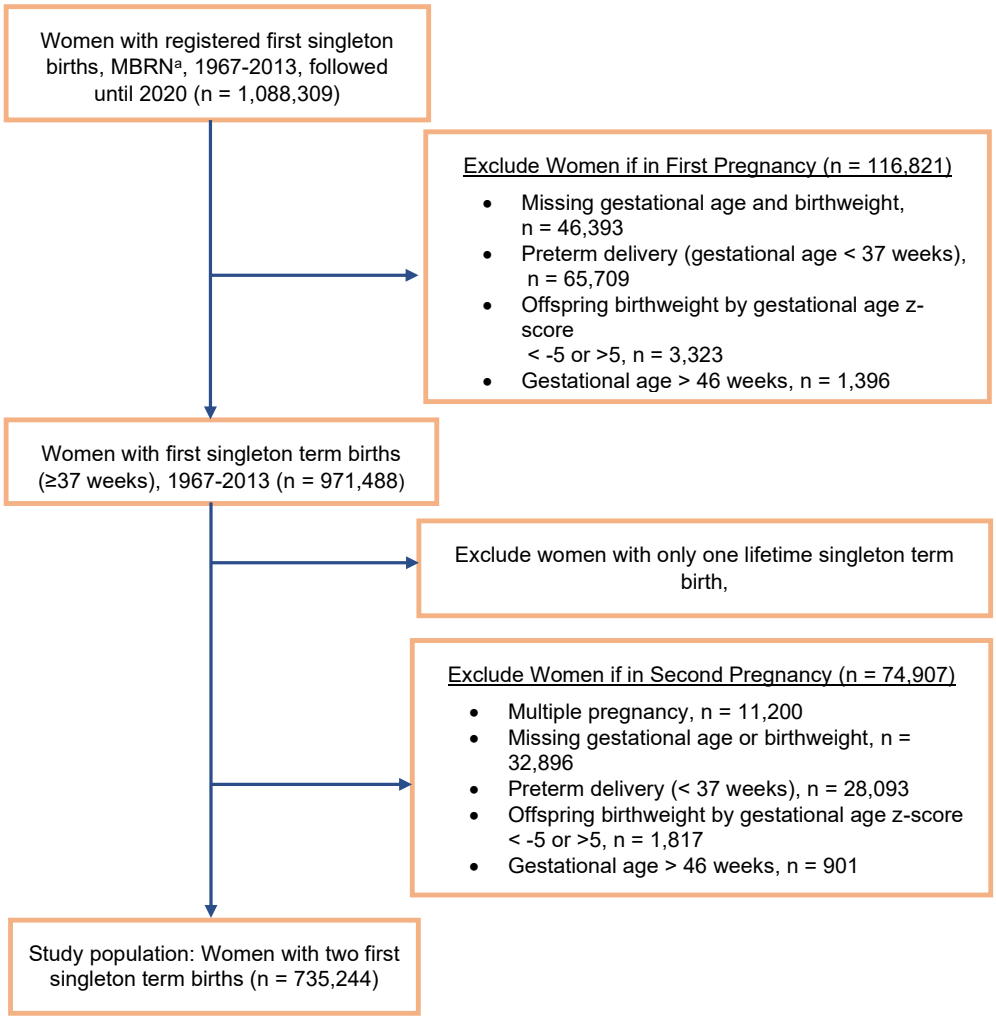

Figure 7: Flowchart of study population, *Paper II*

[a] MBRN stands for Medical Birth Registry of Norway

When examining the relationship between CD and subsequent fecundability (study population 1), we excluded women without prior births and those who had previously used assisted reproduction. Conversely, when investigating the association between

women's fecundability and the risk of CD (study population 2), we excluded pregnancies among women with a history of prior CD to eliminate the possibility of recurrence, leading to a total of 74,025 pregnancies without previous CD.

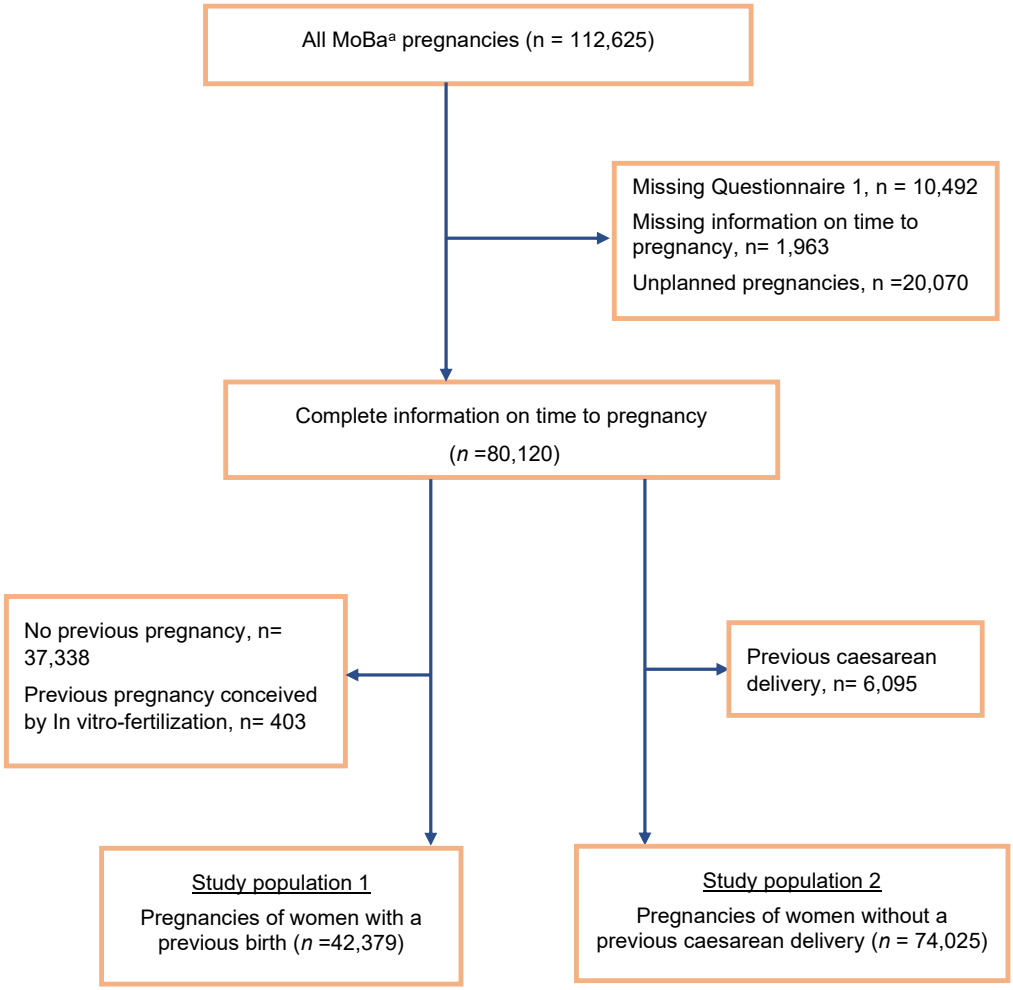

Figure 8. Study population for *Paper Ⅲ*

[a] MoBa stands for Norwegian Mother, Father and Child Cohort Study

Definition of main variables used in this thesis

Caesarean delivery

Before 1988, data on CD in MBRN was collected from text information obtained from either of the two questions: "Was the onset of delivery provoked?" and "Interventions/procedure during delivery". It was then coded as either yes or no[68].

Between 1988 and 1998, the attending clinician was required to provide information on two aspects regarding CD: if there was any indication for CD before delivery and whether the procedure took place during normal working hours (7.00 am to 5.00 pm)[55]. Using this information, the CD cases were categorized into four groups: "Planned and performed as planned", "Planned and performed as Emergency", "Not planned, performed as Emergency," and "Others".

Starting from 1999, data on CD was collected through four questions[68]. The first question asked if the onset of delivery was provoked, with three checkbox alternatives: spontaneous, induced or pre-labour CD. The second question inquired if the CD was planned, with a yes/no response. Additionally, two checkboxes were provided to specify whether the CD was "performed as planned" or "performed as an emergency". Based on these responses, the CD cases were categorized into four groups: "Planned and performed as planned", "Planned and performed as emergency", "Not planned, performed as emergency," and "Unspecified"[91].

Using this information from MBRN, a binary variable was created for CD, classifying deliveries as either "no" (vaginal delivery) or "yes" (CD).

Onset of labour

Data collection in MBRN before 1999 was based on the text response to the question "Was the onset of delivery provoked?"[193]. Checkboxes with three alternatives - "spontaneous," "induced," or "pre-labour CD" - were introduced to gather this information since 1999. The "spontaneous" group includes women whose labour began naturally, characterized by painful uterine contractions lasting up to a minute without any external intervention. Amniotic fluid leakage without contractions was not included

in this group[193]. The "induction" group comprises women whose labour was initiated through pharmacological or other surgical interventions, excluding CD. The third group, "pre-labour CD," consists of cases where the CD was performed before the onset of spontaneous labour.

Birthweight is measured at birth by the attending clinician, registered in grams, in the MBRN forms[193].

Gestational age is based on completed weeks and was calculated from the first day of the last menstrual period (LMP) in the MBRN[193]. From 1999 onwards, ultrasound dating was used for women who did not have data on LMP or whose ultrasound-based estimation and LMP differed by more than 10 days. Date of embryo transfer plus 14 days were used for women who conceived by assisted reproduction.

Time to pregnancy (MoBa)

During recruitment for MoBa, pregnant women were asked if their current pregnancy was planned, with yes/no option[213]. If yes, the woman was asked to specify the duration of her attempt to conceive in months. Response options for this question included "less than one month", "1-2 months", and "3 or more months". If the latter option was chosen, women were requested to provide the exact duration of their attempt.

Contraception use (MoBa)

Women were asked on the type of contraceptive they used before conception and the duration of their usage. The list included condom, diaphragm, spermicides, mini pill, pill, hormonal injection, intrauterine methods, safe period, withdrawal, or others.

Menstrual cycle length (MoBa)

Women were also asked: "how many days are there between the first day in your menstrual period and the first day in the next menstrual period?". Based on their response, we calculated cycle length. For those who did not report cycle length, we assume length of 28 days.

Exposures, outcomes, and covariates

Paper I

The outcome was CD among first time mothers, coded as yes/no. There was a gradual increase in overall CD from 1967-2008 (**Figure 5**), with slight decline afterwards[32].

When looking at the changes in CD, we derived an exposure variable from three variables: onset of labour, maternal age, and year of delivery. When estimating the risk of CD, those with pre-labour CD were excluded due to a 100% risk of CD in this group, leaving us with two options (spontaneous- or induced labour). Maternal age was categorized into six groups: <20, 20-24, 25-29, 30-34, 35-39, and ≥40. Similarly, year of delivery was grouped into three time periods (1967-1983, 1984-1998, and 1999-2020) to account for changes in obstetric practices and registration of the MBRN[68]. Consequently, the exposure variable consisted of 36 categories.

Other variables included in the model were maternal education (≤13 and >13 years), mother's country of birth (Western: Europe, Canada, USA, New Zealand, and Australia; non-Western: all other countries), and offspring birthweight (continuous variable). For the later years, additional covariates were included, such as smoking (categorized as no and yes (sometimes and daily smoking)) from 1999, and pre-pregnancy BMI (weight(kg)/[height(m^2)]) (continuous variable) from 2006 onwards.

Data on maternal education was missing for 18124 (1.7%) women, mostly in the last period (1999-2020), and predominantly among women born in non-western countries (13711, 3.2%). In contrast, data on maternal country of birth was mostly missing during the first period (1967-1982), affecting 72029 (21.9%) women.

In the secondary analysis, we limited the analysis to women without any of the seven pregnancy complications that have been found to be associated with increased risk of CD[74 92]: diabetes mellitus (before or during pregnancy), hypertension (before or during pregnancy), preeclampsia, post-term pregnancy (≥42 weeks), premature rupture of membrane (membrane rupture for > 24 hour and unspecified time), placental abruption and placenta previa.

Paper II

Changes in offspring birthweight by gestational age from first to second birth were the exposure. During the study period, there was a slight increase in mean offspring birthweight, both for first- and second born offspring. Further, there has been a shift in the distribution of gestational ages to lower gestation, both for first- and second born offspring: an increase in the proportion of women giving birth during the early term gestational period (37-38 weeks), while the proportion of women with post-term gestation (≥42 weeks) has decreased.

Parity specific birthweight by gestational age quartiles

Firstborn offspring are usually smaller than second born offspring[110]. To account for differences in birthweight distribution by parity, we adopted parity-specific cut-off points[214]. Using the population mean and standard deviation[110], we constructed parity-specific quartiles (25th, 50th, and 75th percentiles) of offspring birthweight (in grams) for each gestational week, for both first and second births. We made offspring quartiles (Q1, Q2, Q3, and Q4) for first and second birth, respectively. Upon confirming the linear association between offspring birthweight and maternal mortality in our dataset, we decided to merge Q2 and Q3 to decrease the number of cells and simplify the tables and overall message.

We categorized women by the onset of labour as spontaneous onset and iatrogenic onset (induced onset or pre-labour CD). When considering only information from the first birth, 605,419 (82.3%) women experienced spontaneous onset, with 5.7% undergoing CD. In cases where data from both the first and second births were included, 518,961 (70.6%) had spontaneous onset for both births, and among them, 5.8% underwent CD.

When evaluating the future risk of CVD death, we used two approaches (**Table 4**). First, we utilized data solely from women's first pregnancy. The exposure was birthweight quartiles from the first birth: Q1, Q2/Q3 (reference group), and Q4. In stratified analysis, we classified women into spontaneous- and iatrogenic groups based on onset of labour during their first birth. For the second approach, our exposure was based on patterns in offspring birthweight quartiles from first and second birth: Q1-Q1, Q1-Q2/3, Q1-Q4,

Q2/3-Q1, Q2/3-Q2/3 (reference), Q2/3-Q4, Q4-Q1, Q4-Q2/3, and Q4-Q4. In stratified analysis, the spontaneous group comprised of women who had spontaneous onset of labour in both first and second births, while the iatrogenic group included women who had induced labour or pre-labour CD in either first, second, or both births.

Maternal CVD mortality was the outcome. For the main analysis, we included deaths from ischemic heart disease (ICD-10: I20-I25; ICD 8 and 9: 410-414) and cerebrovascular diseases/stroke (160-I69 (ICD-10), 430-438 (ICD-8 and ICD-9)). We also evaluated mortality from all causes, circulatory system (I00-I99 in ICD-10, 390-459 in ICD-8 and ICD-9) and non-circulatory causes (all deaths other than those included in the circulatory system diseases definition).

Table 4. Exposure variable for *Paper II*

Approach 1		
Quartiles of birthweight by gestational age	Stratified by labour onset during first delivery	
Women's first birth only	Spontaneous onset	Iatrogenic Onset [a]
Q1	Q1	Q1
Q2/3 (reference)	Q2/3 (reference)	Q2/3
Q4	Q4	Q4
Approach 2		
Quartiles of birthweight by gestational age	Stratified by labour onset during first and second delivery	
Women's first and second birth	Spontaneous onset in both pregnancies	Iatrogenic onset [a] in any of two pregnancies
Q1-Q1	Q1-Q1	Q1-Q1
Q1-Q2/3	Q1-Q2/3	Q1-Q2/3
Q1-Q4	Q1-Q4	Q1-Q4
Q2/3-Q1	Q2/3-Q1	Q2/3-Q1
Q2/3-Q2/3 (reference)	Q2/3-Q2/3 (reference)	Q2/3-Q2/3
Q2/3-Q4	Q2/3-Q4	Q2/3-Q4
Q4-Q1	Q4-Q1	Q4-Q1
Q4-Q2/3	Q4-Q2/3	Q4-Q2/3
Q4-Q4	Q4-Q4	Q4-Q4

[a] Labour is either induced or pre-labour caesarean delivery is carried out. Q stands for quartiles.

A total of 32,129 women died during follow up, and among them, 3037 deaths were attributed to CVD causes. In our study, around three-quarters of the women who died from CVD had their first birth during 1967 to 1977(**Figure 9**).

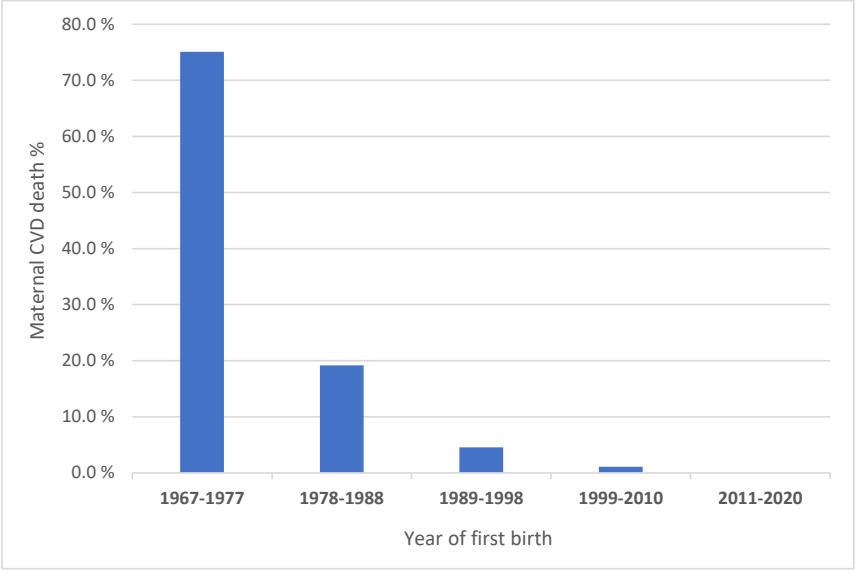

Figure 9. Long-term maternal cardiovascular disease (CVD) mortality by women's year of first birth, Norway, 1967-2020

Variables included in both analyses were maternal age (continuous), education (<11 and ≥11 years), year of last delivery (continuous), pregnancy complications (chronic-/gestational hypertension, preeclampsia, pregestational-/gestational diabetes mellitus, placental abruption, perinatal loss, offspring congenital anomalies, and infertility (conceived by in vitro fertilization) and mother's country of birth (Nordic: Norway, Denmark, Finland, Iceland, and Sweden, and Non-Nordic: all other countries).

Paper III

In study population 1, previous CD (yes/no) was the exposure variable and fecundability and the risk of infertility in the MoBa pregnancy were the outcomes of interest. Fecundability was measured indirectly, by correcting the reported TTP for the women's average menstrual cycle length. Infertility was defined as having TTP ≥12 cycles.

Figure 10 shows the distribution of monthly conception rates by cycle among women with compete information on TTP. Fecundability peaks in the initial cycle and gradually diminishes, as more fertile women leaves the group[153].

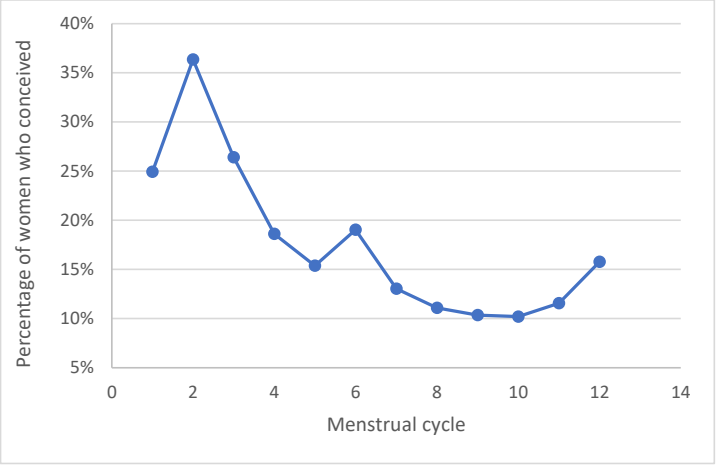

Figure 10. Monthly conception rates among women with complete information on time to pregnancy in our study population

In the main analysis, we excluded women with unplanned pregnancies due to the uncertainty of their TTP[159]. A pregnancy was considered planned if women responded "yes" to the question regarding whether the pregnancy was planned and provided information on the duration it took to achieve pregnancy while not using contraceptives. In the sensitivity analysis, we included all women with complete TTP data. We also stratified by type of CD: elective, emergency, and unspecified. To differentiate the unspecified CD, we used data on the onset of labour[91]. If the onset of labour occurred via CD, it was categorized as planned; however, if the onset was either spontaneous or induced, it was classified as emergency CD.

While we had complete information on previous CD, there was missing data on covariates: education (n=163), smoking (n=752), BMI (n=954), and preterm pregnancy complications (n=858).

In study population 2, fecundability was the exposure while CD in the MoBa pregnancy was the outcome. In this analysis, we categorized fecundability as: < 3, 3-6, 7-11, and ≥12 cycles. The numbers of missing data among covariates were education (n=291), smoking (n=1228), BMI (n=1435), and preterm delivery (n=644).

Variables included in both analyses were maternal age, education, smoking, pre-pregnancy BMI, chronic conditions (yes/no), pregnancy complications (yes/no), and parity (nulliparous (only in study population 2), one, ≥two or more births). A woman with chronic conditions was defined by having any of the following health conditions[91] [92]: asthma, arthritis, diabetes mellitus, chronic hypertension, hyper- and hypothyroidism, endometriosis, ovarian cysts, or myoma. A woman with pregnancy complications was defined as experiencing one or more of the following complications[92]: gestational hypertension, preeclampsia, preterm birth, placental abruption, or placenta previa.

Statistical analysis

STATA IC statistical software version 16 was used for *Paper I*, while version 17 was used for *Paper II* and *Paper III*. For statistical tests, the significance level was set at 5%.

Paper I

Frequency tables were used to describe CD by maternal characteristics and onset of labour across three time periods. We tested linear CD trends within each maternal age category, using year of delivery as a continues variable.

For dichotomous and common outcomes[215], we estimated relative risk (RR) with 95% confidence interval (CI) using generalized linear model with log-link and binominal distribution. Both crude and adjusted models were presented. The estimates were adjusted for maternal education, maternal country of birth and offspring birthweight. We adjusted for smoking in the model (from 1999) and pre-pregnancy BMI (from 2006) in a subset of our analysis. Additionally, we explored the influence of education on the

association between maternal age and CD by introducing an interaction term in the multiplicative models using binomial regression analysis (Likelihood-ratio test).

Paper II

Continuous variables were summarized using mean with standard deviation while categorical variables were summarized using proportions.

In the main analysis, Cox proportional hazard models were used to estimate maternal mortality from CVD causes, among women who were currently alive. Follow up started from women's last birth and continued till the death or censoring, whichever comes first, with maternal age being the underlying time variable. We right censored observations at 70 years. Assumption of proportional hazard was checked using Schoenfeld residuals[216]. In secondary analysis, we estimated mortality from non-CVD causes.

In addition to the Cause specific hazard model, we fitted a sub-distribution hazard model to account for competing risk[217]. This model estimated the hazard function among those who were currently alive or had a competing event (for example, women who died from non-cardiovascular causes).

In sensitivity analyses, we focused on women without known CVD risk factors, specifically those without pregnancy complications[1 2], offspring with congenital anomalies[218], and infertility problems[122 219]. To address the variation in offspring birthweight[127], we limited our analysis to Nordic women, women having offspring from the same father[220] and among full-term gestations (39-41weeks)[136]. We assessed the association between change in offspring birthweight by gestational age and CVD mortality among women with more than two births[138] (among women with first their three term deliveries).

E-values

As we did not have available data on maternal health after delivery and data on smoking and BMI during pregnancy were only available for the more recent years, we estimated

to which extent the observed association could be explained by unmeasured confounders by conducting an E-value-based sensitivity analysis. E-value measures the minimum strength unmeasured confounding needs to have to fully explain away the association between offspring birthweight quartiles and maternal CVD mortality [221]. For HR >1 we used the formula (HR + √[HR × (HR − 1)]), while we took the inverse HR if HR < 1.

Paper III

To explore a potential casual association between CD and fecundability, we utilized Directed Acyclic Graphs (DAGs) version 3.0 (http://www.dagitty.net), a tool that is used to plot prior expertise knowledge and assumption about a causal structure of interest[222]. We assumed that if there was a causal relationship between CD and reduced fecundability (**Figure S1**), the reverse association, lower fecundability leading to CD (**Figure S2**), would not hold true.

We estimated fecundability ratio (FR) with 95% CI by mode of delivery in the prior birth. This was accomplished using proportional probability regression with cycles as the unit of analysis. A FR <1 indicated reduced probability of conceiving in each cycle, while a FR > 1 indicated increased probability of conceiving in each cycle. Additionally, we estimated the RR of infertility using log-binomial regression. To account for cases where women participated with more than one pregnancy, robust clustered variance was used in both analyses.

In our assessment of the risk of CD based on the number of cycles it took for women to conceive, we employed a generalized linear model with a log-link and binomial distribution. To estimate the RR, we used a modified Poisson regression approach along with a robust error variance procedure, due to difficulty with convergence when using log-binominal model.

We provided both crude and adjusted estimates for each model and estimates were adjusted for maternal age, education, BMI, and smoking. Sensitivity analyses explored various aspects of the data: by including unplanned pregnancies, excluding women who

reported trying to conceive for 3 or more months without specifying the exact duration, and excluding women aged ≥35 years. Additionally, we conducted a stratified analysis based on parity and lower-risk group (women without any of the five complications: gestational hypertension, preeclampsia, placental abruption, placenta previa, and preterm births).

In the first analysis, where previous CD was considered as the exposure variable, we examined whether the FR and RR of infertility differed based on the type of mode of delivery (vaginal delivery, planned CD, and emergency CD). We also investigated if these rates varied depending on when the CD occurred (in the prior or earlier deliveries), the number of CD (only one- or multiple CDs) and restricted the interval between the previous delivery and the index pregnancy to intervals of < 3 and 3-7 years.

We applied multiple imputation by chained equations to handle missing information on maternal education, smoking, BMI and gestational age were applied. This method assumes that missing is at random[223].

Ethical considerations

All three studies were conducted in accordance with the Declaration of Helsinki[224] and the Vancouver Recommendations[225]. We have received approval from the Regional Committee for Medical and Health Research Ethics (*Paper I and II* REK VEST 2019/13818 and *Paper III* approval no 2014/404). Our research is part of a larger research project and to identify and minimise the data protection risks of the specific research project, Data Protection Impact Assessment was conducted at the University of Bergen. The data used in these studies are securely stored on research servers at the University of Bergen (SAFE) and the University of Oslo (TSD). Access to this data is protected by password authentication. The data was de-identified, and the researchers did not have any contact with the participants.

Paper I and *II* relied on data from MBRN, where informed consent was not required for data usage. Collecting, registering and the use of MBRN data are regulated by Norwegian law[191]. *Paper III* is based on data from MoBa, and informed consent was obtained from all participants[211 213]. During the recruitment process, participants were provided with an information brochure detailing the purpose of the study and its potential linkages with health registries[213]. Participants had the right to withdraw from the study at any time[213].

Our findings have the potential to cause concerns among women. However, we consider the benefits to be more important for the women. In *Paper II*, early recognition of women at increased risk of future CVD may be valuable for both individual well-being and societal benefits, as it can aid in averting premature CVD deaths[1 2]. In *Paper III*, potential bidirectional association between CD and reduced fecundability is of importance as it can shed light on the causes of CD[165]. This exploration may unveil underlying determinants and alleviate any undue burden placed on women and healthcare providers.

Table 5. Summary of the three papers

	Paper I	Paper II	Paper III
Aims	To describe trends in CD among nulliparous women.	To investigate the relationship between changes in offspring birthweight quartiles from first to second pregnancy, and maternal CVD mortality. To differentiate among spontaneous and iatrogenic term deliveries.	To assess the relationship between a previous CD and subsequent fecundability. To evaluate the association between fecundability and CD.
Design	Population-based cohort study.	Population-based cohort study.	Population-based cohort study.
Data Sources	MBRN and SSB	MBRN, Cause of Death Registry and SSB	MoBa and MBRN
Population	Nulliparous women with singleton cephalic term birth.	Women with their first two singleton term births.	Study population 1: Women with prior births Study population 2: Women without prior CDs.
Study period	1967-2020	1967-2020	1999-2008
Exposure	A composite variable constructed by combining maternal age, onset of labour and time period	Parity specific standardized quartiles (25^{th}, 50^{th} and 75^{th} percentiles) of offspring birthweight by gestational week from for women's first and second birth. Onset of labour: spontaneous and iatrogenic (induced or pre-labour CD)	Analysis 1: Previous CD Analysis 2: Fecundability
Outcome	CD during first birth	Maternal CVD mortality. Mortality from all causes and non-CVD causes.	Analysis 1: Fecundability and risk of infertility. Analysis 2: Risk of CD.
Statistical methods	Cross tables Log binominal regression models	Cross tables Cox regression	Cross tables Log binominal regression models Multinominal regression
Measure of associations	RR with 95% CI	HR with 95% CI	Analysis 1: FR with 95% CI, and RR of infertility with 95% CI Analysis 2: RR of CD with 95% CI

CD: caesarean delivery, CI: confidence interval, CVD: cardiovascular disease, FR: fecundability ratio, MBRN: Medical Birth Registry of Norway, MoBa: Norwegian mother, father and child cohort, RR: relative risk, SSB: Statistics Norway

Results

Paper I

Title of paper: Caesarean delivery in Norwegian nulliparous women with singleton, cephalic term births, 1967-2020

This study included 1,067,356 nulliparous women with singleton cephalic term births. Compared to the earlier period (1967-1982), nulliparous women in the last period (1999-2020) were older, more educated, with a lower proportion experiencing spontaneous onset of labour and a higher proportion undergoing induction or pre-labour CD.

Overall CD rate decreased in women ≥ 35 years. From first to last period, there was a decline in the CD rate among women with spontaneous onset of labour, from 35.0 to 17.5 among those aged ≥ 40 years and from 18.3 to 13.3 for women aged 35-39 years. Among women with induced onset of labour, CD rate was stable among women aged 35-39 years, yet decreased from 45.8 to 35.7 in women ≥40 years. The contribution of pre-labour CD to overall CD rate showed an inverted U-shaped trend among women aged ≥35 years.

From first to last period, there was a rise in CD rates in women<35 years in both spontaneous- and induced labour onset groups. Furthermore, we found an increase in the proportion of women < 35 years undergoing pre-labour CD.

Compared to women aged 20-24 years with spontaneous onset of labour in the earlier period, the RR of CD in women aged ≥40 years decreased in both the spontaneous- (from 14.2 [95% CI 12.4-16.3] to 6.7 [95% CI 6.2-7.4]) and the induced group (from 17.6 [95% CI 14.4-21.4] to 13.4 [12.5-14.3]) during the last period. The RR of CD remained stable in women aged 35-39 years.

Paper II

Title of paper: Birthweight in consecutive pregnancies and maternal cardiovascular disease mortality among spontaneous and iatrogenic term births: a population-based cohort study

We included a total of 735,244 women with their first two singleton term births, from 1967-2020. Women with spontaneous labour onset during first birth were younger and had lower mean offspring birthweight. Women with iatrogenic onset of labour during first birth had more pregnancy complication and more pregnancies conceived by invitro fertilization.

When using data solely from the first birth, we found that women with offspring in Q1 had a higher risk of CVD mortality (HR 1.41 [95%CI 1.30-1.52]), compared to women with first offspring in Q2/3. Mortality was lower among women with an offspring in Q4 (HR 0.84 [95%CI 0.77-0.94]). When stratifying by onset of labour, the risk was higher among those with iatrogenic- than spontaneous onset of labour, although CIs were overlapping.

When including information from both first and second births, women with both offspring in Q2/Q3 were the reference. Among women with a first infant in Q1, the highest CVD mortality was observed among women with their second infant in Q1 (HR 1.66 [95%CI 1.49-1.85]), while the risk was lower if the second infant was in Q4 (HR 0.99 [95% CI 0.75-1.31]). Among women with a first offspring in Q2/Q3, mortality was highest in those who had their second offspring in Q1(HR 1.33 [95%CI 1.18-1.50]), while risk was lowest in those with offspring in Q4 (HR 0.78 [95%CI 0.67-0.91]). Similarly, among women whose first infant was in Q4, CVD mortality was highest if second infant was in Q1 (HR 1.26 [95% CI 0.99-1.60]), and lowest if second infant was in Q4 (HR 0.80 [95% CI 0.69-0.93]). When stratifying by onset of labour, women with iatrogenic onset in either first and/or second delivery had higher risk of dying from CVD causes, when first offspring was in Q1. The distinction was less apparent when first offspring was in Q2/3 and in Q4.

Paper III

Title of paper: The relationship between caesarean delivery and fecundability: a population-based cohort study

We included 42,379 pregnancies from women with prior singleton births. Women with a previous CD were older, had lower education, higher proportions of chronic conditions and pregnancy complications than women with a previous vaginal delivery. Compared to women with previous vaginal delivery, women with prior CD had lower fecundability ratio (FR 0.90 [95% CI, 0.88 to 0.93]) and higher risk of infertility (RR 1.21 [95% CI 1.10-1.33]).

A total of 74,025 pregnancies from women without a history of CD were included when investigating the reverse association, where fecundability was the exposure and CD the outcome. Among these pregnancies, 10% (8038/74025) of women experienced a TTP ≥ 12 months. This group had higher proportions of women with low education, chronic conditions and pregnancy complications, smokers and women with overweight or obesity. Nearly two thirds of the women in this group were nulliparous. Compared to the women who conceived within the first two cycles, women that took ≥12 cycles had higher risk of CD (RR 1.55 [95% CI 1.46 to 1.64]).

In both analysis, associations remained unchanged after controlling for sociodemographic, lifestyle and clinical risk factors, and were also observed across parity groups.

Discussion

Methodological considerations

Study design

The three separate studies in this thesis are based on a historical cohort study design, using national population-based data[190]. The MBRN, which is based on obligatory notification of all births in Norway, covers almost all births in the country[68]. Its linkage with the Cause of Death registry and the National Population Registry ensures a complete registration of data with minimal unmatched residuals. Routine checks of the MBRN are carried out to solve any unmatched cases[188]. Also, the prospective cohort design allows for examination of temporality between cause and outcome[226].

In *Paper I*, our emphasis on first-time births, which are associated with a higher risk of adverse perinatal outcomes[186], allowed us to capture the majority of new CD cases, rather than recurrent cases. Moreover, adopting this approach helps mitigate potential bias that might have emerged if we had examined CD in subsequent pregnancies, as such analysis would be influenced by the women's decision to have a second birth, namely selective fertility[186].

In *Paper II* and *Paper III*, longitudinal cohort design was employed where maternal national identification number was used to link births of the same mother, arranging them in their right order, providing sib-ship files[186]. This approach allowed us to track women from their initial birth to subsequent births (*Paper III*) and even until death (*Paper II*). The mother served as the unit of analysis in *Paper II.* In *Paper III*, the pregnancy was the unit of analysis, however we were allowed to link mother's previous births to the index pregnancy in MoBa. To mitigate potential right truncation bias, we ensured that women had ample time to experience their second birth, providing at least seven years[137]. Moreover, our analytical approach in both papers involved including women with two or more births when studying women's first two births, without restricting it to only two births. By not restricting our analyses to only women with two births we avoided bias related to fixed-sibship design[227 228].

In *Paper III*, the index pregnancy in MoBa could be the women's first, second, or higher birth order pregnancy. As the unit of analysis was pregnancy, women could contribute with more than one pregnancy. To account for dependencies between pregnancies from the same woman, we utilized clustered robust standard errors [229].

Random errors

Random errors measure the variability between the observed and the true values[226]. All papers were based on large historic cohorts and included large study populations[190]. Hence, random errors are considered minimal. Our estimates were precise for most of the analyses, which are shown both in the size of the association and accompanied by narrow CIs. However, specific sub-analyses (such as in *Paper II*) had fewer cases of women who died from CVD. Increasing sample size could further improve the precision. However, as our three papers have utilized population-based data we were not able to increase sample size in our studies.

In *Paper I*, we calculated the RR of CD among nulliparous women. We chose to use RR instead of OR because CD is considered a common outcome. OR tends to overestimate associations when the outcome is common (> 10%), while RR and OR are similar when the outcome is rare[215 230].

In *Paper II, a*lthough merging of offspring birthweight by gestational age quartiles (Q2/Q3) improved the statistical power and data robustness, we may have obscured a potential heterogeneity in CVD mortality within the two groups. In the main analysis, all estimates were precise with narrow CI. In the sub-analysis where we stratified by the onset of labour, we had smaller sample size for some of the groups (Q1-Q4 and Q4-Q1), leading to a wider CI.

In *Paper III*, our analysis revealed a robustness in both the strength of the association and narrow CI when examining previous CD and fecundability, as well as fecundability and subsequent CD. Several sensitivity analyses were conducted, but results were consistent across analyses.

Internal validity

Internal validity measures the ability for which a study to accurately capture the true exposure-outcome association, and whether it is free from systemic errors[226]. Such errors can arise from shortcomings in the study's design or implementation. Common sources of systemic bias that can compromise validity include selection bias, information bias, and confounding.

Selection bias

In Norway, almost all births occur in hospitals, and the MBRN is based on mandatory notification of all births[68]. Pregnancy care is offered free of charge and available for all in the public health system. Therefore, selection bias is not a concern in *Paper I* and *II*. In *Paper III*, we used data from the MoBa study, which had a response rate of 41%[213]. Participants in MoBa are found to be older, more educated and smoked less compared to the general pregnant population in Norway[231]. Additionally, since the study questionnaires were conducted exclusively in Norwegian, the sample predominantly represents Norwegian-speaking women[211]. Hence, selection bias is a potential concern for *Paper III*. However, studying a more homogenous population like the MoBa cohort can be valuable when investigating causal associations between exposures and outcomes[232 233]. By restricting for confounding variables that are linked to both CD and fecundability, this approach may enhance our comprehension of the causal relationship between CD and subsequent fecundability[233]. Moreover, a validation study found no difference in the estimates of the exposure-outcome association within the MoBa study when compared to the MBRN[234].

To focus on the majority of lower risk women giving birth, we restricted our analysis to women with singleton cephalic term births, in *Paper I*. This group accounted for 90% of nulliparous women and approximately 40% of all women registered in MBRN[188]. Most exclusions were due to either missing or implausible gestational age information. The excluded women tended to be younger (< 25 years) and had a higher proportion with low education (<13 years) and exclusions could potentially have biased our estimates towards the null as the risk of CD was higher in this group.

In our study, we excluded women with breech presentation, transverse presentation, and preterm births, which constituted the remaining 10% of nulliparous women. As expected, CD rates were higher in this groups. For instance, among women with breech presentation, the CD rate increased from 10% in 1967-1982 to 60% in 1999-2020. A trend of increasing CD rates was also evident for transverse- and preterm births.

In *Paper II*, by including women with first two term births in the analysis, we excluded women with missing data on offspring birthweight or gestational age. Gestational age accounted for most of the missing cases. Exclusion of women with missing gestational age could possibly introduce bias. Nevertheless, we found similar CVD mortality patterns among women in our study and women with missing gestational age when using birthweight quartiles based on absolute birthweights. In our study, we also excluded women with preterm births. This exclusion may potentially bias our estimate towards the null, as women with preterm births are at increased risk of CVD death[136 137].

In *Paper III*, when examining the effect of CD on subsequent fecundability, we excluded women who had subsequent pregnancy loss before 15-18 weeks. This could bias our estimates toward the null since we are excluding those with more infertility problems[123 137 235].

Our main analysis focused on women with planned pregnancies to address potential unreliability in TTP information among women with unplanned pregnancies, which could introduce selection bias[160 161]. Women with unplanned pregnancies, especially those conceiving while on contraceptives, might have higher fecundability[160]. Furthermore, women who plan their pregnancies may have different characteristics compared to the general population of women[159 161]. Nevertheless, this bias is expected to be smaller in the Nordic countries, where a significant majority of pregnancies are planned[28 178], and where access to contraceptives[34] and legal abortion[36] is good. Importantly, when we included women with unplanned pregnancies, those not using contraceptives, and those who became pregnant while on contraceptives, our results remained unchanged.

Information Bias (misclassification)

Misclassification occurs when there is error in measuring the exposure, outcome, or both[226]. Nondifferential misclassification happens when the errors are not associated with the presence of exposure or outcome, whereas differential misclassification is linked to exposure or outcome.

Data from the MBRN is recorded by general practitioners, midwifes or attending obstetricians, and the possibility of registration errors cannot be ruled out[68]. However, data on the exposures were collected at the same time as the outcome (*Paper I*) and before the outcomes (*Paper II* and *Paper III*), indicating that misclassification are likely to be nondifferential. On the other hand, data from MoBa is based on self-report by the mother, making it prone to recall bias[213].

Misclassification of exposures

Onset of labour

The registration of the onset of labour has the potential to be subjective due to a vague nature of the question[193], along with the reliance on text-based data before 1999[68], and could have led to potential misclassification[193]. The positive predictive value of onset of labour was 28% between 1967 and 1985, and most registered as induced labours were true spontaneous onsets. But predictive value increased to over 80% during 1986-2012, especially among preterm- compared to term births[193].

In *Paper I*, misclassification of onset of labour could lead to an underestimation of the association between iatrogenic onset delivery and CD for the first period. In *Paper II*, since most of the women who died during the study period had their births in the first ten years (**Figure 9**), we would expect this misclassification to underestimate the risk of CVD mortality in women with iatrogenic deliveries, and potentially bias results towards the null. This misclassification is not a concern for *Paper III*, as the included births (about 90%) are mostly after 1999, where data in MBRN was collected based on checkboxes[68].

Birthweight and gestational age

Validity of both birthweight and gestational age in the MBRN is high[193]. Information on birthweight has been almost complete throughout the MBRN period and has also been registered with little error[193].

Gestational age estimation was based on the LMP, which may be prone to misclassification[110]. A more accurate and preferred method is ultrasound dating[67]. However, even ultrasound dating has limitations, as it assumes uniform growth rates for all foetuses, irrespective of sex, and may not account for physiological variations and growth restrictions. These limitations are more pronounced when using ultrasound estimation in the second trimester like in Norway, where differences in foetal growth are more prominent[67].

Missing data on birthweight and gestational age could be a challenge, especially for infants in earlier gestations or those with very small size, particularly in early years of the MBRN[193]. However, both *Paper I* and *II* focused solely on women with term gestations, thereby reducing the potential influence of misclassification on our findings.

Both in *Paper I* and *II*, we excluded infants with implausible birthweight and gestational age combinations, such as those weighing <-5 or >5 standard deviations from the mean birthweight for each gestational week. This will minimize exposure misclassification[110].

In *Paper II*, rather than using absolute birthweight, we used birthweight adjusted for gestational age. This approach not only distinguishes infants who are small due to a shorter gestational length from those who have impaired growth[127], but it also provides more information on maternal constitutional factors [148].

We used birthweight by gestational age charts to group offspring by quartiles, which might have introduced bias due to missing data on the weights of foetuses still in utero [236]. In *Paper II*, we used this chart specifically for women with term birth, which could help to minimize this bias.

In *Paper III*, there were only a few cases with missing gestational age, and it was registered before the exposures. Therefore, if there is any misclassification, it will likely be non-differential.

Maternal health before and during pregnancy

Before 1999, information on maternal health before and during pregnancy was primarily collected as written text, rather than checkboxes[68], which could make it prone to underreporting[237]. Klungsøyr et al. (2012) found underreporting of mild cases of preeclampsia for the years before 1999[237]. Similarly, routine screening for gestational diabetes mellitus was not conducted before mid-1980's[238]. Consequently, such underreporting could potentially categorize women as not having complications when, in fact, they did.

In *Paper I*, the true change in CD rates reported for the lower-risk group before 1999 might be higher than what has been reported. Additionally, the registration of mother's health before- and during pregnancy may have been more thorough among women≥ 35 years compared to younger women, especially in the earlier years of the registry when being older nulliparous women was not that common[107].

In *Paper II*, women without registered CVD risk factors such as pregnancy complications, in case of underreporting could potentially have pregnancy complications. Nevertheless, we do not expect underreporting to be influenced by women's offspring birthweight patterns, hence it will likely be a non-differential misclassification.

In *Paper III*, most identified chronic conditions (except diabetes mellitus and chronic hypertension) were reported by the mothers themselves, which could introduce recall bias. However, we anticipate that reporting of chronic conditions is unlikely to be influenced by the women's previous mode of delivery, resulting in non-differential misclassification. Misclassification of pregnancy complications is not a concern for *Paper III*, since we used data mostly after 1999, based on check boxes.

Misclassification of outcomes

Caesarean delivery

Misclassification of CD is unlikely due to the nature of the reporting. However, there was a reported error rate of 3% between hospital records and MBRN forms before 1984[239]. This error rate has decreased in later years [91].

CVD mortality

Mortality data was collected from the Cause of Death Registry, known for its high coverage and completeness[206]. However, there were frequent use of non-specific codes when filling in the underlying cause of death, which is crucial for understanding disease aetiology[206 240]. As a result, there may have been misclassification when grouping mortality as CVD and Non-CVD cases. Nevertheless, we do not expect this error to be linked to the exposure, indicating a possible non-differential misclassification. We also analysed the association between offspring birthweight by gestational age and maternal mortality from non-CVD causes and total causes of mortality, revealing a similar pattern but with weaker associations.

Lost to follow-up

Differential bias may occur in *Paper II* if the loss to follow-up differs based on the offspring birthweight pattern. Nevertheless, data on CVD death is collected for Norwegian residents even if they died outside of Norway, which helps to minimize the lost to follow-up[206]. Moreover, the emigration rate in Norway is generally low[32], suggesting that any potential bias from loss to follow-up is likely to be minimal.

Competing risk

Recently, cancer-related mortality has risen, becoming the leading cause of death among women in Norway[188]. This increase in cancer-related deaths may affect the occurrence of deaths due to CVD in women, by excluding the women from being at risk for CVD death [217]. To address this competing risk, we utilized a sub-distribution hazard model in addition to the cause-specific model. This sub-distribution hazard model considers the

influence of competing risks from cancer and other causes of death[217]. Despite this consideration, our findings remained unchanged.

Time to pregnancy

Data on TTP was collected through self-report, which introduces the possibility of recall bias[159]. Women who waited longer to get pregnant might remember the duration of trying to conceive differently than women who conceived quickly[161]. To address this potential bias, we focused on including women with more reliable TTP information, specifically those with planned pregnancies and were not on contraceptives[160 161].

Our data lacked information on the last day of contraceptive use. This information is of relevance since certain contraceptive methods might require time to establish a regular menstrual cycle after discontinuation, and ceasing contraception might not always imply active attempts at conception[160]. To address this, we performed a stratified analysis considering cycle regularity, but our findings remained consistent. Moreover, different couples may respond differently to questions about the duration of trying to conceive after discontinuing contraceptives[160 161]. However, even after excluding couples who reported pregnancy occurring in the first cycle, our results remained slightly unchanged.

Previous studies have shown that reporting of early losses or miscarriages could possible vary[153]. However, given that most losses go unnoticed [157], this potential bias is expected to be low. Some women (n=1782, 2.2% of the sample) reported pregnancies during their TTP period. We corrected this by subtracting the duration of the pregnancy (in weeks) from the reported TTP[241]. In cases where no pregnancy length was provided, we used a standard subtraction of 8 weeks. Additionally, we subtracted an extra month to allow time between the miscarriage and the new start of trying. Moreover, due to the uncertainty surrounding TTP in this sub-group, we conducted a sensitivity analysis excluding these women and our results remain unchanged.

There may also be bias due to differences in seeking medical care among couples trying to conceive for a long time[161]. However, restricting the analysis to women who conceived within 12 months, did not change our result.

Potential Confounders

Rothman defines confounder as a variable that affects the results by being associated with both the exposure and outcome[226]. The observational nature of our studies makes the discussion on confounding relevant. While the registries included data on numerous variables, there were important covariates for which we lacked data. As a result, we were not able control for all potential confounders.

We identified maternal education, year of delivery and pregnancy complications as confounders in all three papers. Maternal education was used as a proxy for women's socioeconomic status[55] and year of delivery was considered to account for changes in obstetric practices as well as changes in diagnostic measures. We were not able to adjust for potential confounders like smoking and BMI as data was only available after 1999 and 2006, respectively[68].

The definition of preeclampsia in the MBRN have changed over time in accordance with the clinical criteria applied by the Norwegian Society of Gynaecology and Obstetrics, and the registration has been found to have high quality[203]. A validation study of disease registration in the MBRN also found the sensitivity of Type 1 Diabetes mellitus to be 90%[195].

A key limitation of the three studies lies in the absence of data on CD indications. To distinguish between medically warranted and other cases, we formulated a potential indication list based on the recent Norwegian clinical guideline[74]. However, indications like labour dystocia and foetal distress[43 92], common for emergency CD, were not available in our data. These factors, along with other unmeasured indications, could bias the relationships investigated across all three papers.

In *Paper I*, our estimates were not adjusted for BMI for the years before 2006. Existing literature indicates that maternal weight gain tends to increase with age[50], particularly among women ≥ 35 years, where overweight and obesity are more prevalent[51]. Furthermore, several studies consistently show that overweight and obese women have a greater risk of experiencing prolonged labour and requiring CD[242 243]. As a result, the true change in the risk of CD among older women in our study might be higher than what we have reported.

In *Paper II,* several sub-analyses were caried out to rule out potential factors affecting both offspring birthweight and maternal future CVD risk. However, our results did not change, and offspring birthweight continued to serve as possible marker for maternal CVD mortality[148].

The E-value, pertaining to women who had consecutive births in Q1 and Q4, indicated that unmeasured confounding factors would need to be linked 2.7 times more strongly with both offspring birthweight and CVD mortality. This does not seem unlikely considering we lacked data on other CVD risk factors such as smoking, diet, physical activity, stress, and the mother's health after pregnancy (hypertension, obesity, hyperlipemia). However, in a Swedish study that examined offspring birthweight and maternal CVD, adjusting for BMI and smoking yielded no change on the outcome[132].

In *Paper III,* in examining the bidirectional association between CD and fecundability, we employed DAGs as a tool to identify potential confounders for each association. Despite conducting numerous sensitivity analyses to assess these associations, the possibility of residual confounding cannot be ruled out. Data on the use of other medical treatments for infertility, postoperative complications, or abnormalities of the uterine scar like niche formation were lacking in our study[16]. Therefore, it is important to interpret our conclusions with caution, recognizing the potential limitations of the available data.

Mediation

In *Paper I*, we used the difference method to explore the mediation effect of labour onset between maternal age and CD[244]. Initially, we analysed maternal age and CD along with covariates, excluding labour onset from the model. Then, we repeated the analysis, adding labour onset as a variable. The results indicated that adjusting for labour onset decreased the effect of maternal age on CD but did not eliminate it completely. This suggests that labour onset partially explains the association between maternal age and CD. However, due to assumptions not being met, such as controlling for confounders between labour onset and CD, and the influence of many of these confounders by maternal age, we opted not to conduct a mediation analysis.

In *Paper III*, we investigated the association between fecundability and CD, with pregnancy complications serving as potential mediators. Using the difference method approach[244], we found that pregnancy complications accounted for some of the effect of reduced fecundability on CD, but not all of it. However, the criteria for a mediation analysis were not met due to the presence of unmeasured confounding.

Interaction

In *Paper I*, our findings revealed a statistically significant interaction between maternal age and education on the risk of CD. This implies that the influence of maternal age on CD risk varies among women with different levels of education. Among women experiencing spontaneous onset of labour, the risk of CD for those aged ≥40 years decreased from 14.3 (95% CI 11.2-18.3) in period 1 to 4.9 (95% CI 4.4-5.5) in period 3, in comparison to high educated women < 35 years. For low educated women, the risk decreased from 10.5 (95% CI 8.9-12.4) in period 1 to 6.2 (95% CI 5.4-7.2) in period 3. The decline in CD rates among women ≥ 35 years was more pronounced in those with higher education compared to those with lower education.

External validity

Norway is a rich country with one of the lowest CD rates among high-income countries[8]. The country has universal access to education, healthcare, and a wide range of social benefits, contributing to the well-being of its citizens[28]. All Norwegian women have access to free high-quality antenatal and maternal obstetric care, resulting in good perinatal outcomes[8]. Like other Nordic countries, Norway adopted a less medicalized approach to childbirth, with midwives attending most deliveries[8]. Maternal requested CD was comparatively lower than other European countries[63], while most CD being performed for medical reasons[55].

Both *Paper I* and *Paper II* utilize data from MBRN which covers the entire population of women giving birth in Norway, making our results generalizable to most women of reproductive age. In *Paper II*, the exclusion of one child mothers and women with preterm birth, limit its generalizability to these populations, for obvious reasons. In

Paper III, findings from MoBa offer potential advantages, allowing for the control of confounding factors through restriction and enabling inferences that are applicable to the population of pregnant women[232 233].

It is crucial to exercise caution when applying our findings to other populations. CD and other obstetric interventions are shaped by multiple factors beyond medical indications[22]. Our research has shed light on the influence of some of the societal factors on these patterns. Therefore, understanding the CD rate in a population encompasses a complex interplay of organizational, clinical, economic and psychosocial factors[15]. While our findings are likely relevant to other high-income contexts with similar population characteristics, such as other Nordic countries, their direct applicability to populations with different features may be limited.

Interpretation of findings

Paper I

We used the Robson ten-group classification to assess changes in CD in Norway from 1967 to 2020. Numerous earlier studies have used this classification tool to assess CD rates across various groups[8 22 24 25]. However, due to differences in study settings, time periods and included groups, direct numerical comparisons of CD are challenging. Moreover, some studies have not provided information on crude estimates[8]. With the exception of Muraca et al. (2022), other studies also omitted the inclusion of maternal and offspring characteristics, along with pregnancy complications[27]. A study conducted in the Nordic countries did incorporate maternal age when examining CD changes within the Robson groups[8]. Nevertheless, they did not differentiate on women's pregnancy history.

Caesarean delivery and maternal age

Across all periods, there was a consistent linear rise in the likelihood of CD with advancing maternal age, aligning with findings from other studies[37]. This trend could be explained by three potential factors. First, the biological aging of the myometrium may

play a role. Examination of uterine biopsies has revealed diminished myometrial contraction due to aging[38]. Additionally, these biopsies have highlighted a decrease in the number of receptors to uterotonic agents like oxytocin or prostaglandins[42], potentially leading to compromised contractility[38 39].

The second contributing factor could be the higher prevalence of complications by age. Our study revealed a higher incidence of complications among women aged ≥ 35 years. Notably, hypertensive disorders, prolonged rupture of membranes (lasting more than 24 hours), and diabetes mellitus emerged as the primary contributors to these complications. This observation is consistent with studies from the USA[39], Australia[47], and other Nordic countries[45 51 91], which have documented an elevated risk of similar complications among women of advanced age.

Third, higher frequency of interventions in mothers of advanced age may be an explanation. Across all study periods, women aged ≥ 35 years were less likely to experience spontaneous labour onset. A consistent pattern emerges from several prior investigations, which consistently have showed an escalated probability of labour induction[41 43 46 47 245], utilization of epidural anaesthesia[43 245], and administration of oxytocin[39 42] among women ≥ 35 years, irrespective of the presence of complications.

Caesarean delivery declining among nulliparous women ≥35 years.

Today, more women begin their reproductive career later in life [28]. The widespread accessibility of contraceptives[34], availability of abortion services[36], and assisted reproduction services[35], could have empowered more women to postpone pregnancy until it suits their desire. In our study, approximately 10% of women in the recent period had their first birth at ≥ 35 years. Interestingly, despite the growing number of women in this category, there has been a decrease in CD rates within this group. One potential contributing factor could be the change in clinical practice[45]. Earlier guidelines, before the widespread use of ultrasound and CTG, characterized nulliparous women aged ≥35 years as higher-risk group, irrespective of other complications [102]. Consequently, CD procedures were more frequently performed within this demographic group. In contrast, during the more recent period, a higher proportion of women are embarking on their

first childbirth experiences at age ≥ 35 years[45]. This phenomenon translates into a higher frequency of encounters for healthcare professionals with women of advanced age, a contrast to earlier periods. This trend has prompted clinicians to embrace a more proactive stance, involving vigilant monitoring of labour and intervention only when deemed medically necessary[6 106].

Another possible explanation for decline in CD among nulliparous older women (≥ 35 years) could pertain to the difference between women choosing to delay pregnancy until the age of ≥35 years in the first and last periods. In the earlier period, opting for such delayed pregnancies was relatively infrequent, and the limited number of women who did so might have included individuals with poor health or challenges in conceiving[91]. Conversely, the group of women postponing pregnancy to ≥ 35 years in the later period is likely to be different. A growing number of women are deferring starting family until they have addressed various life priorities, such as pursuing higher education or establishing their careers[28 31]. This is especially the case for the highly educated women, who are more inclined to give birth at more advanced ages, likely to make this group healthier[55 107]. As a result, the subset of mothers delaying childbirth in the later period might exhibit better overall health compared to those of the similar age in earlier periods[91]. Thus, the decrease in CD rate could possibly be explained by a healthier subject effect.

Studies from both Canada[246] and Sweden[45] have reported decreasing trends in CD rates among nulliparous women of higher age. Wood's study revealed an overall CD rate increase from 12.5% to 24% between 1992 and 2018 in Canada[246]. However, the authors concluded that maternal age only had a modest impact on the observed increase in CD. Similarly, Waldenstrom et al. (2012) identified a decreasing pattern in CD rates among nulliparous Swedish women aged ≥35 years [45].

Previous studies have reported that both women's preferences and lower threshold for interventions among healthcare provider could play a role in driving the increase in CD[45 91 247]. We observed a gradual increase in the incidence of pre-labour CD, particularly among women <35 years. To speculate: part of this upward trend could be attributed to maternal request of CD, given that the increase wasn't exclusive to women facing

complications. A prior Norwegian study, using data obtained through the MoBa questionnaire administered during the 30th week of pregnancy, revealed that around 10% of women expressed a desire for CD[61]. This inclination often stemmed from fears related to the birthing process and concerns about potential physical harm[61 95]. Another study involving young nulliparous women from eight OECD nations, reported that approximately one-tenth of nulliparous women preferred a CD [96]. The authors of this study highlighted that there was a knowledge gap regarding childbirth among women who expressed preference for CD. Patient autonomy and fear of litigation where the two main reasons why obstetricians accommodate maternal requested CD [63].

In accordance with previous research[53 55 61], our findings also demonstrated an increased risk of CD among immigrant women and individuals with lower levels of education. However, due to the limited number of immigrant women, particularly in the initial period, we were unable to stratify the data based on maternal country of birth. A recent Norwegian study revealed a twofold increase in the risk of CD among immigrant women from low to middle-income countries[59]. Specifically, the study's authors pinpointed that woman born in sub-Saharan African countries faced an increased risk of emergency CD, regardless of their educational background. Among low-educated women in this subgroup, there was a decreased risk of planned CD compared to Norwegian-born women which could imply underutilization of planned CD among these women[59]. Despite the higher prevalence of obesity and diabetes mellites among immigrants, results did not change when considering these factors including duration of residence[60]. In Sweden[58] and Denmark[57], non-medical factors such as language barriers, cultural views on childbirth, and reduced health literacy among immigrant women compared to the native population have been linked with increased CD risk.

Role of labour induction on caesarean delivery rates

Amidst women experiencing singleton cephalic pregnancies within the term period, an ongoing debate continues concerning the optimal timing of delivery[109]. This becomes particularly challenging when there is no specific medical indication for planned delivery, forcing the decision to rely solely on gestational age[109]. This decision-making

process is further complicated by the fact that what is considered best for the mother might not always align with what is best for the baby[109]. In our study, we found that women who underwent induced labour faced an increased risk of CD compared to those with spontaneous labour onset, across all study periods. Our findings align with those of Davey et al. (2016)[79] and Ehrenthal et al. (2010)[78], both of which reported an elevated CD risk among induced women, regardless of the presence of medical or obstetric complications. In contrast, a retrospective cohort study conducted in Scotland indicated that for each gestational week between 37 to 41 weeks, elective induction of labour was associated with improved perinatal outcomes, while the CD rate remained unchanged[81].

However, both Wood et al. (2014)[86] and Grobman et al.(2018)[82] assert that drawing such conclusions from observational studies can be challenging due to difficulties in accounting for differences in risk factors between women with spontaneous- and induced labour onset. Moreover, they contend that such a comparison might yield limited insight into clinical management decisions. Instead, they propose that a clearer perspective can be obtained through randomized allocation of women into expectant- and induced labour groups based on specific indications[82 86]. Grobman et al. (2018) conducted a comparative study between labour induction and expectant management, focusing on the period from week $39^{+0\ days}$ to $40^{+\ 6\ days}$ weeks of gestation in 6106 lower-risk nulliparous women[82]. This data was derived from a multicentre, randomized controlled trial carried out at 41 hospitals. The study's findings indicated that induction among low-risk nulliparous women is linked with a reduced risk of CD while maintaining similar perinatal outcomes. Other retrospective cohort studies have also reported similar findings[83-85].

Given the recent timeframe of these studies, we can only compare them with our findings from the last period. From 1999-2020, we continue to observe an increased risk of CD among individuals with induced labour onset when compared to those with spontaneous onset. However, what is interesting is that the annual CD rate has remained stable since 2008, despite the ongoing increase in inductions. This suggests that the increased risk associated with inductions has not impacted on the overall CD rates. When assessing the CD contribution from each age group to the overall rates by period,

we observed a decrease in the contribution of CD among women <35 years with spontaneous labour onset, while the rate was stable in the induced group. Among women ≥ 35 years, we observed a small rise in the contribution from the spontaneous onset group, whereas an increase was noted for the induced group (from 2.8% to 6.8%).

Among complications attributing to labour inductions, the prevalence of post-term pregnancies stands out as the most altered. Over the years from 1999 to 2020, the proportion of post-term pregnancies in our study population decreased from 13% to 8.4%. This shift became particularly pronounced after 2011, in alignment with recommended practices[74]. Despite proactive management strategies for post-term pregnancies in recent years, the CD rate has not changed much. This finding aligns with the outcomes of randomized studies carried out in Sweden[72] and the Netherlands[73]. Critics of this recommendation emphasize that, besides impacting most low-risk women, the healthcare costs and burden on health professionals may outweigh the few benefits[65 71].

In summary, we observed a decrease in the risk of CD for women aged ≥ 35 years. However, it's important to interpret our conclusion with caution. The ongoing demographic shift is pushing the population of pregnant women towards a higher risk profile, and advanced maternal age is a well-established risk factor for CD[37]. Consequently, if a larger part of the pregnant population is exposed to higher risk factors, it will inevitably affect the CD rate. The observed reduction in CD rates among the higher age group in our study might be attributed to a higher proportion of healthier women in this category. This situation could potentially change as more individuals become part of this shifting demographic.

Paper II

Among women with their first two singleton term births, those who observed an increase in offspring birthweight by gestational age from first to the second pregnancy had reduced CVD mortality, compared to women whose first two offspring both were within the Q2/3 quartiles. Conversely, those with a decrease in offspring birthweight by gestational age from first to the second pregnancy showed a higher CVD mortality.

These patterns were similar for both women with spontaneous- and iatrogenic deliveries. Changes in offspring birthweight quartiles from first to second pregnancy may capture heterogeneity in mothers' risk of dying from CVD.

CVD mortality has been declining in Norway[32], like other countries[113]. The incidence of acute myocardial infarction has experienced an annual decrease of 4.7% among women[114]. This decline has been attributed to the reduction of risk factors. Notably, the prevalence of smoking in women has dropped, from 32% (1970s) to 7% (2022)[248]. Moreover, there has been a general increase in the proportion of individuals engaging in physical activity, combined with better management of conditions such as hyperlipidaemia and hypertension[249]. However, there have also been unfavourable trends in the prevalence of overweight individuals and diabetes mellitus[250].

In accordance with prior findings[1 2 126], our study confirmed an inverse relationship between a mother's offspring birthweight and her vulnerability to CVD mortality. The highest mortality rates were identified among women with consecutive births with offspring within the lowest quartile (Q1). Adjusting for sociodemographic factors and pregnancy complications did not change our result. Our estimates, however, were lower than those reported in previous investigations[131-133 146 147]. This difference is likely due to difference in composition of the study cohort and methodological factors. Among these, it is important to mention, measurement offspring birthweight, the cutoff point for smaller birthweight, use of different growth charts and inclusion in the definition of CVD (coronary heart disease only, CVD event or CVD death).

Numerous studies have included women with preterm births[131 132 141-147 251], which are acknowledged as an independent risk factor for CVD[1 2], even in the absence of impaired growth[128]. In contrast to these studies, our study focused on women with term births. Some studies have relied on absolute birthweight measurements, overlooking the influence of gestational age[141-144 147]. This approach fails to distinguish between infants who are small due to a short gestational period versus those who suffer from growth constraints[127 148], especially among preterm births[131].

The difference in findings could also be due to the different cutoff points used in each study. We used quartiles as cutoff points with smaller infants being within the lower 25th percentile. In other studies, the lower 10th percentile (small for gestational age)[146 251] and the lowest 20% (quintile)[144] have been used. Like ours, most studies used weight charts that are based on liveborn births, whereas others employed intrauterine growth charts to categorize offsprings[132]. However, the difference in the use of the two charts is expected to be minimal among term births[236]. Another explanation for the different mortality estimates could be the specific endpoints under study. Most other studies[131 136 141-143 145 251], like ours, have evaluated CVD mortality, while other studies exclusively assessed coronary heart disease[144 147] or both morbidity and mortality of CVD[132 146]. Despite these differences, all studies have suggested that women with smaller offspring have underlying predispositions for future CVD.

Women with larger offspring, on the other hand, displayed a reduced risk of CVD mortality in our study. This was the case for babies even in the upper 10th percentile (large for gestational age). Our findings are consistent with other studies[134 141-144], although not all[147 251]. Friedlander et al. (2007)[147] and Lykke et al. (2010)[251] reported increased CVD mortality among women with higher birthweights. The authors suggested that foetal growth acceleration may share underlying risk factors with foetal growth restriction, which could explain the increased risk on both sides of the spectrum[148 252]. Moreover, the likelihood of developing diabetes mellitus was higher among women with larger babies, further increasing the cumulative burden[129 131]. The lower CVD mortality in women with offspring in the upper quartile is a paradox in our study and a possible explanation could be linked to maternal education. Most of the women who gave birth to Q4 babies had a higher level of education. Notably, Morken and colleagues also indicated that the increased CVD risk among women with large babies was not evident in term births, but rather among preterm births[131].

Obstetric interventions

The use of ultrasound and rise in obstetric interventions might have contributed to the shift in birthweight and gestational age in Norway[110]. There has been a rise in births with shorter gestational lengths, coupled with a decline in post-term births. We found higher

frequencies of term complications among women with iatrogenic labour onset. There is evidence suggesting that term complications might share common etiologic pathways with preterm birth[253], possibly linked to placental dysfunction, which in turn could be linked to future CVD[2]. However, we did not observe a clear difference in CVD mortality among women with spontaneous- and iatrogenic births. This could be attributed to the fact that we included a healthier population. Moreover, it's possible that term complications might not be as severe as those occurring in the preterm period[137].

Including subsequent births

Most studies tend to focus on women's first birth while excluding subsequent pregnancies[137]. Concentrating on the first birth may be a logical approach for several reasons. First, the risk of complications is notably higher in first pregnancies[254 255], including the occurrence of low birthweight[110]. This could potentially explain why most of the observed adverse effects of pregnancy on lipid profiles have been primarily observed in first pregnancies[256]. Furthermore, experiences during the first birth could influence a woman's decision on having more children[186]. While desirable family size may vary, instances of secondary infertility or complications might be more prevalent among mothers with only one child[235], which have higher CVD mortality[123 137].

Not including information from subsequent births could potentially mask differences in CVD risk among different groups[128 137 139]. In our study, the increased CVD risk among women with first their birth in Q1 disappeared if second birth was Q4. On the other hand, an increased risk of CVD mortality was evident if the second birth was in Q1, regardless of the offspring birthweight quartile of the first birth. Thus, a woman's last pregnancy history could also provide valuable insights into her future risk of CVD[1]. A publication by Seid et al. (2023) revealed that the risk of CVD mortality was elevated for women with complications in their last pregnancy rather than complications occurring solely in the first pregnancy[139]. Thus, considering only women's first birth might mask differences in CVD mortality.

By tracking the changes from first to second pregnancy, longitudinal design is important for understanding the mechanisms behind changes in patterns of offspring birthweight[1]. Among women with consecutive smaller babies and iatrogenic onset of labour, we might

think of a potential vascular and metabolic maladaptation to pregnancy, while changes in birthweight patterns to women having smaller or larger offspring in a subsequent pregnancy might indicate a possible influence of environmental factors. The longitudinal design also allowed us to capture changes in maternal risk factors, and to measure continued cumulative effects from each pregnancy[1].

Pathophysiology of foetal growth restriction

Poor foetal growth and CVD mortality might potentially share underlying disease mechanisms, as both conditions have been linked to endothelial and vascular dysfunction[121]. Infants affected by poor foetal growth often experience placental under-perfusion[257]. Research suggests that this may be attributed to reduced lipoprotein receptors in the placenta when compared to infants with normal growth[258], although some studies have reported an overexpression of such receptors[259]. This discrepancy could be attributed to variations in the severity of growth impairment[1]. Furthermore, post-pregnancy, women who have given birth to low birthweight infants were found to be at increased risk of subsequent high blood pressure[129] and atherosclerotic vessel remodeling[257]. There is also evidence suggesting the presence of dyslipidaemia, subclinical inflammation, and endothelial dysfunction in mothers who have given birth to low birthweight infants, even in the absence of other complications[260]. Hence, it's plausible that smaller offspring birthweights might serve as early sign of maternal predisposition to CVD[121].

Health implications

Most women have more than one birth, typically occurring earlier in their reproductive career[137]. Hence, incorporating information from subsequent births might help to uncover the diversity in CVD risk[128 137 139]. This, in turn, could aid in the identification of high-risk women, enabling the implementation of early follow-up and targeted interventions, which is of public health importance[1].

Paper III

In women with previous singleton births, we observed reduced fecundability and increased infertility in those who had undergone a CD in their previous delivery compared to those who had a vaginal delivery. Similarly, women who faced infertility were more prone to having a CD. This reciprocal relationship suggests that CD and reduced fecundability might share a common underlying mechanism influencing both outcomes.

Many studies have linked CD with fewer births[162-164], which is an important subject of interest given the rise in CD. The increasing medicalization of childbirth[18], characterized by the adoption of technologies like CTG and a surge in interventions like induction, has contributed to the increase in global CD occurrence[7]. Furthermore, a lower threshold among clinicians to perform CD as well as a growing preference for CD among women have driven the demand for this procedure [45 63 64]. Collectively, these factors could influence reproductive performance of a population.

Use of TTP to measure fecundability.

In contrast to prior studies[162 173 175 261], our analysis benefits from a dataset that includes information on the pregnancy intention and data on TTP, gathered from a population-based cohort. One of the advantages of using TTP is its capacity to indirectly assess women's fecundability[153]. Given that a substantial number of pregnancies result in loss, studying fecundability using TTP is prone to selection[157]. In our study, we were able to explore the association between CD and fecundability from both directions. Nonetheless, the main challenge is that TTP does not exclusively pertain to women; instead, it encompasses the fertility of the couple[122]. Prolonged TTP might emerge due to issues related to the woman's partner, and not the women necessarily.

CD and fecundability

In our study, we observed that women with a history of previous CD were less likely to experience subsequent pregnancies compared to those who had vaginal deliveries. This trend was consistent regardless of whether the CD occurred in a previous or earlier births, whether it occurred once or multiple times, as well as for both the spontaneous-

and induced labour onset groups. After adjusting for sociodemographic factors, maternal health before and during pregnancy, and behavioural factors, we observed only a slight attenuation of the estimate. However, it is important to consider that there might be other indications related to CD that were not accounted for in our analysis. Specifically, we lacked data on indications such as dystocia and foetal distress, which are among the most common reasons for emergency CD[43].

Most studies have indicated a lower probability of pregnancy following CD[165-169 172 173 175 177 179], but not all[170 176]. Three potential explanations have been suggested for the link between infertility and CD: pelvic pathology due to surgical scarring, maternal choice, and underlying predisposition. The concept of pelvic pathology postulates that scarring, tubal damage, or disruption of the placental bed after CD might explain the decrease in conception rates[165 179]. This theory is supported by the increased risk of miscarriage, ectopic pregnancy, and stillbirth following CD[17], although not consistently across all studies[262]. Moreover, studies reported an increase in placental abnormalities after CD[263]. These adverse outcomes resulting from the stress of CD were suggested to predominantly manifest among women with predisposition to infertility[264].

An alternative viewpoint argues that the influence of CD on subsequent fertility appears to be primarily driven by voluntary decisions[265 170 266 267]. This viewpoint was supported by two prior Norwegian studies, which utilized birth interval as a measure of infertility[166 268]. These studies reported that the decline in fertility following a CD was only noticeable when the infant survived. However, a study conducted by Kjerulff et al. (2013) reported no difference in the desire for having subsequent children, regardless of whether women had CD or vaginal delivery[261]. But they did observe that women who had CD were less likely to plan for families with three or more children. In our study, we observed no change in fertility in women with a prior CD when the newborn died, suggesting that part of the reduction in fertility could partly be voluntary.

Some researchers attribute the observed decline in number of pregnancies after CD to potential confounding factors related to the medical indications behind CD[163 164]. To address this concern, both Smith et al. (2006)[170] and Eijsink et al. (2008)[171] conducted comparative analyses between women with uncomplicated vaginal deliveries and those

with singleton breech presentations but found no significant differences. However, these findings are contradicted by results from recent studies that have reported a decrease in fecundability following breech presentations[173 178]. In our study, despite differences in indications for CD, we observed reduced fecundability for both planned and emergency CD, in contrast to a smaller Danish study which found this effect solely among women with planned CD[178]. Interestingly, a population-based Danish study also found that the reduced rate of subsequent births following CD was not limited to women with medical indications[175]. The authors of this study reported that the subsequent pregnancy rate was diminished even among those women who had CD on maternal request.

Fecundability and CD

We observed a trend: as the duration it took a woman to conceive was lengthened, the probability of CD also increased. This is in line with previous studies[46 180 182]. In our study, women with infertility demonstrated a higher prevalence of pregnancy complications, chronic conditions, smoking, and being overweight or obese. Despite adjusting for such confounding factors, the increased risk of CD persisted. Prior studies have also linked infertility treatment with increased adverse pregnancy outcomes[269], which in turn might contribute to a higher likelihood of CD. However, excluding women who used assisted reproduction did not alter our results.

One possible explanation for the increased risk of CD could be linked to underlying infertility causes that we have not comprehensively address in our analyses[180 270]. We observed a consistent pattern in both nulliparous and multiparous women, which was contrary to our initial assumption that multiparous women might be less influenced by infertility[165]. Our finding was particularly intriguing as our study excluded women with previous CD, ruling out the possibility of attributing it to prior CD or a cumulative effect of prior CD occurrences[165]. It could be that the reported TTP merely reflects the average duration taken for couples to achieve the current pregnancy[153]. However, the absence of TTP data from couples' previous pregnancies limits the interpretation of our findings.

Another possible explanation for increased CD among women with reduced fecundability/infertility might be anxiety. Maternal anxiety has the potential to impact the progression of labour by triggering the release of stress hormones, which could

potentially disrupt uterine contractility and lead to poor progress of labour[271]. Also, elevated levels of anxiety during pregnancy or labour have been associated with a modest increase in interventions, including CD[272]. Moreover, women who experienced extended time trying to conceive could become worried about their coming delivery and might desire CD[42], especially among older women[43]. This is supported by a Norwegian study that utilized data from the MoBa questionnaire at the 30th week of pregnancy[61]. This study found a higher likelihood of preferring CD among women with prolonged time to conception. Obstetricians might also exhibit lower threshold for intervention in this group[170]. Similar findings have been reported in studies conducted in the USA[46], UK[182] and other Nordic countries[180].

Possible explanations for a link between CD and fecundability

Our study unveiled a bidirectional link between CD and fecundability, suggesting that the mere presence of a CD might not directly lead to a decline in fecundability. Instead, we propose the existence of shared underlying mechanisms that could explain the link between these two factors. In our study, women experiencing CD and reduced fecundability/infertility tended to exhibit a higher prevalence of pregnancy complications such as preeclampsia, preterm delivery, and placental abruption. Additionally, they report an elevated occurrence of chronic conditions like diabetes mellitus and endometriosis. It is plausible that underlying mechanisms responsible for infertility could potentially be linked with pregnancy complications and increased likelihood of CD. Maternal anxiety is also another factor that has been linked with both reduced fecundability and increased interventions during labour[182 270 272 273]. Unfortunately, our data did not encompass information on maternal anxiety, other indications for CD, or the underlying causes of infertility.

Conclusion

Paper I

Despite the ongoing increase in the age of nulliparous women, CD declined among women ≥ 35 years, while it increased in younger women. The rise in CD cannot be merely explained by the shift in the age of nulliparous women.

Paper II

In women with two term births, a decrease in birthweight by gestational age from the first to second birth was associated with a higher CVD mortality. Conversely, an increase in birthweight by gestational age was associated with decreased CVD mortality. Mortality patterns were similar for both spontaneous and iatrogenic births. Including changes in birthweight by gestational age from the first and second pregnancies might provide additional insights into women's CVD mortality.

Paper III

In women with prior singleton pregnancies, a diminished fecundability and higher risk of infertility were evident among those with a history of previous CD. Among women without a prior CD, an elevated risk of CD was observed in those with reduced fecundability. This suggests a bidirectional association. The reduced fecundability following CD might be due to shared underlying mechanisms, and not due to the CD procedure itself.

Future studies

Norway maintains one of the lowest CD rates among high-income countries[6 8]. While the rate has witnessed an increase compared to earlier periods within the registry, it has remained stable during the last decade. Low CD rates have been achieved without compromising perinatal outcomes[6].

As the age distribution of women age at first birth undergoes changes, there is however a progressive shift towards increased risk for pregnancy complication and chronic conditions[91]. This transition results in more complications and, consequently, an increased number of interventions due to the advancing age[37]. The outcomes of first pregnancy and delivery are important and might influence subsequent reproduction[17]. Simultaneously, incorporating data from subsequent pregnancies offers a more comprehensive understanding of the situation[186]. While our study aims were to address the existing gap in knowledge regarding the enduring effects of CD on fecundability and mortality, further investigation is needed. We recommend that forthcoming research concentrate on the following domains.

- Assessing women's satisfaction and factors influencing their delivery experience, using quantitative and qualitative study design.
- Evaluate the implications of CD by maternal request on subsequent pregnancies.
- Assessing the link between pregnancy complications, obstetric interventions, and other chronic diseases such as cancer, using information from women's full reproduction.
- To assess the changes in fecundability following CD, using data collected from menstrual cycle tracking apps.
- Using linked data from population-based registries to assess the association between CD and other adverse birth outcomes, including miscarriage, ectopic pregnancy, and stillbirth.
- Evaluate the influence of maternal anxiety on the relationship between CD and fecundability.

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Appendix

The MBRN notification form

The first notification form: 1967 to December,1998

VENNLIGST BENYTT SKRIVEMASKIN VED UTFYLLING AV BLANKETTEN

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

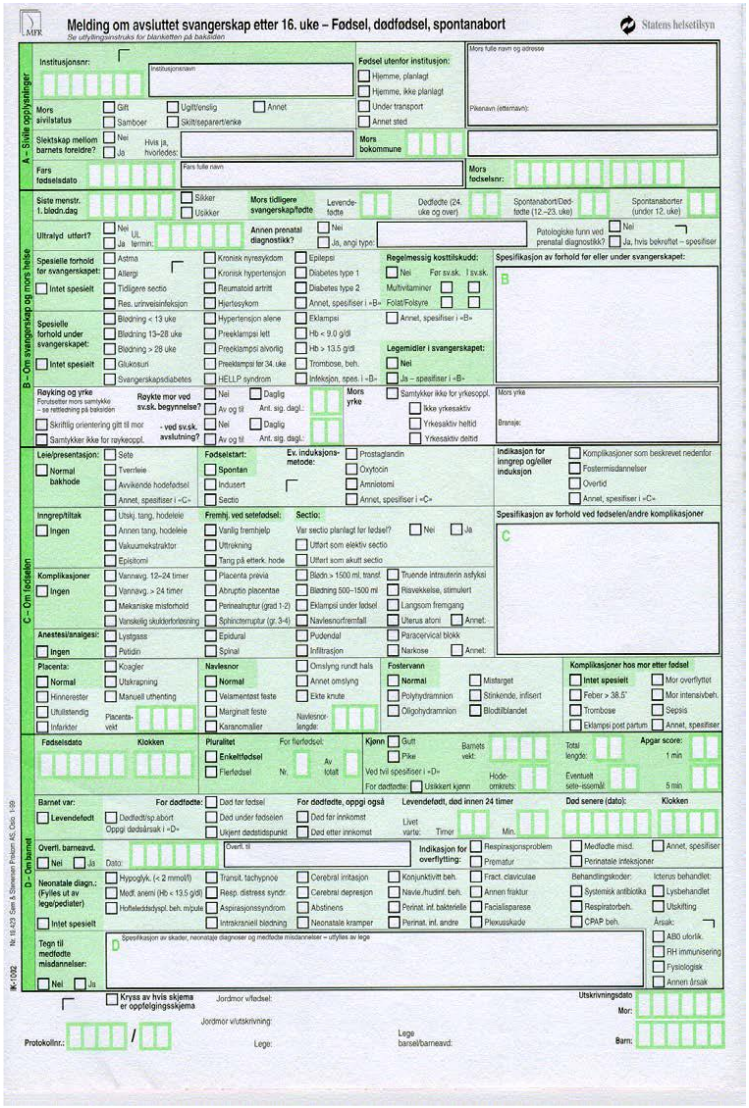
Barnet	Barnet var 1 ☐ Levende født 2 ☐ Dødfødt foster	Født dag, mnd., år	Klokkeslett	Personnr.	Skriv ikke her
	1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling		Kjønn 1 ☐ Gutt 2 ☐ Pike		
	Etternavn, alle fornavn (bare for levendefødte)				
	Fødested. Navn og adresse på sykehuset/fødehjemmet		Kommune		
Faren	Etternavn, alle fornavn		Født dag, mnd., år	Bostedskommune	
Moren	Etternavn, alle fornavn. Pikenavn			Født dag, mnd., år	
	Bosted. Adresse		Kommune		
	Ekteskapelig status 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt			Ekteskapsår (gifte)	
	Antall tidligere fødte (før denne fødselen)	Levende fødte	Av disse i live	Dødfødte	
	Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:				
Morens helse **før** svanger-skapet	1 ☐ Normal 2 ☐ Sykdom (spesifiser):				
			Siste menstruasjons første blødningsdag		
Morens helse **under** svanger-skapet	1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):				
Ble fødselen provosert	1 ☐ Nei 2 ☐ Ja				
Inngrep under fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
	Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor				
Komplika-sjoner i forbindelse med fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
Fostervann, placenta og navlesnor	1 ☐ Normalt 2 ☐ Patologisk (spesifiser):				
Barnets tilstand	Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja		Apgarscore etter 1 min.	etter 5 min.	
	For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:				
	Lengde (i cm)	Hode-omkr. (i cm)	Vekt (i g)	For døde innen 24 timer Livet varte i Timer	Min
	For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen Dødsårsak: Seksjon? 1 ☐ Nei 2 ☐ Ja				
Alvorlige arvelige lidelser i slekten	1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:				

80 000. 12.86. Stat Grafisk

Sted (sykehusets stempel) Dato Jordmor Lege

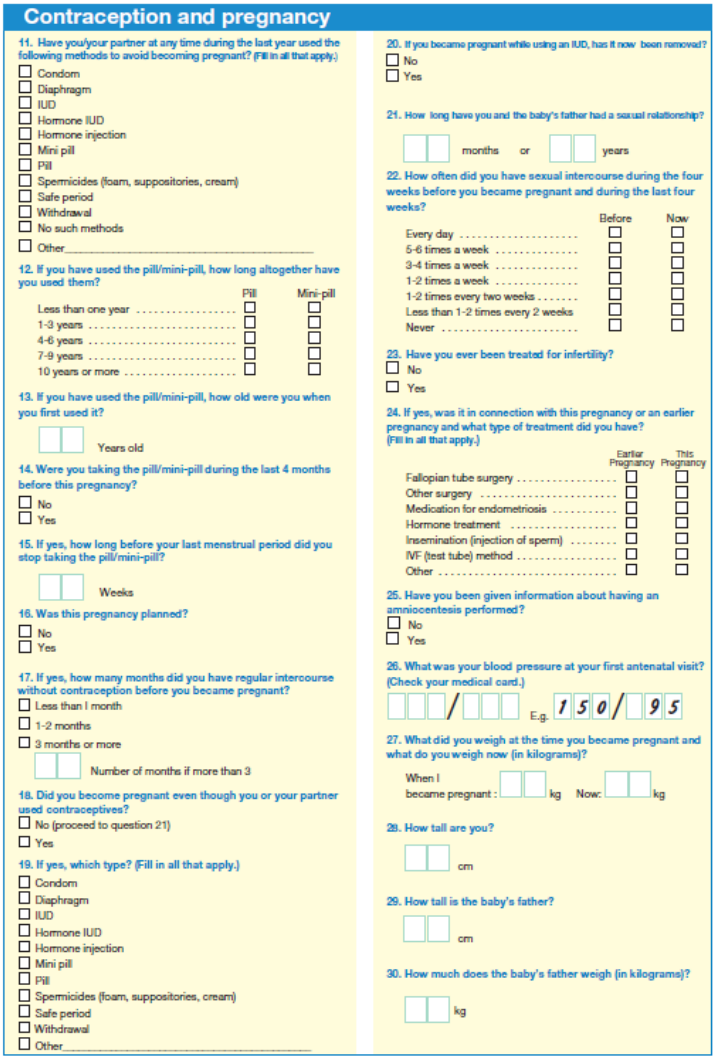
IK - 1002.

Check boxes from 1999-2005



Questionnaire 1, page 2 from MoBa

In English



Contraception and pregnancy

11. Have you/your partner at any time during the last year used the following methods to avoid becoming pregnant? (Fill in all that apply.)

- ☐ Condom
- ☐ Diaphragm
- ☐ IUD
- ☐ Hormone IUD
- ☐ Hormone injection
- ☐ Mini pill
- ☐ Pill
- ☐ Spermicides (foam, suppositories, cream)
- ☐ Safe period
- ☐ Withdrawal
- ☐ No such methods
- ☐ Other_____

12. If you have used the pill/mini-pill, how long altogether have you used them?

	Pill	Mini-pill
Less than one year	☐	☐
1-3 years	☐	☐
4-6 years	☐	☐
7-9 years	☐	☐
10 years or more	☐	☐

13. If you have used the pill/mini-pill, how old were you when you first used it?

☐☐ Years old

14. Were you taking the pill/mini-pill during the last 4 months before this pregnancy?

- ☐ No
- ☐ Yes

15. If yes, how long before your last menstrual period did you stop taking the pill/mini-pill?

☐☐ Weeks

16. Was this pregnancy planned?

- ☐ No
- ☐ Yes

17. If yes, how many months did you have regular intercourse without contraception before you became pregnant?

- ☐ Less than 1 month
- ☐ 1-2 months
- ☐ 3 months or more

☐☐ Number of months if more than 3

18. Did you become pregnant even though you or your partner used contraceptives?

- ☐ No (proceed to question 21)
- ☐ Yes

19. If yes, which type? (Fill in all that apply.)

- ☐ Condom
- ☐ Diaphragm
- ☐ IUD
- ☐ Hormone IUD
- ☐ Hormone injection
- ☐ Mini pill
- ☐ Pill
- ☐ Spermicides (foam, suppositories, cream)
- ☐ Safe period
- ☐ Withdrawal
- ☐ Other_____

20. If you became pregnant while using an IUD, has it now been removed?

- ☐ No
- ☐ Yes

21. How long have you and the baby's father had a sexual relationship?

☐☐ months or ☐☐ years

22. How often did you have sexual intercourse during the four weeks before you became pregnant and during the last four weeks?

	Before	Now
Every day	☐	☐
5-6 times a week	☐	☐
3-4 times a week	☐	☐
1-2 times a week	☐	☐
1-2 times every two weeks	☐	☐
Less than 1-2 times every 2 weeks	☐	☐
Never	☐	☐

23. Have you ever been treated for infertility?

- ☐ No
- ☐ Yes

24. If yes, was it in connection with this pregnancy or an earlier pregnancy and what type of treatment did you have? (Fill in all that apply.)

	Earlier Pregnancy	This Pregnancy
Fallopian tube surgery	☐	☐
Other surgery	☐	☐
Medication for endometriosis	☐	☐
Hormone treatment	☐	☐
Insemination (injection of sperm)	☐	☐
IVF (test tube) method	☐	☐
Other	☐	☐

25. Have you been given information about having an amniocentesis performed?

- ☐ No
- ☐ Yes

26. What was your blood pressure at your first antenatal visit? (Check your medical card.)

☐☐☐/☐☐☐ E.g. 150/95

27. What did you weigh at the time you became pregnant and what do you weigh now (in kilograms)?

When I became pregnant: ☐☐ kg Now: ☐☐ kg

28. How tall are you?

☐☐ cm

29. How tall is the baby's father?

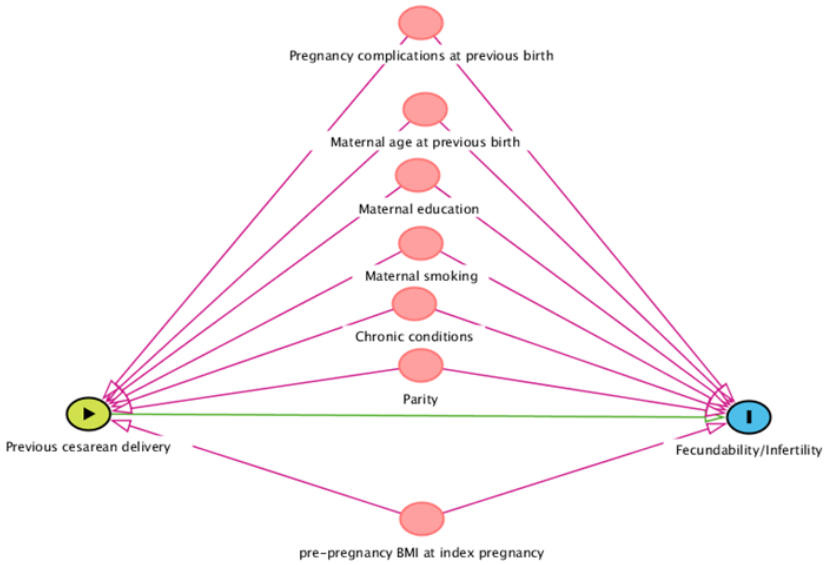
☐☐ cm

30. How much does the baby's father weigh (in kilograms)?

☐☐ kg

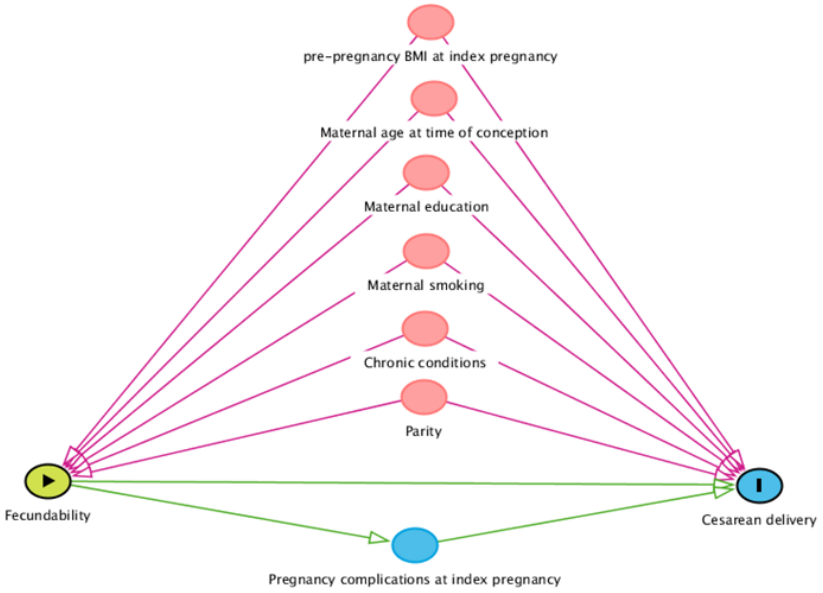
Supplementary figures and table

1. Figure S1. Directed acyclic graph illustrating the associations between our exposure (previous caesarean delivery), outcome (fecundability/infertility) and covariates.



BMI stands for body mass index.

2. Figure S2. Directed acyclic graph illustrating the associations between our exposure (fecundability), outcome (caesarean delivery) and covariates.



BMI stands for body mass index.

3. Table S1: Change in caesarean delivery among women with singleton cephalic term birth, by maternal age and onset of labour, 1967-2020

	1967-1982			1983-1998			1999-2020		
Maternal age (years)	CD rate[a] %	Absolute[b] Contribution %	Relative[c] Contribution %	CD rate[a] %	Absolute[b] Contribution %	Relative[c] Contribution %	CD rate[a] %	Absolute[b] Contribution %	Relative[c] Contribution %
Spontaneous labour onset									
<35	2.86	2.38	53.81	5.79	4.63	49.15	7.37	5.29	40.3
35-39	18.25	0.18	3.96	14.7	0.32	3.35	13.31	0.69	5.28
>=40	34.96	0.07	1.57	28.73	0.07	0.71	17.55	0.12	0.88
Induced labour onset									
<35	8.7	1.29	29.19	18.25	2.86	30.32	21.95	3.77	28.74
35-39	30.8	0.09	2.12	33.26	0.23	2.49	31.22	0.68	5.17
>=40	45.79	0.03	0.67	44	0.04	0.46	35.71	0.21	1.58
Pre-labour CD									
<35		0.33	7.57		1.04	11.09			13.72
35-39		0.03	0.74		0.16	1.73			3.21
>=40		0.02	0.36		0.07	0.7			1.11
Total	4.43		100	9.42		100	13.3		100

CD stands for caesarean delivery.

[a] Calculated by dividing the number of CD cases in the specific age group by the total number of deliveries in the same age group.

[b] Calculated by dividing the number of CD cases in the specific group by the total number of deliveries that occurred during that period.

[c] Calculated by dividing the number of CD cases in the specific group by the total number of CD cases during that period.

Papers I-III

I

Sima *et al. BMC Pregnancy and Childbirth* (2022) 22:419
https://doi.org/10.1186/s12884-022-04755-3

BMC Pregnancy and Childbirth

RESEARCH

Open Access

Cesarean delivery in Norwegian nulliparous women with singleton cephalic term births, 1967–2020: a population-based study

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Abstract

Background: Nulliparous women contribute to increasing cesarean delivery in the Nordic countries and advanced maternal age has been suggested as responsible for rise in cesarean delivery rates in many developed countries. The aim was to describe changes in cesarean delivery rates among nulliparous women with singleton, cephalic, term births by change in sociodemographic factors across 50 years in Norway.

Methods: We used data from the Medical Birth Registry of Norway and included 1 067 356 women delivering their first, singleton, cephalic, term birth between 1967 and 2020. Cesarean delivery was described by maternal age (5-year groups), onset of labor (spontaneous, induced and pre-labor CD), and time periods: 1967–1982, 1983–1998 and 1999–2020. We combined women's age, onset of labor and time period into a compound variable, using women of 20–24 years, with spontaneous labor onset during 1967–1982 as reference. Multivariable regression models were used to estimate adjusted relative risk (ARR) of cesarean delivery with 95% confidence interval (CI).

Results: Overall cesarean delivery increased both in women with and without spontaneous onset of labor, with a slight decline in recent years. The increase was mainly found among women < 35 years while it was stable or decreased in women > = 35 years. In women with spontaneous onset of labor, the ARR of CD in women > = 40 years decreased from 14.2 (95% CI 12.4–16.3) in 1967–82 to 6.7 (95% CI 6.2–7.4) in 1999–2020 and from 7.0 (95% CI 6.4–7.8) to 5.0 (95% CI 4.7–5.2) in women aged 35–39 years, compared to the reference population. Despite the rise in induced onset of labor over time, the ARR of CD declined in induced women > = 40 years from 17.6 (95% CI 14.4–21.4) to 13.4 (95% CI 12.5–14.3) while it was stable in women 35–39 years.

Conclusion: Despite growing number of Norwegian women having their first birth at a higher age, the increase in cesarean delivery was found among women < 35 years, while it was stable or decreased in older women. The increase in cesarean delivery cannot be solely explained by the shift to an older population of first-time mothers.

Keywords: Cesarean delivery, Population-based study, Robson groups, Norway

Introduction

Cesarean delivery (CD) has increased in all developed countries with Nordic countries having the lowest rates [1]. There has been a moderate increase in CD rates also in the Nordic countries [2]. Between 2000 and 2011 the rates increased by 26%, 15% and 10% in Denmark, Norway, and Sweden, respectively, after which they have

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levelled off during the most recent years [3]. Higher CD rates may be associated with future adverse complications in the mother and her baby [4] and have economic costs for the society [5].

The ongoing changes in clinical interventions as well as society composition including maternal age at childbirth and cultural background or ethnicity in relation to immigration, make it crucial to monitor CD rates and identify groups with too high CD rates and contributing factors [1]. Nulliparous women and women with previous CD are the two groups contributing strongly to increasing CD in the Nordic countries [2]. Major risk factors for the rise in CD include advanced maternal age [6], change in clinical practice such as management of breech pregnancies [7] and more induced deliveries [8]. Women's preferences [9] and change in population risk profile such as higher body mass index (BMI) [10] are also important.

Increasing maternal age is associated with increased risk of pregnancy complications and obstructed labor [6], and may be explained by biological changes to the uterine contractility [11, 12]. However, a prior study among low risk nulliparous women in Norway and Sweden reported declining CD rates in women older than 35 years [13]. This study only focused on women older than 30 years and thus excluded most nulliparous women and did not take into consideration women's different risk profiles and clinical handling.

Other factors influencing CD rates include changes in induction policy and pre-labor CD [8, 14]. The link between induction and CD has been much debated, with many studies reporting conflicting findings. Some observational studies report induction of labor in low-risk nulliparous women to increase risk of CD [15, 16] while others have reported unchanged or even lower risk of CD [17–19]. In Norway, induction rates have increased from 12.5% in 2003 to 20.3% in 2013, with one in ten inductions performed without any medical indication [20]. In 2020, the induction rate in Norway was 27.1% [21].

To address heterogeneity in risk of CD, the Robson classification has been used as a framework for comparing CD rates between groups with similar, clinically relevant risk factors for CD [22]. Robson groups R1 and R2 include nulliparous women with singleton, cephalic and term pregnancy, covering majority of nulliparous reproductive women [21]. The aim of our study was to describe changes in CD rates among these groups in relation to change in clinical intervention and sociodemographic factors in Norway across 50 years.

Methods

Data sources

In this population-based cohort study we analyzed data from the Medical Birth Registry of Norway (MBRN) between 1967 and mid-2020. The MBRN is based on mandatory notification of all live- and stillbirths from 16 weeks of gestation since 1967 [23] and prospectively collects data on mother's health before and during pregnancy, as well as complications during and after delivery until discharge. Attending midwives or physicians are responsible for providing information to the registry. Before 1998, information was based on free text descriptions, which were coded using the International Classification of Diseases (ICD), 8th version. After 1998, checkboxes were introduced in addition to free text, and ICD-10 was used for coding. Information on maternal smoking habits was included in the MBRN in 1999, and mother's height and weight gradually introduced from 2007. Data from the MBRN was linked to the Country-of-Origin Database and the National Education Database at Statistics Norway.

Robson classification

We used the Robson classification to identify the study population [22]. This tool stratifies women based on five obstetric parameters: number of fetuses, fetal presentation, gestational age, previous CD, and onset of labor. Our study population included nulliparous women with singleton, cephalic, term birth with onset of labor as either spontaneous (Robson group R1), induced (Robson group R2a) or pre-labor CD (Robson group R2b). Similarly, to account for the acknowledged increased risk of CD in complicated pregnancies, separate analysis was done after excluding women with complications in their first pregnancy/delivery. Due to no direct information on indication for CD, we used the following complications as proxy for the indication: diabetes mellitus (before or during pregnancy), hypertension (chronic or during pregnancy), preeclampsia, post-term (>=42 weeks), premature rupture of membranes (membrane rupture for >24 h and unspecified time), placental abruption and placenta previa [21]. We adopted this potential indication list from the recent national Norwegian clinical guideline, provided by the Norwegian Society of Gynecology and Obstetrics [8].

Study population

The study population included women who gave birth to their first singleton baby between 1967 and mid-2020. We excluded women with pregnancies ending before 22 weeks' or infants weighting below 500 g, gestational ages outside of 46 completed weeks, infant's birthweight by gestational age Z score [24] less than -5 or greater than 5 and women with missing information on Robson classification. Women in the other Robson groups (breech presentation (R6), transverse presentation (R9) and preterm delivery (R10)) were also

excluded in order to have a homogenous population of nulliparous woman which makes up the majority of women of reproductive age. The final study population included women with singleton, cephalic term birth (Fig. 1).

Cesarean delivery (CD)

CD was the outcome variable and proportions (CD rates) were calculated by dividing the number of CD by the number of deliveries during the specific period per 100 births. We showed the changes in CD over 50 years period. In addition, to capture changes in reporting format and obstetric practices across decades, we divided the years of delivery into three time periods: (1967–1982), (1983–1998) and (1999- 2020).

Statistical analysis

Frequency and contingency tables were used to describe CD by maternal characteristics and onset of labor. Statistical analysis was carried out with STATA IC statistical software (version 16). Change in CD by onset of labor and maternal age groups (< 20, 20–24,25–29, 30–34, 35–39 and > = 40) were assessed yearly and across three time periods, 1967–1982, 1983–1998 and 1999–2020. Generalized linear models with log link, binomial distribution and exponentiated regression coefficients were used to calculate adjusted relative risks (ARR) with 95% confidence intervals (CI) by periods. *P*-values below 0.05 were considered significant. A compound variable was made by combining maternal age, onset of labor (spontaneous (reference), induced and pre-labor CD) and time period, keeping women who had their first birth 20–24 years,

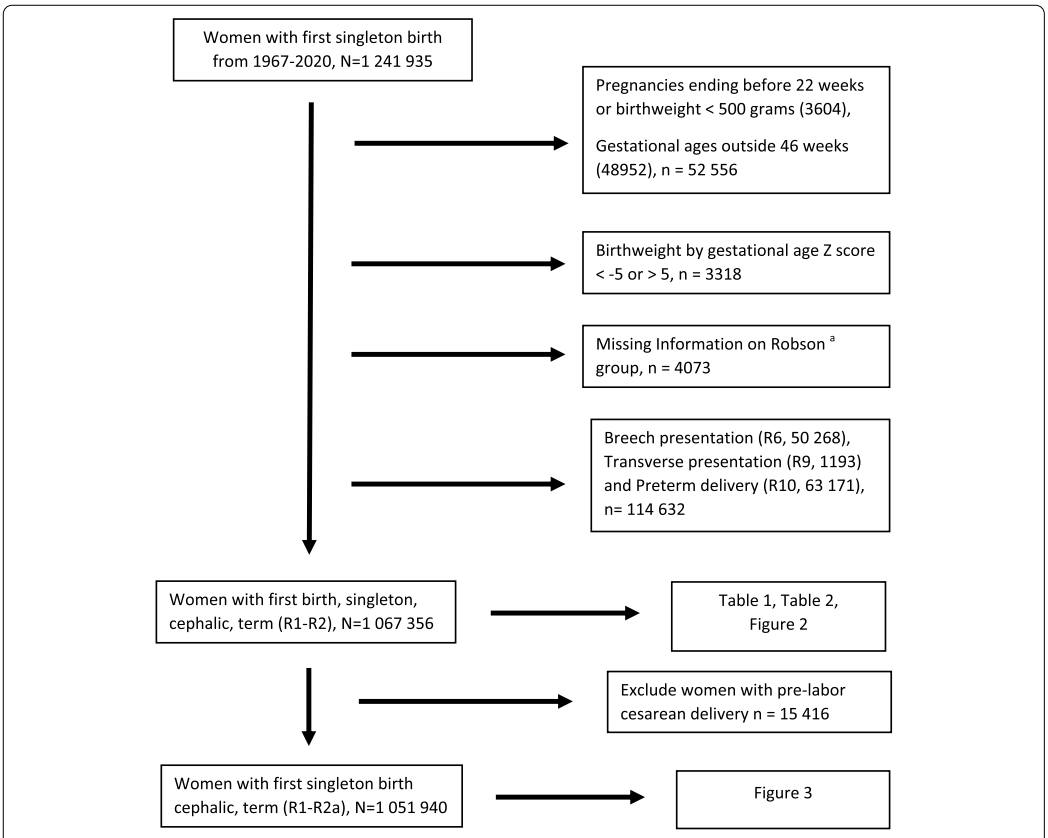

Fig. 1 Flowchart of our study population. **a** Robson group stratifies women based on five obstetric parameters: number of fetuses, fetal presentation, gestational age, previous cesarean delivery and onset of labor

with spontaneous labor onset in 1967–1982 as reference in the statistical model. Other variables included in the adjusted models were mother's country of birth (Western women (reference): Europe, Canada, USA, New Zealand, and Australia, Non-western women: all other countries), offspring birthweight (continuous scale, in grams), smoking during pregnancy: (no (reference) and yes (daily/sometimes), restricted to births after 1999) and pregestational BMI (continuous scale, restricted to births after 2007). To test for linear CD trends within each maternal age category, we used year of delivery as a continuous variable. In addition, to evaluate the association between CD and maternal age (< 35, 35–39 and > = 40) over time in relation to maternal education, we included an interaction term (Likelihood ratio test) between maternal age and maternal education (high: > 13 years (reference) and low: < = 13 years). Associations were considered statistically significant at the 5% level.

Results

A total of 1 067 356 nulliparous women with singleton, cephalic, term births were included. Table 1 shows sociodemographic changes across the three time periods. The proportion of women having their first birth > = 35 years increased from 1.6% in 1967–1982 to 9.2% in 1999–2020. From first to last period, the proportion of women with > 13 years education more than doubled (from 26% to 58.7%) while the proportion of non-western women increased from 0.5% to 10.5%. The proportion of women with any of the seven pregnancy/delivery complications increased slightly, from 23.6% (1967–82) to 27.4% (1999–2020). The seven complications associated with CD were post-term (153,747, 14.4%), premature rupture of membrane (52,678, 4.9%), preeclampsia (38,362, 3.6%), chronic or gestational hypertension (23,302, 2.2%), pregestational or gestational diabetes mellitus (14,191, 1.3%), placental abruption (2706, 0.3%) and placenta previa (1170, 0.1%).

Overall CD increased, both in women with spontaneous onset of labor (R1) and those with either induction or pre-labor CD (R2) (Fig. 2a). There was a slight decline in CD in recent years, especially in the R2 group. In relation to the introduction of new reporting formats in 1999, the apparent change in the proportion of CD was limited to women in R2 group. CD increased with maternal age (Fig. 2b). The overall increase was mainly found among women < 35 years while it was stable or decreased in women > = 35 years.

From first to last period, the proportion of women with term birth having spontaneous onset of labor

Table 1 Maternal characteristics at first singleton, cephalic, term birth, by three time periods in Norway, The Medical Birth Registry of Norway, 1967–2020, *N* = 1 067 356

Time period	1967–1982		1983–1998		1999–2020	
	N	%	N	%	N	%
Maternal age (years)						
< 20	66 043	20.1	27 505	9.0	17 639	4.1
20–24	163 585	49.8	114 526	37.5	97 448	22.5
25–29	76 728	23.3	113 394	37.2	168 214	38.8
30–34	17 184	5.2	39 245	12.9	110 421	25.5
35–39	4264	1.3	9198	3.0	33 832	7.8
> = 40	922	0.3	1210	0.4	5998	1.4
Maternal education						
Low (≤ 13 years)	241 227	73.4	171 373	56.2	165 305	38.1
High (> 13 years)	85 388	26.0	131 503	43.1	254 536	58.7
Missing	2211	0.7	2202	0.7	13 711	3.2
Maternal country of birth						
Western women	254 926	77.5	270 875	88.8	383 222	88.4
Non-western women	1771	0.5	10 546	3.5	45 689	10.5
Missing	72 029	21.9	23 657	7.8	4641	1.1
Pregnancy complications						
No pregnancy complications	251 152	76.4	232 605	76.2	314 718	72.6
Any pregnancy complications[a]	77 574	23.6	72 473	23.8	118 834	27.4
Total	328 726	100.0	305 078	100.0	433 552	100.0

[a] Women with one or more of the seven complications: diabetes mellitus (before or during pregnancy), hypertension (before or during pregnancy), preeclampsia, post-term, premature rupture of membrane (membrane rupture for > 24 h and unspecified time), placental abruption and placenta previa

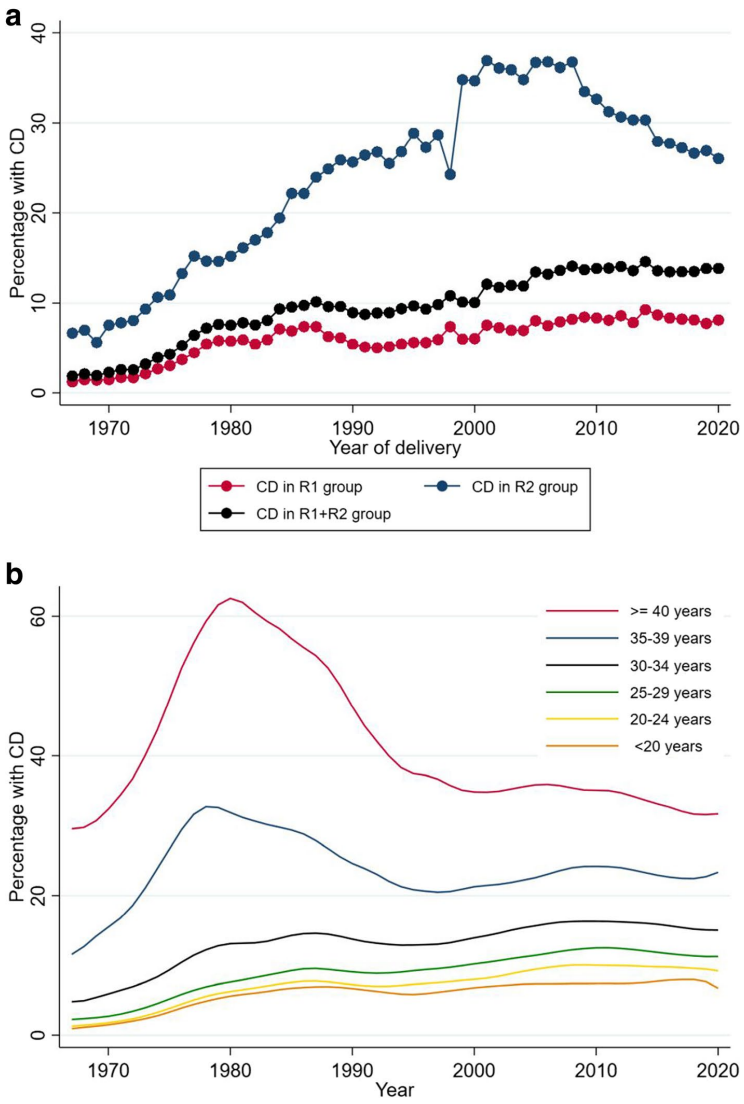

Fig. 2 **a** The Proportion of cesarean delivery (CD) among nulliparous women with singleton, cephalic and term birth by onset of labor: spontaneous onset (R1) and those with induction onset and pre-labor cesarean delivery (R2), 1967–2020, *N* = 1 067 356. **b** The Proportion of cesarean delivery (CD) among nulliparous women with singleton, cephalic and term birth by maternal age, 1967–2020, *N* = 1 067 356

declined, from 84.4 (1967–82) to 77.7% (1999–2020), while women having labor onset by induction or pre-labor CD increased, from 15.2% to 20.0% and from 0.4% to 2.4% respectively (Table S1). Women > = 40 years had the highest decline in spontaneous onset of birth, from 71.0% (1967–82) to 47.4% (1999–2020), followed by women aged 35–39, from 74.0% (1967–82) to 66.7% (1999–2020). On the other hand, proportion of women with induced labor onset increased from 23.2% to

42.0% in women > = 40 years and from 23.2 to 27.9% in women aged 35–39 years.

CD rates by onset of labor (spontaneous, induction and pre-labor CD), stratified by maternal age and time period, are presented in Table 2. The overall proportion of women having CD increased from 3.1% (1967–82) to 7.9% (1999–2020) and from 9.3% to 23.4% in the spontaneous onset- and induced onset group respectively. Among women with spontaneous onset of labor, CD increased in women < 35 years while it declined for women aged 35–39 years (from 18.3% to 13.3%) and for women above 40 years (35.0% to 17.5%). Similar changes in distribution across time and age groups were noted in women with induced onset of labor. For each respective maternal age group, proportion of CD was higher in women with onset of labor by induction than spontaneous labor, across all time periods. The contribution of pre-labor CD (R2b) to the group of women with induced or pre-labor CD (Robson R2) increased from 2.5% (1967–82) to 10.6% (1999–2020). This increment was found among women below 35 years while there was an inverse U form in women > = 35 years.

Table 2 Cesarean delivery (CD) among nulliparous women with singleton, cephalic and term birth by onset of labor: spontaneous onset (R1), induction (R2a) and pre-labor cesarean delivery (R2b) and time period, *N* = 1 067 356

Time period	1967–1982		1983–1998		1999–2020	
	n	CD (%)[a]	n	CD (%)	n	CD (%)
Spontaneous onset (R1)						
< 20	57,484	3.5	23,403	4.5	14,725	4.6
20–24	139,406	2.4	96,312	5.0	79,317	5.9
25–29	63,139	3.7	93,270	6.1	133,935	7.3
30–34	13,571	7.2	30,746	8.6	83,395	9.5
35–39	3156	18.3	6551	14.7	22,576	13.3
> = 40	655	35.0	710	28.7	2844	17.5
Total	277,414	3.1	250,992	6.1	336,792	7.9
Onset by induction (R2a)						
< 20	8406	7.0	3886	13.2	2657	13.7
20–24	23,718	7.9	17,266	15.7	16,688	18.5
25–29	13,253	9.6	18,922	19.2	31,240	21.4
30–34	3459	14.8	7678	24.1	23,958	25.9
35–39	1000	30.8	2150	33.3	9427	31.2
> = 40	214	45.8	300	44.0	2520	35.7
Total	50,050	9.3	50,202	19.0	86,490	23.4
Pre-labor cesarean delivery (R2b/R2[c])						
< 20	150	1.8	216	5.3	257	8.8
20–24	461	1.9	948	5.2	1443	8.0
25–29	336	2.5	1202	6.0	3039	8.9
30–34	154	4.3	821	9.7	3068	11.4
35–39	108	9.7	497	18.8	1829	16.2
> = 40	53	19.9	200	40.0	634	20.1
Total	1262	2.5	3884	7.2	10,270	10.6
All (R1 + R2a + R2b)						
< 20	66,043	2.9	27,505	6.5	17,639	7.3
20–24	163,585	3.5	114,526	7.4	97,448	9.4
25–29	76,728	5.1	113,394	9.3	168,214	11.6
30–34	17,184	9.5	39,245	13.6	110,421	15.6
35–39	4264	23.3	9198	23.7	33,832	23.0
> = 40	922	41.2	1210	44.3	5998	33.9
Total	328,726	4.4	305,078	9.4	433,552	13.1

[a] Total number of CD within the specific age group divided by total deliveries in the specific age group

[c] Summation of R2a and R2b

The sensitivity analysis, excluding women with any of the seven pregnancy/delivery complications, showed similar changes in CD over time and age groups for both the spontaneous—and induced onset groups. Within the group of women with either induced or pre-labor CD (R2), the proportion of pre-labor CD (R2b) was even higher after excluding women with complications, across all time periods. This shows that the increase in pre-labor CD over time was considerable among women without any of the seven pregnancy/delivery complications. Change in CD among nulliparous women in other Robson groups (breech (R6), transverse (R9) and preterm (R10)) is shown in Table S2.

Compared to women 20–24 years with spontaneous onset of labor and giving birth in 1967–82, the ARR of CD increased across periods in all age groups < 35 years while it was stable or slightly decreased in women > = 35 years (Fig. 3). ARR of CD in women > = 40 years decreased from 14.2 (95% CI 12.4–16.3) in 1967–82 to 6.7 (95% CI 6.2–7.4) in 1999–2020 in women with spontaneous labor onset and from 17.6 (95% CI 14.4–21.4) to 13.4 (95% CI 12.5–14.3) in those with induced onset. Except for women aged 35–39 with induced onset of labor, we found a linear trend in CD across all other maternal age groups (Table S3). Excluding women with any of the seven pregnancy/delivery complications did not change the CD trend across time and age groups. The ARR of CD was higher in women from non-western countries (1.7, 95% CI 1.70–1.73). There was an interaction between the effect of maternal age and education on the risk of CD (Likelihood-ratio test, $p < 0.001$). Our main results stratified on maternal education are shown in Table S4. The gradual declining risk of CD among women > = 35 years was more evident in those with high education than among those with low education. Results were similar after adjusting for smoking (restricted to births after 1999) and pre pregnancy BMI (restricted to births after 2007) (Table S5).

Discussion

Overall CD increased over time in nulliparous women with singleton, cephalic and term birth. The increment was mainly observed among women < 35 years, while it was stable or decreased in women > = 35 years. Although there has been increase in induction, risk of CD among women with induced labor decreased over time in women > = 40 years, while it was stable in women 35–39 years. On the contrary, induction was associated with more CD over time in younger women.

Our study focused on nulliparous women with singleton, cephalic and term births. These women account for 90% of nulliparous and 40% of all reproductive women in Norway [21]. The proportion of women aged > = 35 years at their first birth increased by time which is consistent to

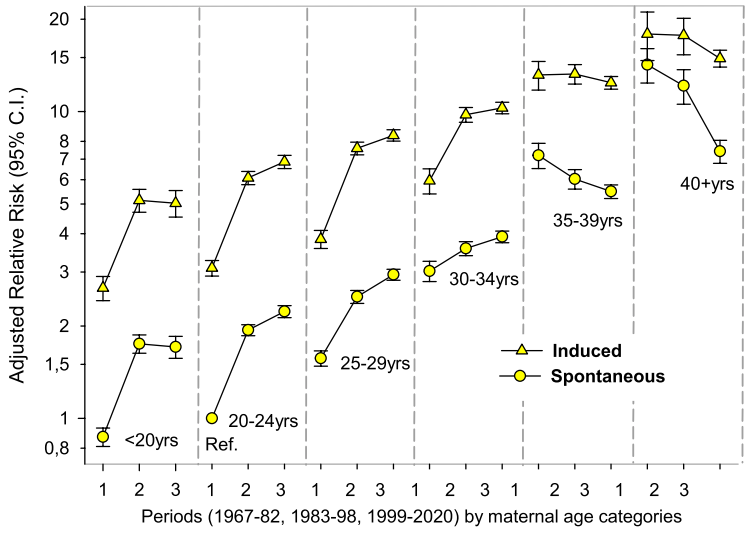

Fig. 3 Adjusted Relative risk (ARR[a]) of cesarean delivery in nulliparous women with singleton, cephalic and term birth, stratified by maternal age, onset of labor: spontaneous onset, and induction onset, and time periods, $N = 1\,051\,940$. **a** Adjusted for maternal education, mother's country of birth and birthweight

trends in other developed nations [11, 13, 15, 25]. Despite the growing number of Norwegian nulliparous women having their birth at a higher age, the increase in CD over time was found mainly among women < 35 years, while it was stable or reduced in older women. As advanced maternal age is strongly associated with higher risk of intrapartum CD due to higher prevalence of pregnancy complications [6] and biological changes in uterine contractility [11, 12], we expect a higher CD risk in the population of women > = 35 years in the last period. However, since first time delivery at advanced age was less frequent in the first period of our study, it may be that clinicians more often viewed advanced age in nulliparous women as an independent indication for CD in the first time period than in the last. This could explain the stable/decreasing trend in CD among older women. The occurrence of the seven pregnancy complications increase with maternal age [6], which in turn is associated with increased risk of CD [26]. However, excluding these women from our analyses did not change CD trend across time or age groups.

Change in women's preferences has been found to be another factor contributing to increased CD [9]. We found an increase in the proportion of R2b/R2 in the last relative to the first period and mainly among women < 35 years. This change over time was in fact larger in women without the common indications for CD. This increment could therefore not be explained by the studied pregnancy/delivery complications or other well-known obstetric indications, as we have excluded preterm, breech and multifetal pregnancies from our study population. It could be due to increased fear of giving birth or that women request CD for other reasons, without any evident medical or pregnancy complications [27]. An increase over time in other complications not captured by our list may also contribute some of this increment. A study from eight high income countries revealed knowledge gap as well as misconceptions about childbirth was more frequent in women who requested CD [9]. One out of 10 Norwegian women seemed to request CD with fear of pain, physical damages, and fear of insufficient support during delivery [28]. The recent increment in overweight and obesity in Norway, may also increase CD rates for all women [21]. For the years 2007–2020, we found the prevalence of overweight and obesity to be higher in nulliparous women aged > = 35 years than younger women, similar to the findings from Denmark [29].

Despite the demographic changes to women's age at first birth, CD declined over time among nulliparous Norwegian women > = 35 years. This reduction suggests an important scope with tackling higher CD rates in other countries. The general less medicalized approach to childbirth in the Nordic countries where majority of births are attained by midwives [2], could explain the low CD rates in Norway compared to other developed countries [15, 25]. The national recommendations regarding induction of labor in women versus expectant management of labor [8, 14] may also explain the gradual decline of CD rates for women > = 35 years.

On the relation between induction and CD, a recent Cochrane review on management of labor in women with term pregnancy found fewer CD in the induced group than those waiting for spontaneous onset of labor [14], in line with other studies [17–19]. In our study, the risk of CD was higher in women with induced than spontaneous onset of labor. We found that one out of five women with induced onset of labor had CD in 1999–2020, similar to a recent hospital based Norwegian study [26]. And only 8% of women with spontaneous onset of labor had CD in this period. Similarly, Ehrenthal et.al 2010 [16] and Davey et.al 2016 [15], reported higher risk of CD following induction in nulliparous women with term birth. Bergholt and colleagues reported that for every five-year increase in women's age, the risk of CD increased 3 to 5 times for women with induced labor [30]. Despite the increase in induction among women > = 40 years during our study period, the risk of CD declined in this age group. It could be argued that a more effective surveillance of labor with adherence to obstetric evidence-based practice could explain the decline in CD for this group [8, 14]. Besides women who have their first birth at advanced age are usually educated and with better socioeconomic support and with less risk factors such as smoking and overweight [31]. Declining CD rates among women > 35 were also reported in Sweden [13] and Canada [25].

A shift where CD is becoming more common among relatively younger nulliparous women should be concerning. The outcome of first pregnancy may affect women's further reproduction including CD recurrence [4]. This is especially the case for countries where having two or more children is common, like Norway [21]. Hence it is important to keep the CD rate low among all nulliparous women, and especially in the younger women without complications. Policy makers and clinicians need to adapt measures that aim at lowering CD in first-time mothers, especially in women with low education and from non-western countries. Future research assessing the impact of current CD trends on long-term women's health and reproduction is recommended.

Strength and limitations

Strengths of this study are the large sample size, the comprehensive prospective population follow-up over almost five decades, which make both selection bias and recall bias less likely. In addition, missing data were

low for most variables (< below 4%), except for country of birth during 1967–82. However, missing values for country of birth were evenly distributed by maternal age and education. Also, immigration to Norway during these years was low [21].

The study inherently has some limitations. Lack of data on the clinical indications for CD was handled by using pregnancy complications as a proxy for CD indication [26, 32]. We did, however, not have information on the two most common indications for CD, fetal distress and failure to progress [32]. Instead, we identified pregnancy complications that increase risk of both these two common indications. Changes in the reporting format in the MBRN is another limitation. Unlike checkboxes, notification based on free text may be linked to underreporting, especially of less severe complications [33] and a 3% error rate in completeness of CD notification for the years before 1984 has been reported [34]. This will likely have biased the result towards the null. Likewise, validity of data on initiated onset of labor (induced or pre-labor CD) was poor before the mid-1980s [35]. The findings after 1999 offer more precise and valid results. It's however important to highlight that there have been several changes in clinical practice and sociodemographic factors within the last period. Our findings may have also underestimated changes for women without the seven pregnancy complications as complications may have been underreported in the early years of the MBRN [23]. Some women assumed to be without complications in the early period may in fact have been with complications. However, this means that the true increase in CD in women without seven complications is likely larger than reported here. Data on smoking and BMI were only available after 1999 and 2007, respectively.

Conclusion

Monitoring CD is crucial to identify groups and factors contributing to high rates. This study described long-term changes in CD among Norwegian nulliparous women with singleton, cephalic term birth using large population-based data across five decades. A growing number of women are having their first birth at a higher age in Norway. The increase in CD rates in nulliparous women was mainly found among women < 35 years while it was stable or decreased in women > = 35 years. Despite the increase in induction among women > = 35 years during our study period, the risk of CD decreased in women > = 40 years while it was stable in women 35–39 years. The overall increase in CD rates cannot be explained solely by the shift in age of first-time mothers.

Abbreviations

CD: Cesarean delivery; MBRN: Medical Birth Registry of Norway; ARR: Adjusted relative risk; CI: Confidence interval; BMI: Body mass index.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-022-04755-3.

Additional file 1.

Acknowledgements

The Medical Birth Registry of Norway and Statistics Norway provided data for the analysis.

Authors' contributions

YTS, LMS and RS designed this study. YTS analyzed the data, wrote the draft manuscript text and is responsible for the reviewing and editing of the manuscript. LMS, RS, LGK, NHM and KK contributed with critical comments to the analyses, and in the writing and reviewing of this manuscript. YTS and LMS prepared Fig. 1 and Fig. 2. RS prepared Fig. 3. RS is guarantor for data quality. The author(s) read and approved the final manuscript.

Funding

This study was financially supported by The European Research Council under the European Union's Horizon 2020 Research and Innovation Program (ERC advanced grant 2018, agreement No 833076). The Norwegian Research Centre for Women's Health at Oslo University Hospital also contributed with financial support by adding human resources.

Availability of data and materials

Data belongs to the Norwegian Institute of Public Health and are only available to researchers who have applied for the data at the Medical Birth Registry of Norway. Restrictions apply to the availability of the data according to the license from the Regional Committee on Medical and Health Research Ethics. Data are however available from the Medical Birth Registry of Norway upon reasonable request and with permission from the Norwegian Institute of Public Health, [Access to data—NIPH (fhi.no)].

Declarations

Ethics approval and consent to participate

This observational study complies with the Decelerations of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics (REK VEST 2015/1728 and REK VEST 13818). Informed consent was not required as data were de-identified, and the researchers did not have any contact with participants.

Consent for publications

Note applicable.

Competing interests

The authors have stated no conflicts of interest in connection with this article.

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Received: 12 November 2021 Accepted: 10 May 2022
Published online: 18 May 2022

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Publisher's Note

Supplementary Information

Table S1. The proportion of nulliparous women with singleton, cephalic, term birth by onset of labor: spontaneous onset (R1), induction (R2a) and pre-labor cesarean delivery (R2b), stratified by maternal age and time period, N=1 067 356

Time period	1967-1982		1983-1998		1999-2020	
	n	(%) [a]	n	(%)	n	(%)
Spontaneous onset (R1)						
<20	57484	87	23403	85.1	14725	83.5
20-24	139406	85.2	96312	84.1	79317	81.4
25-29	63139	82.3	93270	82.3	133935	79.6
30-34	13571	79	30746	78.3	83395	75.5
35-39	3156	74	6551	71.2	22576	66.7
>=40	655	71	710	58.7	2844	47.4
total	277414	84.4	250992	82.3	336792	77.7
Onset by induction (R2a)						
<20	8406	12.7	3886	14.1	2657	15.1
20-24	23718	14.5	17266	15.1	16688	17.1
25-29	13253	17.3	18922	16.7	31240	18.6
30-34	3459	20.1	7678	19.6	23958	21.7
35-39	1000	23.5	2150	23.4	9427	27.9
>=40	214	23.2	300	24.8	2520	42
total	50050	15.2	50202	16.5	86490	20
Pre-labor cesarean delivery (R2b/R2 [b])						
<20	150	0.3	216	0.8	257	1.5
20-24	461	0.3	948	0.8	1443	1.5
25-29	336	0.4	1202	1.1	3039	1.8
30-34	154	0.9	821	2.1	3068	2.8
35-39	108	2.5	497	5.4	1829	5.4
>=40	53	5.8	200	16.5	634	10.6
total	1262	0.4	3884	1.3	10270	2.4
Total	328 726	100.0	305 078	100.0	433 552	100.0

[a] Number of women within the specific R group divided by total women in the specific age group.

[b] Summation of R2a and R2b

Table S2: Cesarean delivery (CD) among nulliparous women in the other Robson groups (Breech (R6), Transverse (R9) and Preterm (R10)) stratified by maternal age and time period

Time period	1967-1982		1983-1998		1999-2020	
	n	CD (%) [a]	n	CD (%)	n	CD (%)
Breech presentation (R6)						
<20	2219	26,9	885	41,9	570	31,2
20-24	5771	17,2	4425	40,9	3879	41,9
25-29	3246	7,8	5818	33,4	8856	58,7
30-34	834	4,3	2375	22	7310	73,7
35-39	214	4,2	611	18	2576	77,8
>=40	55	6,3	93	14,7	531	79
Total	12339	9,5	14207	30,8	23722	59,8
Transverse Presentation (R9)						
<20	27	47,9	15	29,1	12	22,9
20-24	61	27,1	66	31,1	79	41,8
25-29	45	12,8	87	25,3	198	62
30-34	24	6,3	57	17,3	242	76,3
35-39	4	2,2	23	12,2	164	85,6
>=40	7	8	8	8	74	84,1
Total	168	12,7	256	20,6	769	66,6
Preterm (R10)						
<20	5031	23,1	2072	43,2	1325	33,6
20-24	8403	16,7	6729	44,6	5598	38,7
25-29	3882	9	6551	37,2	9307	53,8
30-34	1184	6,6	2655	29,5	6198	63,9
35-39	370	7,5	813	26,3	2295	66,3
>=40	114	8,7	132	18,9	512	72,4
Total	18984	11,3	18952	36,4	25235	52,3

[a] Total number of CD within the specific age group divided by total deliveries in the specific age group

Table S3. Adjusted relative risk (ARR) of cesarean delivery among nulliparous women with singleton, cephalic, term birth by maternal age and time period, stratified on onset of labor, N=1 051 940

Variables		All women		Excluding women with complications [b]	
		Cesarean delivery by onset of labor ARR[a] (95% CI)		Cesarean delivery by onset of labor ARR[a] (95% CI)	
		Spontaneous onset (R1)	Onset by induction (R2a)	Spontaneous onset (R1)	Onset by induction (R2a)
<20 years	1967-82	0.9 (0.8-0.9)	2.7 (2.5-3.0)	0.9 (0.8-0.9)	3.4 (3.0-3.9)
	1983-99	1.8 (1.6-1.9)	5.2 (4.7-5.6)	1.8 (1.7-2.0)	5.6 (4.9-6.4)
	1999-2020	1.7 (1.6-1.9)	5.1 (4.6-5.6)	1.9 (1.8-2.1)	6.2 (5.3-7.3)
	P for trend	0.000(↑)	0.000(↑)	0.000(↑)	0.000(↑)
20-24 years	1967-82	1 (Ref)	3.1 (2.9-3.3)	1 (Ref)	3.5 (3.2-3.8)
	1983-99	1.9 (1.8-2.0)	6 (5.7-6.3)	2.0 (1.9-2.2)	6.3 (5.9-6.8)
	1999-2020	2.2 (2.1-2.3)	6.7 (6.4-7.0)	2.4 (2.2-2.5)	7.8 (7.3-8.3)
	P for trend	0.000(↑)	0.000(↑)	0.000(↑)	0.000(↑)
25-29 years	1967-82	1.5 (1.4-1.6)	3.7 (3.4-4.0)	1.6 (1.4-1.7)	4.1 (3.7-4.5)
	1983-99	2.4 (2.2-2.5)	7.2 (6.8-7.5)	2.5 (2.3-2.6)	7.7 (7.2-8.2)
	1999-2020	2.7 (2.6-2.8)	7.7 (7.4-8.0)	2.9 (2.8-3.1)	9 (8.4-9.5)
	P for trend	0.000(↑)	0.000(↑)	0.000(↑)	0.000(↑)
30-34 years	1967-82	2.9 (2.7-3.2)	5.7 (5.2-6.3)	3.1 (2.8-3.4)	6.5 (5.6-7.4)
	1983-99	3.3 (3.2-3.5)	9.1 (8.6-9.6)	3.6 (3.4-3.9)	10 (9.2-10.8)
	1999-2020	3.5 (3.4-3.7)	9.3 (8.9-9.7)	3.9 (3.7-4.1)	11 (10.3-11.7)
	P for trend	0.000(↑)	0.000(↑)	0.000(↑)	0.000(↑)
35-39 years	1967-82	7.0 (6.4-7.8)	12.9 (11.5-14.4)	7.6 (6.7-8.6)	15.8 (13.6-18.3)
	1983-99	5.6 (5.2-6.1)	12.5 (11.6-13.4)	6.3 (5.7-6.9)	14.4 (12.9-13.4)
	1999-2020	5.0 (4.7-5.2)	11.3 (10.8-11.8)	5.6 (5.2-5.9)	13.1 (12.3-11.8)
	P for trend	0.000(↓)	0.000(↓)	0.000(↓)	0.27(↓)
>=40 years	1967-82	14.2 (12.4-16.3)	17.6 (14.4-21.4)	16.7 (14.2-16.3)	19.6 (14.8-25.8)
	1983-99	11.4 (9.9-13.1)	16.9 (14.7-19.5)	13.2 (11.3-15.6)	20.8 (17.2-25.1)
	1999-2020	6.7 (6.2-7.4)	13.4 (12.5-14.3)	7.6 (6.8-8.5)	16.5 (15.1-18.0)
	P for trend	0.000(↓)	0.000(↓)	0.000(↓)	0.000(↓)
Mother's country of birth					
	Western women	1		1	
	Nonwestern women	1.7 (1.70-1.73)		1.83 (1.8-1.9)	
Birthweight [c]		1.00 (1.00-1.00)		1.00 (1.00-1.00)	

[a] adjusted for country of birth and birthweight

[b] Excluding women with any of the seven pregnancy complications (diabetes mellitus (before or during pregnancy), hypertension (before or during pregnancy), preeclampsia, post-term, premature rupture of membrane (membrane rupture for > 24 hour and unspecified time), placental abruption and placenta previa)

[c] Modeled as a continuous, linear term

(↑): increase in trend

(↓): decrease in trend

Table S4. Adjusted relative risk (ARR) of cesarean delivery among nulliparous women with singleton, cephalic, term birth by maternal age and time period, stratified on onset of labor and maternal education, N=1 051 940

		All women ARR[a] (95% CI)		Spontaneous onset (R1) ARR[a] (95% CI)		Onset by induction (R2a) ARR[a] (95% CI)	
		Low [b] education	High [c] education	Low education	High education	Low education	High education
<35years	1967-82	0.9 (0.8-0.9)	1.0 (Ref)	0.9 (0.8-0.9)	1.0 (Ref)	1.0 (0.9-1.1)	1.0 (Ref)
	1983-99	1.9 (1.8-1.9)	1.8 (1.7-1.8)	1.9 (1.7-1.9)	1.7 (1.6-1.8)	2.1(2.0-2.3)	2.0 (1.9-2.1)
	1999-2020	2.4 (2.3-2.5)	2.2 (2.1-2.3)	2.3 (2.2-2.4)	2.0 (1.9-2.1)	2.5 (2.4-2.7)	2.3 (2.2-2.5)
35-39years	1967-82	4.9 (4.4-5.4)	6.0 (5.3-6.7)	5.3 (4.6-6.0)	6.3 (5.4-7.3)	3.5 (3.0-4.0)	4.5 (3.8-5.3)
	1983-99	5.2 (4.8-5.6)	3.9 (3.7-4.3)	5.0 (4.5-5.6)	4.0 (3.6-4.4)	4.3 (3.9-6.4)	3.3 (2.9-3.7)
	1999-2020	4.7 (4.5-5.0)	3.8 (3.8-4.2)	4.4 (4.1-4.8)	3.7 (3.5-3.9)	3.8 (3.5-4.1)	3.2 (3.0-3.5)
>=40 years	1967-82	8.6 (7.5-9.9)	11.3 (9.3-13.7)	10.5 (8.9-12.4)	14.3 (11.2-18.3)	5.1 (3.9-6.4)	5.6 (4.0-7.7)
	1983-99	9.4 (8.2-10.8)	6.9 (5.9-8.1)	11.6 (9.7-13.8)	7.1 (5.8-8.8)	5.0 (4.1-6.2)	5.1 (4.2-6.2)
	1999-2020	6.6 (6.0-7.2)	5.9 (5.6-6.4)	6.2 (5.4-7.2)	4.9 (4.4-5.5)	4.2 (3.8-4.7)	4.0 (3.7-4.3)

[a] adjusted for country of birth and birthweight

[b] <=13 years

[c] > 13 years

Table S5: Adjusted relative risk (ARR) of cesarean delivery among nulliparous women with singleton, cephalic, term birth by smoking and pregestational body mass index, The Medical Birth Registry of Norway, 1999-2020

a. Smoking: The Medical Birth Registry of Norway, 2007-2020, n= 346 241

Variables	Crude RR (95% CI)	ARR[a] (95% CI)
Maternal age (years)		
<20	0.8 (0.7-0.8)	0.7 (0.7-0.8)
20-24	Reference	Reference
25-29	1.3 (1.2-1.3)	1.3 (1.3-1.4)
30-34	1.7 (1.6-1.7)	1.7 (1.7-1.8)
35-39	2.1 (2.1-2.2)	2.2 (2.1-2.3)
>=40	2.7 (2.5-2.8)	2.7 (2.6-2.9)
Year of delivery [b]	1.00 (0.9-0.9)	1.00 (0.9-0.9)
Onset of labor		
Spontaneous onset (R1)	1	1
Induced onset (R2a)	2.6 (2.6-2.7)	2.6 (2.5-2.6)
Maternal Education		
High (> 13 years)	1	1
Low (<=13 years)	1.3 (1.2-1.3)	1.2 (1.2-1.3)
Mother's country of birth		
Western women	1	1
Nonwestern women	1.7 (1.6-1.7)	1.8 (1.7-1.8)
Birthweight [b]	1.00 (1.0-1.0)	1.0 (1.0-1.0)
Smoking		
No		1
daily/sometimes		1.2 (1.1-1.2)

[a] adjusted for smoking

[b] Modeled as a continuous, linear term

a. Pregestational body mass index (BMI): The Medical Birth Registry of Norway, 2007-2020, n=181 148

Variables	Crude RR (95% CI)	ARR [a] (95% CI)
Maternal age (years)		
<20	0.7 (0.6-0.8)	0.7 (0.6-0.8)
20-24	Reference	Reference
25-29	1.3 (1.3-1.4)	1.3 (1.3-1.4)
30-34	1.8 (1.7-1.8)	1.8 (1.7-1.8)
35-39	2.3 (2.2-2.4)	2.2 (2.1-2.3)
>=40	2.7 (2.5-2.9)	2.6 (2.4-2.8)
Year of delivery [b]	0.99 (0.98-0.99)	0.99 (0.98-0.99)
Onset of labor		
Spontaneous onset (R1)	1	1
Induced onset (R2a)	2.4 (2.3-2.5)	2.2 (2.2-2.3)
Maternal Education		
High (> 13 years)	1	1
Low (<=13 years)	1.3 (1.2-1.3)	1.2 (1.1-1.2)
Mother's country of birth		
Western women	1	1
Nonwestern women	1.7 (1.7-1.8)	1.8 (1.8-1.9)
Birthweight [b]	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Smoking		
No	1	1
daily/sometimes	1.3 (1.2-1.4)	1.2 (1.1-1.3)
BMI [b]		1.04 (1.03-1.04)

[a] adjusted for BMI

[b] Modeled as a continuous, linear term

II

American Journal of Epidemiology

Vol. 192, No. 8
https://doi.org/10.1093/aje/kwad075
Advance Access publication:
May 30, 2023

Original Contribution

Birth Weight in Consecutive Pregnancies and Maternal Cardiovascular Disease Mortality Among Spontaneous and Iatrogenic Term Births: A Population-Based Cohort Study

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Initially submitted July 15, 2022; accepted for publication March 27, 2023.

Knowledge on the association between offspring birth weight and long-term risk of maternal cardiovascular disease (CVD) mortality is often based on firstborn infants without consideration of women's consecutive births. We studied long-term CVD mortality according to offspring birth weight patterns among women with spontaneous and iatrogenic term deliveries in Norway (1967–2020). We constructed birth weight quartiles (Qs) by combining standardized birth weight with gestational age in quartiles (Q1, Q2/Q3, and Q4) for the women's first 2 births. Mortality was estimated using Cox regression and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Changes in offspring birth weight quartiles were associated with long-term maternal CVD mortality. Compared with women who had 2 term infants in Q2/Q3, women with a first offspring in Q2/Q3 and a second in Q1 had higher mortality risk (HR = 1.33, 95% CI: 1.18, 1.50), while risk was lower if the second offspring was in Q4 (HR = 0.78, 95% CI: 0.67, 0.91). The risk increase associated with having a first infant in Q1 was eliminated if the second offspring was in Q4 (HR = 0.99, 95% CI: 0.75, 1.31). These patterns were similar for women with iatrogenic and spontaneous deliveries. Inclusion of information from subsequent births revealed heterogeneity in maternal CVD mortality which was not captured when using only information based on the first offspring.

birth weight; cardiovascular disease; cardiovascular disease mortality; consecutive pregnancies; iatrogenic delivery; pregnancy; spontaneous delivery; term birth

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; ICD, *International Classification of Diseases*; MBRN, Medical Birth Registry of Norway; Q, quartile.

Low infant birth weight is associated with increased risk of maternal cardiovascular disease (CVD) mortality (1). However, there are inconsistent findings regarding the association between large infants and long-term maternal mortality (1). While the lowest CVD mortality is found among women with large infants in some populations (2–5), other investigators report a higher risk of CVD mortality among women with large babies (6–8). Most of these studies include preterm births, which are known to be independently associated with long-term maternal CVD mortality (9). To our knowledge, no previous studies have focused on these relationships among term births only, which comprise the majority of all births. Furthermore, most of the published literature pertains to women's firstborn infants (2–8, 10) without consideration of subsequent births, which could lead to biased estimates (11). Both recurrence and order of complications in subsequent pregnancies affect mortality risk (9).

When studying the relationship between offspring birth weight and future maternal health, measures that account for birth weight variation by gestational age may be more informative than absolute birth weight (7), especially when preterm births are included (6). However, gestational age variation, even within the term period, has been shown to be related to future maternal CVD mortality (9), indicating that when studying term births only, standardizing birth weight for gestational age may also be needed. Moreover, the gradual rise in labor induction and cesarean delivery might

influence both offspring gestational age and birth weight distribution (12). Except for the study by Rich-Edwards et al. (9), no study (to our knowledge) has investigated the relationship between gestational age and long-term maternal mortality specifically with regard to spontaneous and iatrogenic deliveries in term pregnancies.

In the present study, we wanted to evaluate heterogeneity in maternal CVD mortality risk according to change in offspring birth weight by gestational age among women with 2 term births. Using linked data from population-based registries in Norway, we tested the hypothesis that changes in offspring birth weight quartiles from the first pregnancy to the second influence long-term risk of maternal CVD mortality. We also wanted to evaluate whether associations differ by type of delivery (spontaneous vs. iatrogenic delivery).

METHODS

Data sources

This was a population-based cohort study using data from the Medical Birth Registry of Norway (MBRN), which has been based on mandatory notification of all births taking place in the country from 16 gestational weeks onward since 1967 (13). Data are collected on demographic characteristics, reproductive history, and the mother's health before and during pregnancy, including delivery complications and infant outcomes. The attending clinician is responsible for filling out the forms. Information was based on free text descriptions until 1998, while checkboxes were added in 1999. By means of the national identification number assigned to all residents of Norway, data from the MBRN were linked to the Norwegian Cause of Death Registry and the National Education Database of Statistics Norway. Births to the same women were identified, keeping the mother as the unit of analysis.

Our study complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics. Informed consent was not required, since the data were deidentified, and the researchers did not have any contact with participants. We followed the STROBE checklist (Strengthening the Reporting of Observational Studies in Epidemiology; https://www.strobe-statement.org/) for cohort studies (see Web Table 1, available at https://doi.org/10.1093/aje/kwad075).

Inclusion and definitions

We included women with 2 or more births whose first birth was registered between 1967 and 2013, providing women with at least 7 years to have finished their reproduction. About 95% of Norwegian women have their second child within 7 years of the first (11). We focused on women's first 2 births, and among these we excluded women with multiple pregnancies, women who were missing data on gestational age or birth weight, preterm deliveries (<37 weeks), pregnancies with a standardized offspring birth weight (z score) less than −5 or greater than 5, and pregnancies with a gestational age greater than 46 weeks.

Term delivery was defined as birth at 37 weeks' gestation or later. Estimation of gestational age was based on the date of the last menstrual period. Ultrasound-based gestational age estimation, available in the MBRN from 1999 onward, was used for women with missing information on the last menstrual period or with a difference of more than 10 days between the last menstrual period and ultrasound-based estimation. The date of embryo transfer plus 14 days was used for infants conceived by in vitro fertilization (available in the MBRN from 1985). Birth weight was registered in grams. The validity of registered gestational age and birth weight data in the MBRN is high (14). Estimates of birth weight by gestational age z score were calculated using mean values and standard deviations from the Norwegian population (12). We calculated parity-specific standardized quartiles (25th, 50th, and 75th percentiles) of offspring birth weight (in grams) by gestational week for women's first and second births, respectively. The parity-specific cutoff points for offspring birth weight quartiles were defined from a population of women with singleton term births. Based on the linear trend between quartiles of birth weight by gestational age and maternal CVD mortality, we merged Q2 and Q3. Offspring birth weight quartiles for the first and second births (Q1, Q2/3, Q4) were combined into one exposure variable consisting of 9 categories: Q1-Q1, Q1-Q2/3, Q1-Q4, Q2/3-Q1, Q2/3-Q2/3 (reference category), Q2/3-Q4, Q4-Q1, Q4-Q2/3, and Q4-Q4. The changes in offspring birth weight quartiles from the first pregnancy to the second constituted the pattern of offspring birth weight by gestational age quartile.

Medical interventions that end pregnancies before their natural endpoint, such as induction of labor and prelabor cesarean delivery, might influence offspring birth weight quartiles. To assess whether our results differed among women who delivered spontaneously or had iatrogenic deliveries, we stratified the analyses on the basis of type of labor onset. "Spontaneous delivery" included women with spontaneous labor onset in both pregnancies, while women with either induced labor or prelabor cesarean delivery in the first and/or second pregnancy were grouped as having "iatrogenic delivery."

Information on cigarette smoking (no (referent) or yes (daily/sometimes)) and body mass index (BMI; weight (kg)/height $(m)^2$) was available from 1999 onwards and 2006 onwards, respectively.

Maternal mortality was registered in the Cause of Death Registry using *International Classification of Diseases* (ICD) codes. For our main analyses, we combined deaths due to ischemic heart disease (*International Classification of Diseases, Eighth Revision* (ICD-8) and *International Classification of Diseases, Ninth Revision* (ICD-9) codes 410–414; *International Classification of Diseases, Tenth Revision* (ICD-10) codes I20–I25) and cerebrovascular disease/stroke (ICD-8 and ICD-9 codes 430–438; ICD-10 codes 160–I69) into one group ("cardiovascular deaths"). We also examined all-cause mortality, circulatory system diseases (ICD-8 and ICD-9 codes 390–459; ICD-10 codes I00–I99), and noncirculatory diseases (all deaths other than those included in the "circulatory system diseases" definition) mortality.

Statistical analyses

Frequency and contingency tables were used when constructing parity-specific cutoff points for all first and second births (Web Table 2). Categorical variables were summarized using proportions, while continuous variables were summarized with mean values and standard deviations. Mortality was estimated using Cox proportional hazards models providing hazard ratios (HRs) and 95% confidence intervals (CIs), with woman's age as the underlying time variable. Women were considered at risk of CVD mortality from their last pregnancy to either death or censoring, whatever came first. In our data there seemed to be no excess maternal CVD mortality by pregnancy complications after the age of 70 years. As a result, we right-censored all observations at the age of 70 years (if women were not already deceased). Schoenfeld residuals were checked for any evidence of deviation from the proportional hazards assumption. In addition to the cause-specific hazard models, we also fitted a subdistribution hazard model to account for competing risk (15).

We performed 2 main analyses when estimating maternal CVD mortality risk. First, we used only information from women's first birth. Women with spontaneous first deliveries in Q2/3 were designated the reference group. Second, we calculated mortality risks by combining standardized birth weight data from first and second births. Women with both offspring in Q2/3 and spontaneous delivery were the reference group in these analyses. Estimates were adjusted for maternal age at first birth (years; continuous), year of last delivery, maternal education ($<$11 years (low) vs. $\geq$11 years (high; referent)), and pregnancy complications.

Several sensitivity analyses were performed. We excluded women with known risk factors for CVD (in both pregnancies), including pregnancy complications (chronic/gestational hypertension, pregestational/gestational diabetes mellitus, perinatal loss (included stillbirths and early neonatal death occurring within 1 week after birth), placental abruption and preeclampsia (16), offspring congenital malformations (17), and subfertility issues (conception by in vitro fertilization) (18)). In addition, we performed separate analyses to minimize confounding by ethnicity (19) (analyzing only women of Nordic origin), to account for the potential influence of different fathers (20) (analyzing women with the same partner), to account for interpregnancy interval (categorized as $<$12.0 months, 12.0–23.9 months, 24.0–35.9 months, and $\geq$36.0 months) (21), to account for full-term gestations (restricted to 39–41 weeks) (9), and to assess the influence of higher parity on mortality patterns (analyzing the first and third offspring among the first 3 term deliveries).

Due to missing information on maternal smoking and prepregnancy BMI, we also performed E-value–based sensitivity analysis to determine the extent to which unmeasured confounding may have influenced the observed association (22). The E-value estimates the HR for an unmeasured confounder and is interpreted as the magnitude of the unmeasured confounder required to draw the observed HR closer to the null (22). The formula $\mathrm{HR} + \sqrt{[\mathrm{HR} \times (\mathrm{HR} - 1)]}$ was applied to HRs greater than 1; for HRs less than 1, we took the inverse of the observed HR and then applied the formula.

STATA, version 17 (StataCorp LLC, College Station, Texas), was used for all statistical analyses.

RESULTS

After exclusions (Figure 1), the study sample consisted of 735,244 women who had their first 2 singleton term births during the period 1967–2020 (Table 1). Spontaneous delivery was registered in 82.3% of first pregnancies and iatrogenic delivery in 17.7%. Women with spontaneous deliveries in the first pregnancy had lower mean maternal age and offspring birth weight, were more frequently smokers, and more often had a low educational level than women with iatrogenic deliveries. On the other hand, women with iatrogenic deliveries had a higher proportion of pregnancy complications, a higher proportion of offspring with congenital anomalies, and more frequently conception by in vitro fertilization. The most common complications among iatrogenic births were preeclampsia, chronic/gestational hypertension, and pregestational/gestational diabetes mellitus.

Among the 735,244 included women, 32,129 died, with 3,037 deaths being from cardiovascular causes. In Figure 2 (Web Table 3), we present data on maternal CVD death based on first offspring quartiles (overall model) and stratified by onset of labor in the first pregnancy. Compared with women whose first offspring was delivered spontaneously with a standardized birth weight in Q2/3, mortality was highest among women whose first offspring's birth weight was in Q1, ranging from HR = 1.41 (95% CI: 1.28, 1.54) for spontaneous delivery to HR = 1.48 (95% CI: 1.26, 1.74) for iatrogenic delivery. On the other hand, mortality was lowest (HR = 0.86, 95% CI: 0.77, 0.96) among women with spontaneous delivery and a first offspring in Q4. Figure 3 (Web Table 4) presents adjusted HRs for CVD mortality based on information from both the first and second offspring birth weight quartiles. Regardless of first offspring birth weight quartile, there was a decreasing trend in HR estimates if the second offspring was larger. Maternal mortality was highest if both offspring were in Q1 (HR = 1.66, 95% CI: 1.49, 1.85), as compared with women whose first 2 births were in Q2/3. The risk increase associated with a first infant in Q1 was eliminated, however, if the second offspring was in Q4 (HR = 0.99; 95% CI: 0.75, 1.31). For women with a first offspring in Q2/3, the risk of CVD death was higher if the second offspring was in Q1 (HR = 1.33, 95% CI: 1.18, 1.50) but lower if the second offspring was in Q4 (HR = 0.78, 95% CI: 0.67, 0.91). Similarly, for women who started out with an offspring in Q4, the relative mortality risk was highest if the second child was in Q1 (HR = 1.26, 95% CI: 0.99, 1.60) and lowest if the second child was also in Q4 (HR = 0.80, 95% CI: 0.69, 0.93).

A total of 518,961 women (70.6%) had spontaneous deliveries in both pregnancies, while 216,283 women (29.4%) had an iatrogenic delivery in the first and/or second pregnancy. Among women with a spontaneous first delivery, 11.8% had an iatrogenic delivery in the second pregnancy, while 5.6% of the women had an iatrogenic delivery in both pregnancies. Figure 4 (Web Table 5) shows maternal CVD mortality based on information from both the first

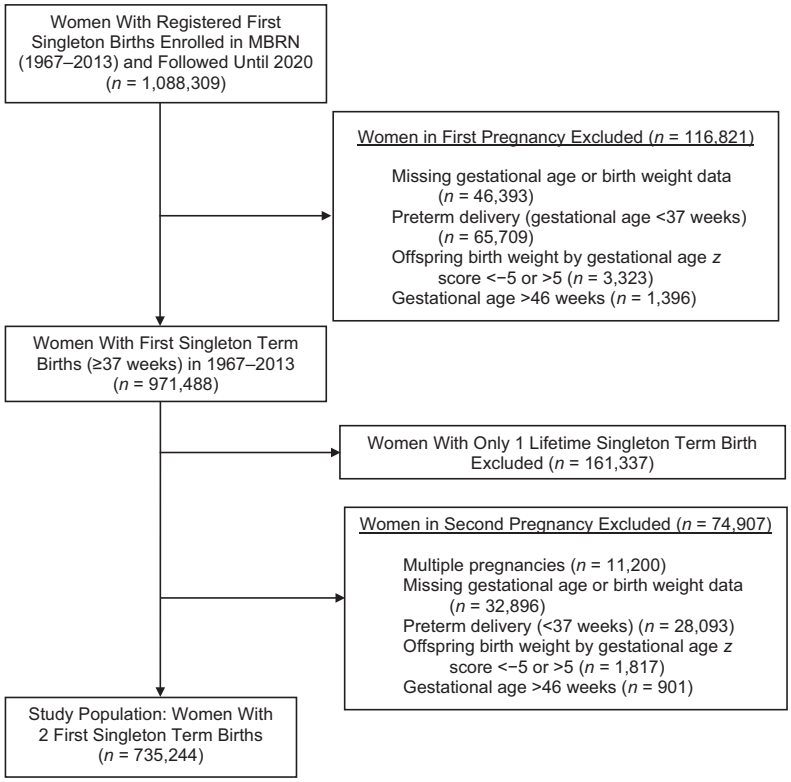

Figure 1. Selection of women with 2 first singleton term births from the Medical Birth Registry of Norway (MBRN) for a study of heterogeneity in maternal cardiovascular disease mortality risk according to change in offspring birth weight by gestational age, Norway, 1967–2020.

and the second births, stratified by labor onset. Compared with having 2 births in Q2/3, HR estimates decreased if the second offspring was larger than the first and increased if it was smaller, independent of delivery type (iatrogenic or spontaneous). In most of the quartile groups, women with iatrogenic delivery had higher relative mortality risk than women with spontaneous delivery; however, 95% CIs overlapped. If first births were in Q1, point estimates for women with induced deliveries were higher. The differences were smaller for women with first births in Q2/Q3 and not visible for first births in Q4.

Sensitivity analysis excluding women with pregnancy complications, offspring congenital anomalies, and conception by in vitro fertilization did not change the CVD mortality pattern but attenuated risk (Web Table 6). Similarly, restricting the analysis to women born in Nordic countries who had children with the same partner or to births with a gestational age of 39–41 weeks did not change the mortality pattern. Adjusting for all of these factors, including interpregnancy interval, did not change the mortality patterns.

E-values ranged from 1.11 to 2.71, implying that unmeasured confounding of this extent was required to explain the observed associations. We also observed similar patterns between change in offspring birth weight quartiles from the first pregnancy to the second pregnancy and maternal risk of dying from all causes, circulatory causes, and noncirculatory causes (Web Table 7). Mortality estimates were similar in both hazard models (cause-specific and subdistribution) (Web Table 8). Finally, mortality patterns were similar for women with 3 term births (Web Table 9).

Out of 1,088,309 women, 7.3% (n = 79,289) had missing data on either offspring gestational age or birth weight for the first 2 births. These women were younger and had higher proportions of persons with low education, pregnancy complications, and iatrogenic deliveries than the study population (data not shown). For those who gave birth after 1998, women with missing data were also more often smokers.

DISCUSSION

Including information on both the first and the second infant's birth weight by gestational age revealed heterogeneity in long-term maternal CVD mortality which was

Table 1. Characteristics of First Pregnancies (as Registered in the Medical Birth Registry of Norway) for 735,244 Women Whose First 2 Offspring Were Singleton Term Births, Norway, 1967–2020

Characteristic	All Women		Type of Labor Onset in First Pregnancy			
			Spontaneous Delivery[a]		Iatrogenic Delivery[b]	
	No.	%	No.	%	No.	%
No. of women	735,244	100	605,419	82.3	129,825	17.7
Maternal age, years[c]	24.7 (4.4)		24.5 (4.4)		25.5 (4.7)	
Offspring birth weight, g[c]	3,514.8 (474.9)		3,505.6 (459.8)		3,557.8 (537.7)	
Maternal education, years[d]						
<11 (low)	129,526	17.7	107,723	17.9	21,803	16.9
≥11 (high)	601,642	82.3	494,450	82.1	107,192	83.1
Maternal birth in a Nordic country[e]	605,684	91.9	498,125	92.1	107,559	90.9
Pregnancy complications						
Pregestational/gestational diabetes mellitus	4,860	0.7	2,470	0.4	2,390	1.8
Chronic/gestational hypertension	15,018	2.0	9,759	1.6	5,259	4.1
Perinatal mortality	3,271	0.4	1,869	0.3	1,402	1.1
Placental abruption	1,826	0.3	1,174	0.2	652	0.5
Preeclampsia	25,800	3.5	11,644	1.9	14,156	10.9
Full-term birth (39–41 weeks' gestation)	527,206	71.6	452,920	85.9	74,286	14.1
Congenital anomaly in offspring	24,773	3.4	19,185	3.2	5,588	4.3
In vitro fertilization[f]						
No	472,808	98.8	346,670	98.9	81,138	98.2
Yes	5,394	1.2	3,927	1.1	1,468	1.8
Cigarette smoking[g]						
No	172,757	91.5	138,205	91.2	34,552	92.6
Yes	16,131	8.5	13,375	8.8	2,756	7.4

[a] Women with spontaneous onset of labor during the first pregnancy.
[b] Women with either induced labor onset or prelabor cesarean delivery during the first pregnancy.
[c] Values are expressed as mean (standard deviation).
[d] Information was missing for 4,076 women (0.6%).
[e] Nordic countries included Norway, Denmark, Finland, Iceland, and Sweden. Information was missing for 76,149 women (10.4%).
[f] Data on in vitro fertilization were available from 1985 onward (n = 478,202).
[g] Data on smoking were available from 1999 onward (n = 237,016). Information was missing for 48,128 women (20.3%).

not captured when only using information based on the first offspring. Women whose first infants had similar birth weights differed in their long-term mortality risk depending on their second infants' birth weights. This was true for both women with spontaneous deliveries and women with iatrogenic deliveries.

In the present study, we found that women with 2 term births in the lowest birth weight quartile (Q1) had up to 66% increased CVD mortality risk compared with women with 2 births in Q2/3. On the other hand, giving birth to a term second offspring in the highest quartile (Q4) was associated with similar or lower long-term maternal mortality, independent of the first offspring's birth weight quartile. This was unexpected, as fetal growth acceleration is associated with reduced glucose tolerance (6, 23, 24). One plausible explanation could be that the prevalence of diabetes in Norway was generally low in the earlier years of the registry (25), when 75% of the mothers who died from CVD in our study had their first child. Other explanations could be socioeconomic status and behavioral risk factors. Women giving birth to large infants were highly educated and less likely to smoke (during the years when smoking was registered).

Changes in offspring birth weight quartiles from the first birth to the subsequent birth seem to capture heterogeneity in maternal CVD mortality risk and illustrate that moving from one birth weight quartile to another between the first birth and the second adds valuable information with regard to a woman's future risk of CVD death: Within all birth weight quartiles of first offspring, maternal relative risk of CVD death decreased by increasing second offspring quartile. Moving from higher quartiles of offspring birth weight to

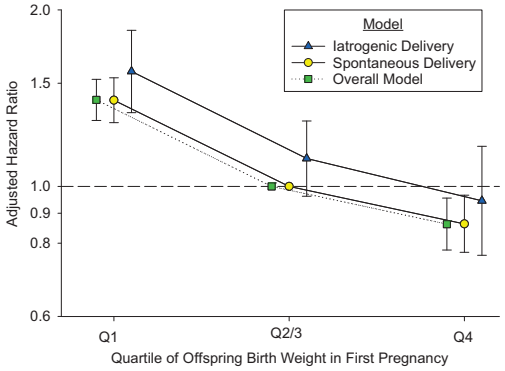

Figure 2. Adjusted hazard ratios for long-term maternal cardiovascular disease mortality by quartile (Q) of offspring birth weight among women whose first 2 singletons were born at term (*n* = 735,244), based on women's first birth and stratified by onset of labor, Norway, 1967–2020. Iatrogenic deliveries included women with either induced onset of labor or prelabor cesarean delivery during the first pregnancy; spontaneous deliveries included women with spontaneous onset of labor during the first pregnancy. Women with offspring in Q2/3 and spontaneous labor onset during the first pregnancy were the common reference group for the model including spontaneous and iatrogenic deliveries. Women with the first offspring in Q2/3 were the reference group in the overall model. Hazard ratios were adjusted for maternal age at first birth, year of last delivery, maternal education, and pregnancy complications (chronic or gestational hypertension, pregestational or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, congenital malformations, and conception by in vitro fertilization) in the first and/or second pregnancies. Bars, 95% confidence intervals.

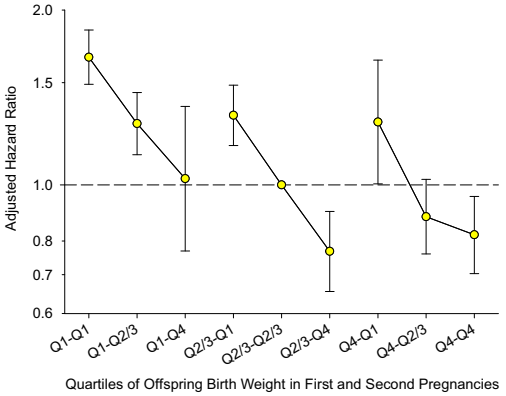

Figure 3. Adjusted hazard ratios for long-term maternal cardiovascular disease mortality by quartile (Q) of offspring birth weight among women whose first 2 singletons were born at term (*n* = 735,244), based on women's first and second births, Norway, 1967–2020. Hazard ratios were adjusted for maternal age at first birth, year of last delivery, maternal education, and pregnancy complications (chronic or gestational hypertension, pregestational or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, congenital malformations, and conception by in vitro fertilization) in the first and/or second pregnancies. Women whose first 2 offspring were in Q2/3 were the reference group. Bars, 95% confidence intervals.

lower quartiles in consecutive births was, in most cases, associated with a higher mortality risk than was found for women with both infants in the middle birth weight quartiles. However, moving from a lower birth weight quartile to a higher quartile was only associated with reduced mortality risk when the first offspring was in Q2/Q3 and the second was in Q4, indicating that having a first infant in the lowest birth weight quartile is a relatively stable marker of future mortality risk. This heterogeneity in CVD risk according to change in offspring birth weight quartiles might be masked if only the first infant's birth weight information is used, as previous studies have done (2–8, 10).

CVD mortality has been found to be higher in iatrogenic deliveries than in spontaneous preterm deliveries (9, 26). The explanation for this is likely to be the higher risk of additional adverse pregnancy complications in women with iatrogenic preterm deliveries which also may be the underlying cause of preterm delivery (26). However, in this study, we found a less clear distinction between spontaneous and iatrogenic term deliveries, which could have been due to a healthier population of women, since we included only term births. For women with a first birth in Q1, however, the risk seemed higher in the iatrogenic group. In general, term complications were more common in the iatrogenic group, which could indicate that pregnancies in this group were more often affected by conditions related to placental dysfunction (27). Preeclampsia, for instance, is a well-known complication associated with women's long-term CVD mortality (16). However, it is possible that term complications are associated with future CVD mortality risk to a lesser extent than preterm complications, since complications that reach term may be less severe than similar complications with preterm delivery. Severity of complications may also be a factor of importance for future maternal mortality risk—shown, for instance, for preterm preeclampsia, which has a stronger association with future CVD mortality than does term preeclampsia (11). Changes in obstetrical practice have resulted in an increase in the number of women undergoing induction of labor or prelabor cesarean delivery (28), which could influence offspring gestational age and birth weight (12) and may also have influenced our classifications of birth weight quartiles. With the rise in interventions, there has been an increase in the number of women giving birth at early term, which is associated with increased risk of CVD mortality (9). However, excluding these women did not change the pattern of mortality by offspring birth weight quartile.

Strengths of this study include its population-based design, the large sample size, prospectively collected data, and low proportions of missing data. Long-term mortality risk was assessed using information from women's 2 subsequent

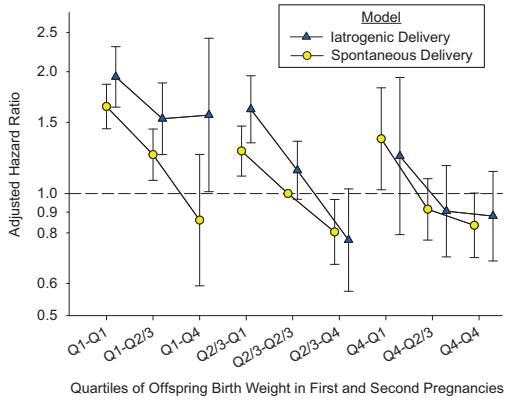

Figure 4. Adjusted hazard ratios for long-term maternal cardiovascular disease mortality by quartile (Q) of offspring birth weight among women whose first 2 singletons were born at term (n = 735,244), based on women's first and second births and stratified by onset of labor, Norway, 1967–2020. Iatrogenic deliveries included women with either induced onset of labor or prelabor cesarean delivery in the first and/or second pregnancy (n = 216,283); spontaneous deliveries included women with spontaneous labor onset in both the first and second pregnancies (n = 518,961). Women with offspring in Q2/3 and spontaneous onset of labor during both the first pregnancy and the second pregnancy were the reference group. Hazard ratios were adjusted for maternal age at first birth, year of last delivery, maternal education, and pregnancy complications (chronic or gestational hypertension, pregestational or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, congenital malformations, and conception by in vitro fertilization) in the first and/or second pregnancies. Bars, 95% confidence intervals.

births (both live births and stillbirths). We had follow-up for maternal deaths occurring up to 53 years after women's first birth, median follow-up being 24 years. By using standardized offspring birth weight and parity-specific cutoff values when grouping infants into quartiles, we minimized the possibility of exposure misclassification. The use of observed birth weight–by–gestational age charts in the term population is likely to have been reasonably valid, with little variation and bias (29). The majority of women in Norway continue on to a second pregnancy (11), and restricting our analysis to the first 2 births among women with 2 or more births was likely to limit the influence of selection.

There were some limitations in our study, however, including lack of data on CVD risk factors such as nutritional intake, physical activity, and other environmental factors. Pregnant women were not routinely screened for gestational diabetes before the mid-1980s in Norway (25). Similarly, the validity of data on the onset of labor was low during this first period (14). Our study population included women with the first 2 term births, while excluding those with missing data on birth weight and gestational age. Most of the missing information was accounted for by missing data on gestational age. We therefore used absolute birth weight quartiles to compare CVD mortality patterns among all women and excluding those with missing gestational age data in the first 2 pregnancies. We used 2,500 g as the lower limit of the first quartile to have a "cutoff value" leaning towards preterm births. We found a similar mortality pattern, showing that exclusion of the women with missing gestational age data did not change our result. Data on smoking and BMI were only available for the later years. To account for unmeasured confounding by smoking and BMI, we conducted a sensitivity analysis using E-values, which revealed that a substantial unmeasured confounder with an HR of at least 2.71 would be required to explain the observed HR associated with consecutive births in Q1. Given that not all unmeasured confounders are working in the same direction, the E-value of 2.71 was probably a minimum value of what would be needed for smoking to fully explain our observed association in the Q1-Q1 birth weight category, where smoking was estimated to be most prevalent. Furthermore, in a Swedish cohort study evaluating fetal growth and later maternal CVD, results were not altered after adjustment for smoking and BMI (10). Moreover, we argue that our most robust finding is likely to hold even after adjustment for both BMI and smoking, as the Swedish and Norwegian populations are similar in terms of population characteristics and universal free and accessible health care. Some women may give birth to constitutionally small babies whose small size was not caused by any pathological processes (19). Finally, we expect that these results would apply to other populations with similar population characteristics.

Health implications

Current guidelines (30) recommend enhanced screening for CVD among women with a history of low offspring birth weight. Given that a majority of women have more than 1 child (84% in Norway) (11), failing to include information on subsequent offsprings' birth weight may be a missed opportunity for identifying women at high risk of CVD mortality. Moreover, risk factor identification based solely on the first birth may in fact be erroneous. Change in offspring birth weight quartiles could capture heterogeneity in CVD risk, allowing for more precise prediction of mothers' future risk of CVD death.

Conclusion

Changes in offspring birth weight quartile from the first pregnancy to the second may offer important information on heterogeneity in women's future risk of CVD death. Within all birth weight quartiles of first offspring, maternal relative risk of dying from CVD decreased by increasing quartile of the second offspring, with a similar pattern being observed among spontaneous and iatrogenic deliveries. Women with a first offspring in the lowest birth weight quartile seem to have more consistently increased CVD mortality risk and may benefit from intervention aimed at preventing and reducing future risk of CVD. Our findings highlight the importance of including information from women's subsequent births for identification of high-risk subgroups for specific follow-up.

ACKNOWLEDGMENTS

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This work was supported by the European Research Council (ERC) under the European Union's Horizon 2020 Research and Innovation Programme (ERC advanced grant 2018; agreement 833076).

The data underlying this article were provided by the Norwegian Institute of Public Health by permission. The Norwegian Institute of Public Health can provide access to data from the Medical Birth Registry of Norway, after an application for the data has been approved.

This work was presented at the 35th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, Chicago, Illinois, June 13–14, 2022.

The views expressed in this article are those of the authors and do not reflect those of the funder.

Conflict of interest: none declared.

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WEB MATERIAL

Birth Weight in Consecutive Pregnancies and Long-Term Maternal Cardiovascular Disease Mortality Among Spontaneous and Iatrogenic Term Births: A Population-Based Cohort Study

Yeneabeba Tilahun Sima, Rolv Skjaerven, Liv Grimstvedt Kvalvik, Nils-Halvdan Morken, Kari Klungsøyr, Janne Mannseth, and Linn Marie Sørbye

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Contents:

Web Table 1. STROBE Statement—Checklist of Items That Should Be Included in Reports of Cohort Studies

	Item No.	Recommendation	Author's Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	See Title.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	See Abstract.
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	See Introduction, paragraph 1 and 2.
Objectives	3	State specific objectives, including any prespecified hypotheses	See Introduction, paragraph 3.
Methods			
Study design	4	Present key elements of study design early in the paper	See Title and "Data sources" in Material and Methods, paragraph 1.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	See "Data sources" in Material and Methods, paragraph 1.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	See "Inclusions and definitions" in Material and Methods, paragraph 1 and Figure 1.

		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	See "Inclusions and definitions", in Material and Methods, paragraph 2 and 3. Diagnostic criteria see "Inclusions and definitions", paragraph 2.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	See "Data sources" and "Inclusions and definitions", in Material and Methods.
Bias	9	Describe any efforts to address potential sources of bias	See "Statistical analyses".
Study size	10	Explain how the study size was arrived at	See "Inclusions and definitions", in Material and Methods, paragraph 1 and Figure 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	See "Inclusions and definitions" in Material and Methods, paragraph 2 and 3. See Table1
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	See "Statistical analyses". See S5 Table, S6 Table and S7 Table.
		(*b*) Describe any methods used to examine subgroups and interactions	See "Statistical analyses", paragraph 2.
		(*c*) Explain how missing data were addressed	See "Table 1"
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	See "Statistical analyses", paragraph 3.

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	See "Inclusions and definitions" in Material and Methods, paragraph 1 and Fig1 shows the flow-chart.
		(b) Give reasons for non-participation at each stage	See "Inclusions and definitions" in Material and Methods, paragraph 1, and Figure 1 flow chart.
		(c) Consider use of a flow diagram	See Figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See Table1.
		(b) Indicate number of participants with missing data for each variable of interest	See Table1.
		(c) Summarise follow-up time (eg, average and total amount)	See Discussion, paragraph 5.
Outcome data	15*	Report numbers of outcome events or summary measures over time	See Result, paragraph 2.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	See all Figures, Tables and Supplementary Tables
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	See Supplementary Tables.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	See all Supplementary files

Discussion			
Key results	18	Summarise key results with reference to study objectives	See Discussion, paragraph 1.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	See Discussion, paragraph 5 and 6.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	See the different paragraphs of the Discussion.
Generalisability	21	Discuss the generalisability (external validity) of the study results	See Discussion, paragraph 5 and "Health Implications".
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See information in the "Financial Disclosure" field in the submission form.

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of *PLoS Medicine* at http://www.plosmedicine.org/, *Annals of Internal Medicine* at http://www.annals.org/, and *Epidemiology* at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Web Table 2. Parity specific cutoff points for quartiles of offspring birth weight by gestational age among women with first and second singleton term births during 1967–2020, The Medical Birth Registry of Norway

Gestational Age (weeks)	Mean	Standard Deviation	Q1(≤25th Percentile)	Q2/3 (>25th & ≤75th Percentile)	Q4 (>75th Percentile)
First birth [a]					
37	3058	486	2760	3060	3350
38	3234	454	2950	3230	3520
39	3396	439	3110	3390	3678
40	3528	442	3235	3520	3810
41	3637	455	3330	3630	3930
42	3697	473	3380	3690	4000
43	3664	492	3340	3650	3980
44	3582	486	3260	3570	3900
45	3576	488	3270	3560	3900
46	3578	503	3260	3570	3900
Second birth [b]					
37	3197	505	2880	3180	3500
38	3389	466	3080	3372	3680
39	3546	449	3250	3530	3830
40	3684	451	3380	3670	3970
41	3794	463	3480	3780	4100
42	3842	484	3520	3830	4160
43	3771	508	3430	3760	4100
44	3695	484	3370	3700	4000
45	3700	495	3380	3685	4020
46	3678	516	3335	3680	4010

[a]All women with first singleton term birth, between 1967–2014.

[b]All women with second singleton term birth, between 1968–2020.

Web Table 3. Long-term cardiovascular disease mortality by quartiles (Q) of offspring birth weight by gestational age, based on women's first birth, and stratified by onset of labor: Women with first two singleton births at term, Norway, 1967–2020 (*n* = 735,244)

Quartile of Birth Weight by Gestational Age	Model 1				Model 2							
	Overall Model				Spontaneous Deliveries [a]				Iatrogenic Deliveries [b]			
	n	N	n/N	aHR[c] (95% CI)	n	N	n/N	aHR[c] (95% CI)	n	N	n/N	aHR[c] (95% CI)
1st birth												
Q1	1,118	179,230	0.62	1.41 (1.30-1.52)	939	147,182	0.64	1.41 (1.28-1.54)	179	32,048	0.56	1.48 (1.26-1.74)
Q2/3	1,389	371,517	0.37	1.00 (reference)[d]	1,172	310,690	0.38	1.00 (reference)[e]	217	60,827	0.36	1.07 (0.92-1.23)
Q4	530	184,497	0.29	0.84 (0.77-0.94)	438	147,547	0.30	0.86 (0.77-0.96)	92	36,950	0.25	0.86 (0.70-1.07)

[a] Women with spontaneous labor onset during first pregnancy.

[b] Women with either induced onset of labor or pre-labor caesarean delivery during first pregnancy.

[c] Adjusted for maternal age at first birth, year of last delivery, maternal education pregnancy complications (chronic- or gestational hypertension, pregestational- or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, offspring with congenital malformations and women who conceived by In vitro fertilization) in first and/ second pregnancies

[d] Women with first offspring in Q2/3.

[e] Women with offspring in Q2/3 and spontaneous onset of labor during first pregnancy, were the common reference group for the model including spontaneous and iatrogenic births.

Web Table 4. Long-term maternal cardiovascular mortality by quartiles (Q) of offspring birth weight by gestational age, based on woman's first and second birth: Women whose first two singleton births at term, Norway, 1967–2020 (*n* = 735,244)

Quartile of Birth Weight by Gestational Age		n	N	n/N	aHR[a] (95% CI)
1st birth	2nd birth				
Q1	Q1	648	86,259	0.75	1.66 (1.49-1.85)
Q1	Q2/3	417	79,729	0.52	1.31 (1.13-1.48)
Q1	Q4	53	13,242	0.40	0.99 (0.75-1.31)
Q2/3	Q1	453	82,832	0.55	1.33 (1.18-1.50)
Q2/3	Q2/3	732	208,993	0.35	1.00 (reference)
Q2/3	Q4	204	79,692	0.26	0.78 (0.67-0.91)
Q4	Q1	72	13,979	0.52	1.26 (0.99-1.60)
Q4	Q2/3	240	80,331	0.30	0.89 (0.77-1.03)
Q4	Q4	218	90,187	0.24	0.80 (0.69-0.93)

[a] Hazard ratio with 95% confidence interval, adjusted for maternal age at first birth, year of last delivery, maternal education and pregnancy complications (chronic- or gestational hypertension, pregestational- or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, offspring with congenital malformations and women who conceived by In vitro fertilization) in first and/ second pregnancies.

Web Table 5. Long-term maternal cardiovascular disease mortality by quartiles (Q) of offspring birth weight by gestational age, based on women's first and second birth: Women with first two singleton births at term, Norway, 1967–2020 (*n* = 735,244)

Quartile of Birth Weight by Gestational Age		Spontaneous Deliveries [a]				Iatrogenic Deliveries [b]			
		n	N	n/N	aHR[c] (95% CI)	n	N	n/N	aHR[c] (95% CI)
1st birth	2nd birth								
Q1	Q1	466	61,404	0.76	1.66 (1.46-1.88)	182	24,855	0.73	1.86 (1.56-2.20)
Q1	Q2/3	297	57,355	0.52	1.30 (1.13-1.50)	120	22,374	0.54	1.49 (1.22-1.81)
Q1	Q4	29	8,859	0.33	0.83 (0.57-1.20)	24	4,383	0.55	1.46 (0.96-2.22)
Q2/3	Q1	314	59,489	0.53	1.30 (1.13-1.50)	139	23,343	0.60	1.55 (1.28-1.87)
Q2/3	Q2/3	532	153,358	0.35	1.00 (reference)	200	55,635	0.36	1.11 (0.94-1.31)
Q2/3	Q4	154	56,155	0.27	0.84 (0.70-1.00)	50	23,537	0.21	0.71 (0.53-0.95)
Q4	Q1	51	9,238	0.55	1.35 (1.01-1.79)	21	4,741	0.44	1.19 (0.77-1.84)
Q4	Q2/3	175	54,809	0.32	0.94 (0.79-1.11)	65	25,522	0.25	0.86 (0.66-1.11)
Q4	Q4	150	58,294	0.26	0.83 (0.69-1.00)	68	31,893	0.21	0.80 (0.62-1.04)

[a] Women with spontaneous labor onset in first and second pregnancies (n = 518,961).

[b] Women with either induced onset of labor or pre-labor caesarean delivery, in first and/ second pregnancies (n = 216,283).

[c] Hazard ratio with 95% confidence interval, adjusted for maternal age at first birth, year of last delivery, maternal education and pregnancy complications (chronic- or gestational hypertension, pregestational- or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, offspring with congenital malformations and women who conceived by In vitro fertilization) in first and/ second pregnancies.

Web Table 6. Adjusted hazard ratios (HRs) for long-term maternal cardiovascular disease mortality by quartiles(Q) of offspring birth weight by gestational age, based on woman's first and second birth: Women with first two singleton births at term, Norway, 1967–2020 (*n* = 735,244)

Quartile of Birth Weight by Gestational Age		Model [a]	Model [b]	Model [c]	Model [d]	Model [e]	E-Value [f]	
		aHR[a] (95% CI)	aHR[a] (95% CI)	aHR[a] (95% CI)	aHR[a] (95% CI)	aHR[a] (95% CI)	For aHR	For CI
1st birth	2nd birth							
Q1	Q1	1.80 (1.61-1.99)	1.66 (1.49-1.85)	1.62 (1.45-1.82)	1.52 (1.31-1.77)	1.67 (1.46-1.91)	2.71	2.24
Q1	Q2/3	1.37 (1.22-1.55)	1.31 (1.16-1.48)	1.30 (1.14-1.49)	1.25 (1.05-1.48)	1.34 (1.16-1.56)	1.95	1.49
Q1	Q4	1.08 (0.82-1.42)	0.99 (0.75-1.31)	0.98 (0.70-1.35)	1.08 (0.73-1.60)	1.24 (0.90-1.71)	1.11	1.00
Q2/3	Q1	1.38 (1.23-1.55)	1.33 (1.18-1.50)	1.29 (1.13-1.47)	1.27 (1.08-1.50)	1.34 (1.16-1.56)	1.99	1.54
Q2/3	Q2/3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-	-
Q2/3	Q4	0.78 (0.67-0.91)	0.78 (0.67-0.91)	0.80 (0.67-0.94)	0.78 (0.62-0.96)	0.86 (0.71-1.03)	1.88	1.00
Q4	Q1	1.28 (1.01-1.63)	1.26 (0.99-1.60)	1.28 (0.98-1.67)	1.26 (0.89-1.78)	1.30 (0.96-1.76)	1.83	1.00
Q4	Q2/3	0.88 (0.76-1.02)	0.89 (0.77-1.03)	0.87 (0.74-1.02)	0.82 (0.67-1.01)	0.92 (0.77-1.10)	1.49	1.00
Q4	Q4	0.80 (0.68-0.93)	0.80 (0.69-0.93)	0.77 (0.65-0.92)	0.82 (0.66-1.01)	0.75 (0.62-0.91)	1.81	1.37

[a] All first and second term births, unadjusted.

[b] All first and second term births, adjusted for maternal age at first delivery, year of last delivery, maternal education and pregnancy complications (chronic- or gestational hypertension, pregestational- or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, offspring with congenital malformations and women who conceived by In vitro fertilization) in first and/ second pregnancies.

[c] Excluding women with any of the listed pregnancy complications during any of their two first pregnancies. Models adjusted for maternal age at first delivery, year of last delivery, maternal education.

[d] Restricted to births within 39-41 gestational weeks, in both pregnancies. Model adjusted for maternal age at first delivery, year of last delivery, maternal education and above listed pregnancy complications in first and/ second pregnancies.

[e] Restricted to women born in the Nordic countries with offspring from the same father. Model adjusted for maternal age at first delivery, year of last delivery, maternal education, inter-pregnancy-interval and above listed pregnancy complication in first and/ second pregnancies.

[f] E-value is the minimum strength of association that an unmeasured confounder would need to have with both the exposure and outcome, conditional on the measured covariates, to fully explain away a specific exposure–outcome association. E-values for HR and CI was calculated, according to the formula introduced by Tyler J. VanderWeele and Peng Ding (2017), based on model[b].

Web Table 7. Adjusted hazard ratios (HRs) for maternal mortality from all-causes, circulatory, and non-circulatory causes by quartiles (Q) of offspring birth weight by gestational age, based on woman's first and second birth: Women with first two singleton births at term, Norway, 1967–2020 (*n* = 735,244)

Quartile of Birth Weight by Gestational Age		All-Cause Mortality	Circulatory Disease Mortality	Non-Circulatory Disease Mortality
		aHR[a] (95% CI)	aHR[a] (95% CI)	aHR[a] (95% CI)
1st birth	2nd birth			
Q1	Q1	1.30 (1.26-1.35)	1.55 (1.43-1.68)	1.24 (1.19-1.30)
Q1	Q2/3	1.11 (1.06-1.16)	1.23 (1.13-1.35)	1.08 (1.03-1.13)
Q1	Q4	0.98 (0.89-1.07)	1.00 (0.81-1.24)	0.97 (0.87-1.08)
Q2/3	Q1	1.20 (1.16-1.25)	1.35 (1.24-1.48)	1.17 (1.11-1.22)
Q2/3	Q2/3	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2/3	Q4	0.92 (0.88-0.97)	0.88 (0.78-0.98)	0.93 (0.88-0.98)
Q4	Q1	1.15 (1.05-1.25)	1.17 (0.97-1.41)	1.14 (1.04-1.26)
Q4	Q2/3	0.94 (0.90-0.99)	0.96 (0.86-1.06)	0.94 (0.89-0.99)
Q4	Q4	0.90 (0.86-0.95)	0.90 (0.80-1.00)	0.90 (0.86-0.95)

[a] Adjusted for maternal age at first delivery, year of last delivery, maternal education and pregnancy complications (chronic- or gestational hypertension, pregestational- or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, offspring with congenital malformations and women who conceived by In vitro fertilization) in in first and/ second pregnancies.

Web Table 8. Adjusted hazard ratios (HRs) for long-term maternal cardiovascular disease mortality by quartiles (Q) of offspring birth weight by gestational age from cause-specific and sub distribution hazard models, based on woman's first and second birth: Women with first two singleton births at term, Norway, 1967–2020 (*n* = 735,244)

Quartile of Birth Weight by Gestational Age		Cause-Specific Hazard Model aHR[a] (95% CI)	Subdistribution Hazard Model aHR[a] (95% CI)
1st birth	2nd birth		
Q1	Q1	1.66 (1.49-1.85)	1.64 (1.48-1.83)
Q1	Q2/3	1.31 (1.13-1.48)	1.31 (1.13-1.48)
Q1	Q4	0.99 (0.75-1.31)	0.99 (0.75-1.32)
Q2/3	Q1	1.33 (1.18-1.50)	1.33 (1.18-1.49)
Q2/3	Q2/3	1.00 (reference)	1.00 (reference)
Q2/3	Q4	0.78 (0.67-0.91)	0.78 (0.67-0.91)
Q4	Q1	1.26 (0.99-1.60)	1.26 (0.99-1.60)
Q4	Q2/3	0.89 (0.77-1.03)	0.89 (0.77-1.03)
Q4	Q4	0.80 (0.69-0.93)	0.80 (0.69-0.93)

[a] Adjusted for maternal age at first delivery, year of last delivery, maternal education and pregnancy complications (chronic- or gestational hypertension, pregestational- or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, offspring with congenital malformations and women who conceived by In vitro fertilization) in in first and/ second pregnancies

Web Table 9. Adjusted hazard ratios (aHRs) for long-term maternal cardiovascular disease mortality by quartiles (Q) of offspring birth weight by gestational age, based on first and third birth: Women with first three singleton births at term, Norway, 1967–2020 (*n* = 268,377)

Quartile of Birth Weight by Gestational Age		Model [a]	Model [b]	Model [c]	
		aHR[a] (95% CI)	aHR[a] (95% CI)	Spontaneous Deliveries [d] aHR[a] (95% CI)	Iatrogenic Deliveries [e] aHR[a] (95% CI)
1st birth	3rd birth				
Q1	Q1	1.81 (1.51-2.16)	1.85 (1.51-2.26)	1.88 (1.50-2.36)	1.92 (1.46-2.52)
Q1	Q2/3	1.19 (0.97-1.47)	1.14 (0.90-1.45)	1.20 (0.92-1.57)	1.34 (0.98-1.84)
Q1	Q4	0.89 (0.55-1.41)	0.90 (0.51-1.57)	0.97 (0.54-1.75)	0.87 (0.41-1.86)
Q2/3	Q1	1.36 (1.11-1.66)	1.29 (1.03-1.62)	1.24 (0.95-1.61)	1.77 (1.33-2.35)
Q2/3	Q2/3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.14 (0.88-1.47)
Q2/3	Q4	0.86 (0.67-1.11)	0.80 (0.60-1.07)	0.78 (0.56-1.10)	1.11 (0.77-1.59)
Q4	Q1	1.42 (0.98-2.06)	1.32 (0.85-2.05)	1.60 (0.99-2.57)	1.35 (0.75-2.43)
Q4	Q2/3	0.86 (0.67-1.11)	0.85 (0.64-1.12)	0.87 (0.63-1.21)	0.95 (0.65-1.39)
Q4	Q4	0.71 (0.53-0.93)	0.75 (0.55-1.01)	0.82 (0.58-1.15)	0.63 (0.40-0.99)

[a] All first three term births, adjusted for maternal age at first delivery, year of last delivery, maternal education and pregnancy complications (chronic- or gestational hypertension, pregestational- or gestational diabetes mellitus, placental abruption, preeclampsia, perinatal loss, offspring with congenital malformations and women who conceived by In vitro fertilization) in any of the first three pregnancies.

[b] Excluding women with any of the above listed complications during any of their first three pregnancies. Model adjusted for maternal age at first delivery, year of last delivery, maternal education.

[c] All first three term births, stratified by onset of labor. Model adjusted for maternal age at first delivery, year of last delivery, maternal education and above listed pregnancy complications in any of the first three pregnancies.

[d] Women with spontaneous labor onset in first, second and third pregnancies.

[e] Women with either induced onset of labor or pre-labor caesarean delivery, in any of their first three pregnancies.

III

Paper III

The relationship between cesarean delivery and fecundability: a population-based cohort study

Sima YT, Magnus MC, Kvalvik LG, Morken N-H, Klungsøyr K, Skjærven R, Sørbye LM. The relationship between caesarean delivery and fecundability: a population-based cohort study. In Manuscript.

Tweetable statement

- Large prospective cohort study found that caesarean delivery procedure in itself may not explain the subsequent reduced fecundability.

Short title

- Cesarean delivery and fecundability

AJOG at Glance

- *Why was this study conducted?*
    - To assess the bidirectional relationship between caesarean delivery and fecundability.
- *What are the key findings?*
    - We observed that women with a history of caesarean delivery had an increased risk of reduced fecundability and infertility, and that women with lower fecundability were more likely to have caesarean delivery.

- *What does this study add to what is already known?*
    - Previous studies have linked caesarean delivery and subsequent reduced fecundability, but this could be due to common underlying etiology explanatory mechanism, not due to the surgical procedure itself.

Abstract

Background: Previous studies have found that women with caesarean delivery have fewer pregnancies. Caesarean delivery is also more common among women with lower fecundability. The potential role of caesarean delivery on reduced fecundability is not known.

Objective: To assess the bidirectional relationship between caesarean delivery and fecundability.

Study Design: This is a prospective cohort study based on data from the Norwegian Mother, Father, and Child Cohort study linked with the Medical Birth Registry of Norway. We estimated the fecundability ratio (per cycle probability of pregnancy) and relative risk of infertility (time to pregnancy ≥ 12 months) according to mode of delivery in the previous delivery among 42,379 women. For the reverse association, we estimated the relative risk of having a caesarean delivery by fecundability (the number of cycles women needed to conceive) among 74,025 women.

Results: The proportion of women with infertility was 6.2% (2711/43936) among women with prior vaginal delivery, and 8.6% (518/6036) among women with a prior caesarean delivery, yielding an adjusted relative risk of 1.21 (95% confidence interval:

1.10 to 1.33). Women with previous caesarean delivery also had lower fecundability ratio (0.90, 95% confidence interval 0.88 to 0.93), compared to women with prior vaginal delivery. When assessing the reverse association between fecundability and caesarean delivery, we found that women who did not conceive within 12 or more cycles had higher risk of caesarean delivery (adjusted relative risk 1.55, 95% confidence interval 1.46 to 1.64) compared to women who conceived within the first two cycles. Associations remained after controlling for sociodemographic and clinical risk factors and were observed across parity groups.

Conclusion: Among women with more than one child, those who had caesarean delivery had subsequent lower fecundability ratio and increased infertility risk compared to those who had vaginal delivery. However, women who needed longer time to conceive were also more prone to be delivered by caesarean delivery. We therefore found evidence of a bidirectional relationship between caesarean delivery and fecundability. This could be due to a common underlying explanatory mechanism, and the surgical procedure itself may not directly influence fecundability.

Key words: Bidirectional, cesarean delivery, fecundability, fecundability ratio, infertility, prospective, time to pregnancy.

Introduction

Time to pregnancy (TTP), which refers to the duration of attempts a couple makes to conceive before succeeding [159], is an important measure of fecundability which is defined as the capacity to establish a clinical pregnancy in a cycle [152 159]. Infertility, defined as having tried to conceive for more than 12 months without success, is indicative of decreased fecundability[152]. It can persist without resolution, or it may be resolved either through spontaneous means, treatment, or by changing partners[159 160]. Couples' biology, social, behavioral, and environmental factors may contribute and influence the likelihood of pregnancy [159 160].

Findings of a relationship between CD and later fertility is inconclusive. Previous reviews have found fewer pregnancies and longer inter-pregnancy intervals following caesarean delivery (CD) [161-163], although others found no difference [169 175]. Several mechanisms, including medical indications for CD, uterine scarring, and placental abnormalities, have been proposed as explanations for reduction in fecundability following CD [162 164]. Others argue that this reduction may be attributed to a voluntary decision made by couples [165 263 264]. However, most of these studies used inter-pregnancy interval to measure fecundability [161-163 165 169 175] which is largely determined by the couple's desire for pregnancy spacing, and therefore cannot differentiate between voluntary and involuntary delays in pregnancy [164]. They also failed to account for potential risk factors such as smoking, contraceptive use [165 169] or access to infertility treatment [164 169 175], while other studies have short follow up [178]. On the other hand, CD is also more prevalent among women with reduced fecundability [164 179 181 182]. Murphy and colleagues found correlation between CD and infertility in both directions in the

Avon Longitudinal study [164]. However, they were unable to account for indications of CD, and intrapartum and postpartum complications, hence unable to distinguish between the indications and the procedure itself. No other studies have assessed the potential bidirectional relationship between CD and fecundability in a Nation-wide cohort.

Over the years, changes in reproductive behavior (use of contraception, delayed childbearing) [152], along with changes in obstetrical practices, may have contributed to a lower threshold for CD in numerous countries [162] [163] including Norway [8]. As a consequence, more first-time mothers are exposed to CD [273], making it important to examine the link between CD and fecundability. This study utilized a large prospective cohort to investigate the bidirectional relationship between CD and fecundability.

Materials and methods

We studied women participating in the Norwegian Mother, Father, and Child Cohort Study (MoBa). MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health [212]. Pregnant women were recruited from all throughout Norway at the time of routine second trimester ultrasound screening between 1999 and 2009, and the participation rate was 41%. Version 12 of the quality-assured data files, released in January 2019, served as the basis for this study. We used information from a self-reported questionnaire completed by the women at 15-18 weeks gestation. As women could participate with more than one pregnancy, the MoBa cohort study consisted of 95,200 women and 114,500 children. Additional information on the mother's health and pregnancy outcomes was collected by linking to the Medical Birth Registry of Norway (MBRN) using the mother's personal identification number. The

MBRN comprises all births that occurred from 16 weeks of gestation onwards since 1967 in Norway, based on mandatory notification [68]. The attending health professionals are responsible for providing this information to the MBRN.

This study had been approved by Regional Committees for Medical and Health Research Ethics (2014/404) and informed consent was obtained from all participants in MoBa.

Study population

We included women with at least one recorded pregnancy in MoBa (**Figure 1**). We excluded women who did not complete the recruitment questionnaire, and women with incomplete TTP data. The included MoBa pregnancy is referred to as the index pregnancy.

When exploring the association between CD in the prior pregnancy and fecundability, we included women with a previous singleton birth registered in the MBRN, while we excluded women without a registered birth prior to the index pregnancy and those with a history of in vitro fertilization in their prior pregnancy, due to the possibility of pre-existing fertility problems[269].

To examine the reverse association between fecundability and risk of CD, women with a prior history of CD were excluded, as the likelihood of recurrence is high[8].

Fecundability

At recruitment, participants were asked if their pregnancy was planned or not. If the pregnancy was planned, women were asked to indicate how long they had been trying

to conceive in months: "less than 1 month", "1-2 months", or "3 months or more". If the latter, they were asked to specify the exact number of months.

A pregnancy was considered planned if the participant answered affirmatively to the question about whether the pregnancy was intended and provided information on the duration of trying to conceive while not using contraceptives. Women were also asked about their average menstrual cycle length, and we used this information, along with TTP information, to determine their cycles at risk until they reported pregnancy. In cases where participants did not provide information about cycle length (4943, 6.2%), cycle length of 28 days were assumed.

8061 (10.1%) women reported taking "3 months or more" to conceive without specifying the exact duration. For analysis, we assumed a 3-month duration. Additionally, 1782 (2.2%) women reported pregnancies during their TTP period (mostly miscarriages), so we corrected the reported TTP by subtracting the pregnancy length. For index pregnancies conceived by in vitro fertilization with missing TTP information, we assumed a waiting time of ≥12 months.

Data on the mode of delivery in the previous- and index birth was obtained from the MBRN.

Covariates

In our analysis, we included maternal age (years) (<24, 25-34, ≥35), education(years) (low: ≤13 and high: >13), smoking status (non-smoker, quit smoking in the current pregnancy, smoker) and pre-pregnancy body-mass index (<18.5 (underweight), 18.5-24.9 (normal weight), 25-29.9 (overweight), ≥ 30 (obese)). We identified mothers with

chronic conditions such as asthma, arthritis, hyper- and hypothyroidism, endometriosis, ovarian cysts, and myoma. Data on all these covariates were collected at the time of recruitment of the index pregnancy. Data on diabetes mellitus, chronic hypertension and pregnancy complications (gestational hypertension, preeclampsia, preterm birth, placental abruption, and placenta previa) were retrieved from MBRN, as risk factors for CD and reduced fecundability [74]. Women were grouped on the absence (no) or presence of one or more (yes) of the above-mentioned chronic conditions and pregnancy complications.

Statistical analysis

STATA, version 17, was used for all statistical analyses. To handle missing values on maternal education, smoking, pre-pregnancy body-mass index, and pregnancy complications, we conducted multiple imputation by chained equation (MICE, 20 datasets).

Previous CD and fecundability

We estimated the monthly probability of pregnancy (fecundability ratio (FR)) with 95% confidence intervals (CI), according to CD in the previous birth using proportional probability regression with cycles as the unit of analysis. Robust cluster variance estimation was used to account for women participating with more than one pregnancy in the cohort. A FR > 1 indicates a greater likelihood of conceiving in each menstrual cycle, while a FR < 1 indicates a lower likelihood of conceiving in each cycle. We also estimated the relative risk (RR) of infertility (TTP ≥12 months) with 95% CI using proportional probability regression with pregnancies as the unit of analysis. Women

with previous vaginal delivery were the reference in both models. Models were adjusted for maternal age and complications at previous birth, maternal education, smoking status, and chronic conditions (**Figure S1)**. To account for lack of body-mass index data in the MBRN, we adjusted for pre-pregnancy body-mass index at the index pregnancy as a proxy.

In the main analyses, we excluded women who had unplanned pregnancies. This group comprises women who either answered "no" to the question of planning their pregnancy or answered "yes" but reported using contraceptives, as they lack reliable TTP [159 160 235]. To evaluate the likelihood of selection bias, we performed a sensitivity analysis including women with unplanned pregnancies, and a separate sensitivity analysis excluding pregnancies to women reported "3 months or more" of trying to conceive without specifying the exact duration. To account for change in CD trends over the years, we also conducted an analysis restricted to women below the age of 35 years at time of exposure [273]. Further, we restricted our analysis by the number of years between the previous delivery and the index pregnancy (up to 3 and 3 to 7 years). About 95% of Norwegian women give birth to their second child within seven years [274].

Given that the indications may differ between emergency and planned CD [92], we conducted stratified analyses based on the type of previous delivery (vaginal delivery, planned CD, or emergency CD). Similarly, we stratified analysis to see whether CD influenced fecundability according to whether it occurred during the prior- or in earlier deliveries. Finally, to account for the possible variation in social and behavioral risk factors [164], we stratified by parity.

Fecundability and risk of CD

We also investigated the reverse association: the risk of CD by number of cycles women needed to conceive (< 3 (reference), 3-6, 7-11 and ≥12). To obtain RR with 95% CI, we used a generalized linear model with a log-link and binomial distribution. Due to the convergence difficulty with the log-binominal model, Poisson regression models were used. The model was adjusted for maternal age at the time of conception, maternal education, pre-pregnancy body-mass index, smoking status, and chronic conditions (**Figure S2)**. Similar sensitivity analyses as those described earlier were also conducted. In addition, we adjusted for complications of the index pregnancy to account for the possibility of them serving as mediators and potentially increasing the risk of CD.

Results

Previous CD and fecundability

This analysis included 42,379 pregnancies from women with a prior birth (**Figure 1**).

Among women with previous birth, two-thirds had only one prior birth (**Table 1**). Women with prior CD were older, had lower education, higher proportion of chronic conditions and complications than women with a prior vaginal delivery (**Table S1**).

The FR was lower (0.90, 95% CI 0.88-0.93) in women with a previous CD compared to those with a previous vaginal delivery (**Table 2**). The absolute risk of infertility was 7.3% (2707/37226) and 9.9% (508/5153) among women with a previous- vaginal delivery and CD, respectively, with a corresponding RR among women with previous CD of 1.21 (95% CI 1.10-1.33) (**Table 3**). Restricting our analysis to only complete observed cases did not change the estimates.

Excluding women above 35 years of age or pregnancies where women reported "3 months or more" without specifying the duration did not appear to influence the observed results (**Table S2 and Table S3).** Further, the fecundability appeared similar among women with planned- and emergency CD and across different parity groups. CD occurring in the previous birth had a slightly stronger effect on fecundability, while the association seemed weaker when it occurred in earlier births. Restricting the time interval between the year of previous birth and the start of trying to conceive for the index pregnancy to either less than 3 years or 3-7 years did not change the pattern. The proportion of younger women (< 25 years) were higher among women with unplanned pregnancies **(Table S4).** However, including them in the analysis did not alter our results.

Fecundability and risk of CD

This analysis included 74,025 index pregnancies. A total of 10.9% pregnancies (8038/74025) were to women with infertility (**Table S5**). These women had lower education, smoked more, were more overweight or obese and more often had chronic conditions and pregnancy complications than women who conceived within 12 months. Nearly two thirds of these pregnancies were to nulliparous women.

The risk of CD increased linearly by the number of cycles it took to achieve pregnancy, as shown in **Table 4**. The absolute risk of CD of among women who conceived within the first two cycles was 10.3% (3967/38602), while 17.4% (1521/8723) among women who conceived after ≥12 cycles. In comparison to women who conceived within the first two cycles, those who did not conceive within 12 or more cycles had a 55% higher risk of CD (RR 1.55, 95% CI 1.46-1.64). These patterns were similar across parity groups

(**Table S6**). Adjusting for complications in the index pregnancy attenuated the risk but did not change the pattern.

Comment

Principal findings

Among women with more than one child, we identified a decreased fecundability following a previous CD. However, we also confirmed the reverse association, that women with reduced fecundability were more likely to have a CD. Associations remained after controlling for sociodemographic and clinical risk factors and were observed among different parity groups. Our study suggested that CD may not be causally linked to decreased fecundability, but associations may be explained by shared underlying mechanisms leading to CD and reduced fecundability.

Results in the Context of What is Known

Our study found a decrease in fecundability following both planned and emergency CD, in contrast to a smaller Danish study which only observed a decline in women who had undergone planned CD [177]. Further, we found the impact of CD on fecundability to be stronger if it occurred in the prior- than earlier deliveries. However, it is important to consider that the observed differences may be attributed to the fact that women with CD in earlier pregnancies had two or more previous births and may therefore be more fecund, while women with CD in the prior birth may have a different fecundability profile.

We also found an increased risk of CD among women with reduced fecundability, in line with previous studies[179 181 182 269]. In our study, most women who took a longer time

to conceive were nulliparous, who generally have higher risk of CD [8 273]. The increased CD risk remained even after accounting for parity and other potential underlying medical and obstetrical risks, albeit to a lesser extent.

The occurrence of uterine scarring due to previous CD has been linked to adverse pregnancy outcomes, such as ectopic pregnancy and abnormal placentation [161-163]. Similar mechanisms have been proposed to explain the difficulty in conceiving after a CD [178]. However, our findings of a bidirectional relationship between CD and fecundability support the idea that there may be common underlying explanatory mechanisms behind both conditions, rather than the surgical procedure of a CD itself influencing fecundability. Common underlying mechanisms could be maternal stress response caused by emotional stress (fear, anxiety, pain). A preconception cohort study conducted among couples attempting to conceive in the US and Canada revealed that women who took a longer time to achieve pregnancy may encounter anxiety [272], which could possibly lead to increased interventions during childbirth [181 269 271]. Maternal anxiety during labor may involve the activation of the sympathetic nervous system, leading to the release of stress hormones that have the potential to disrupt the contractile function of the myocytes and ultimately the need for CD[270].

Clinical implications

With some exceptions [169 175], prior studies have found that women without known fecundability problems may experience decreased fecundability/infertility following a CD [161-163]. In addition, a systemic review and meta-analysis of seven observational studies among women undergoing assisted reproductive technology treatment also

showed a decrease in clinical pregnancy rates among those with a history of CD [275]. In light of these findings, it has been suggested that the global rise in CD together with the delayed childbearing trend [152], may have substantial implications for subsequent reproduction [162 163 178]. Our study found an association between CD and subsequent reduced fecundability, and an even stronger association between reduced fecundability and risk of CD, indicating a potential shared etiology between decreased fecundability and CD. Despite adjusting for pregnancy complications and chronic conditions, the association persisted. Further research assessing the role of maternal anxiety on fecundability and interventions during childbirth is needed.

Strength and Limitations

This study has several strengths, including a large sample size from a prospective population-based pregnancy cohort, with comprehensive information on both exposure and outcome, minimizing recall bias. The use of linked data allowed for the investigation of bidirectional relationship between CD and fecundability. Additionally, unlike most previous studies[161-163 165 169], we had access to data on pregnancy intention and for women who planned their pregnancy, TTP. Our analysis also went beyond the conventional 12-month cut-off and estimated FR, providing a more comprehensive overview of the relationship of interest [152 159 160].

Our study has some limitations. Firstly, our study only included women who successfully conceived after their initial CD. This means that couples who were unable to conceive after their first CD were not included, resulting in the exclusion of women with very poor fecundability, which could bias our estimates towards the null [159 160].

Secondly, information on TTP was obtained through self-report by women who were pregnant during recruitment, which could lead to underestimation of the true magnitude of the association [160]. However, we only included women with planned pregnancies in the main analyses, which would reduce any potential recall bias. Another limitation is that the MoBa cohort participants were older, highly educated, less likely to smoke and predominately first-time mothers compared to the general population of pregnant women in Norway during the recruitment period [233]. Thus, generalizing our findings to the entire population may be difficult. However, overall CD prevalence among participants was comparable with that of the Norwegian population[273]. Moreover, epidemiological estimates of associations based on more homogeneous populations, like MoBa, could be less confounded due to restrictions[212 231]. Finally, in contrast to other high-income countries such as the US, the UK, and other European nations, Nordic countries generally have lower rates of CD [8]. Nevertheless, finding associations in a low-prevalence context could suggest that they may be even stronger in settings with higher CD rates.

Conclusion

We found evidence of a bidirectional relationship between CD and fecundability. This supports the idea that there may be common underlying explanatory mechanisms, and that the surgical procedure itself may not directly influence fecundability.

Acknowledgment

The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this cohort study. We are also grateful for the Medical Birth Registry of Norway kindly provided data for the analyses, and for Jannicke Igland from the Core Facility in Biostatistics and Data Analysis at the University of Bergen for statistical guidance.

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Table 1. Characteristics of study participants, The Norwegian Mother, Father and Child Cohort (1999–2008), with linked data from the Medical Birth Registry of Norway

	Pregnancies in women with previous birth	Pregnancies in women without previous caesarean delivery
	n (%)	n (%)
Total	42379	74025
Mode of delivery [a]		
Vaginal delivery	37226 (87.8)	65434 (88.4)
Cesarean delivery	5153 (12.2)	8591 (11.6)
Time to prior pregnancy (months)		
< 12	39164 (92.4)	65987 (89.1)
≥ 12	3215 (7.6)	8038 (10.9)
Maternal age (years) [a]		
< 25	9128 (21.7)	8560 (11.6)
25-34	32225 (74.0)	56373 (76.2)
≥ 35	1917 (4.4)	9092 (12.2)
Maternal education (years)		
≤ 13	14023 (33.1)	21856 (29.5)
>13	28193 (66.5)	51878 (70.1)
Missing	163 (0.4)	291 (0.4)
Smoking		
Non-smoker	31154 (73.5)	53268 (72.0)
Quit smoking in the current pregnancy	7275 (17.2)	14473 (19.6)
Current smoker	3198 (7.6)	5056 (6.8)
Missing	752 (1.8)	1228 (1.6)
Pre-pregnancy body mass index (kg/m^2)		
<18.5	1052 (2.5)	2076 (2.8)
18.5-24.9	26265 (62.0)	48290 (65.2)
25-29.9	9882 (23.3)	15813 (21.4)
≥30	4226 (10.0)	6411 (8.7)
Missing	954 (2.3)	1435 (1.9)
Chronic conditions [b]		
None	34947 (82.5)	60548 (81.8)
One or more	7432 (17.5)	13477 (18.2)
Pregnancy complications [a c]		
None	36427 (86.0)	65579 (88.6)
One or more	5094 (12.0)	7802 (10.5)
Missing	858 (2.0)	644 (0.9)
Parity (previous births)		
Nulliparous	0	35369 (47.8)
One	28607 (67.5)	26222 (35.4)
Two or more	13772 (32.5)	12080 (16.3)
Missing	0	354 (0.5)

[a] Measured at the time of previous pregnancy in the first column, and at the time of index pregnancy in the second column

[b] Self-reported chronic conditions: asthma, arthritis, chronic hypertension, diabetes mellitus, endometriosis, epilepsy, hypo/hyper thyroids, ovarian cyst and myoma.

[c] Includes gestational hypertension, pre-eclampsia, placental abruption, placental previa, preterm.

Table 2. Cesarean delivery in the previous birth and fecundability ratio in the pregnancy registered in the Norwegian Mother, Father, and Child Cohort Study, N=42,379

Previous mode of delivery	N(total)	N Cycles	Fecundability ratio		
			Unadjusted (95% CI)	Adjusted [a] (95% CI)	Adjusted [b] (95% CI)
All women	42379				
vaginal delivery	37226	145512	1.00 (reference)	1.00 (reference)	1.00 (reference)
cesarean delivery	5153	22909	0.87 (0.85-0.89)	0.90 (0.88-0.93)	0.86 (0.80-0.93)

[a] Complete case analysis. Model adjusted for maternal age and pregnancy complications in the previous birth, maternal education, smoking, pre-pregnancy body mass index and chronic conditions, accounting for women participating with several pregnancies.

[b] Multiple imputation carried out to include 10,451 cycles. Model adjusted for same factors as [a].

Table 3. Cesarean delivery in the previous birth and relative risk (RR) of infertility in the pregnancy registered in the Norwegian Mother, Father, and Child Cohort Study, N=42,379

Previous mode of delivery	N(total)	N (%) cases infertility	Relative risk of infertility		
			Unadjusted RR (95% CI)	Adjusted [a] RR (95% CI)	Adjusted [b] RR (95% CI)
All women	42379				
vaginal delivery	37226	2707 (7.3)	1.00 (reference)	1.00 (reference)	1.00 (reference)
cesarean delivery	5153	508 (9.9)	1.36 (1.24-1.48)	1.21 (1.10-1.33)	1.20 (0.97-1.47)

[a] Complete case analysis. Model adjusted for maternal age and pregnancy complications in the previous birth, maternal education, smoking, pre-pregnancy body-mass index and chronic conditions, accounting for women participating with several pregnancies.

[b] Multiple imputation carried out to include 3234 cases. Model adjusted for same factors as [a].

Table 4. Fecundability and relative risk (RR) of cesarean delivery in the pregnancy registered in the Norwegian Mother, Father, and Child Cohort Study, N=74,025

			Relative risk of cesarean delivery		
Categorization of fecundability (N cycles to conception)	**N (total)**	**N (%) Caesarean deliveries**	**Unadjusted RR (95% CI)**	**Adjusted [a] RR (95% CI)**	**Adjusted [b] RR (95% CI)**
All women	74025				
< 3 cycles	38602	3967 (10.3)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3-6 cycles	20299	2342 (11.5)	1.12 (1.07-1.18)	1.09 (1.04-1.15)	1.12 (1.00-1.26)
7-11 cycles	6401	761 (11.9)	1.15 (1.07-1.24)	1.11 (1.03-1.19)	1.10 (0.92-1.31)
≥ 12 cycles	8723	1521 (17.4)	1.69 (1.60-1.79)	1.55 (1.46-1.64)	1.47 (1.29-1.67)

[a] Complete case analysis. model adjusted for maternal age (at the time of trying to conceive), maternal education, smoking, Pre-pregnancy body-mass index and chronic conditions (with one or more of these conditions: asthma, arthritis, chronic hypertension, diabetes mellitus, endometriosis, epilepsy, hypo/hyper thyroids, ovarian cyst and myoma), accounting for women participating with several pregnancies.

[b] Multiple imputation carried out to include 4220 cases. Model adjusted for same factors as [a].

Figure Caption List

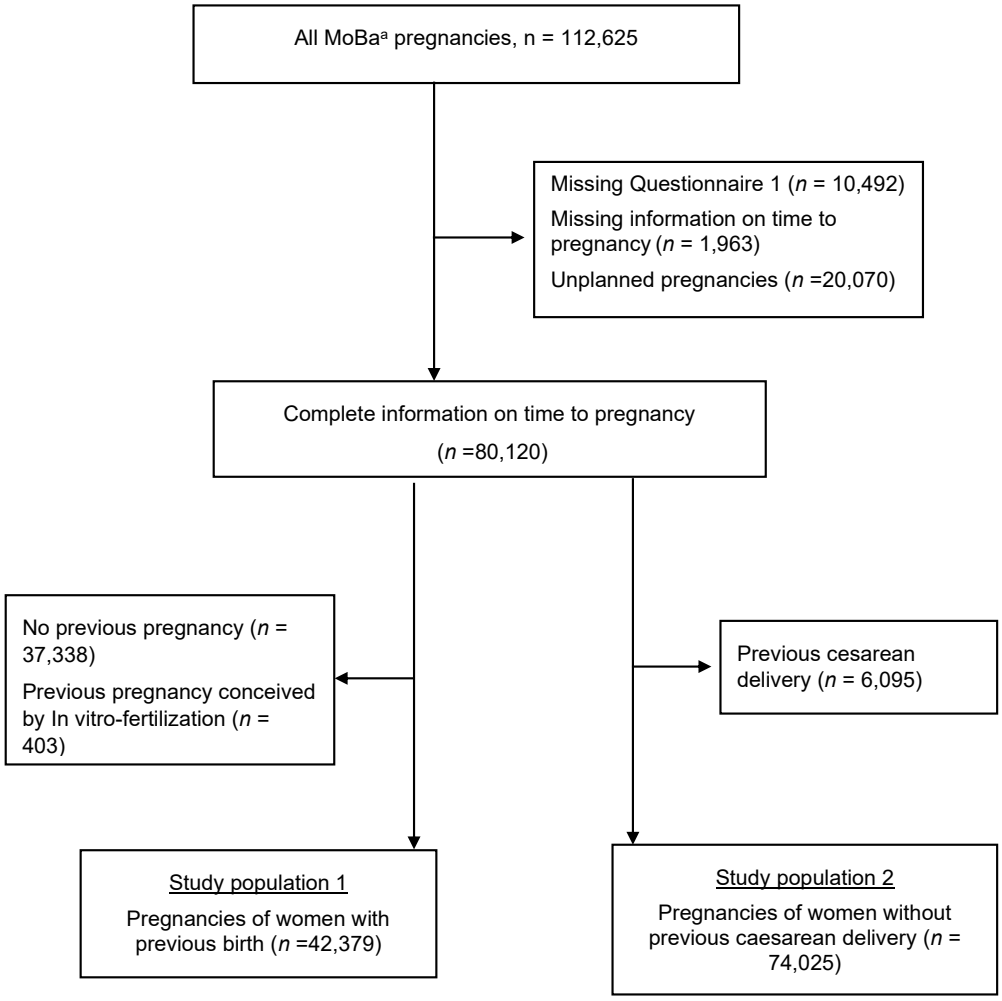

Figure 1. Flowchart of study populations

[a] Norwegian Mother, Father, and Child Cohort Study

Supplementary Material

1.

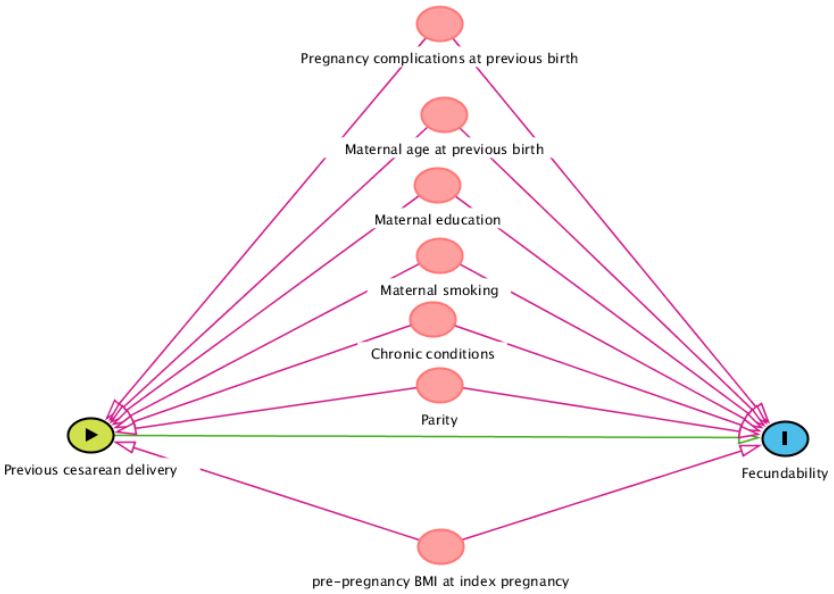

Figure S1. Directed acyclic graph illustrating the associations between our exposure (previous caesarean delivery), outcome (fecundability) and covariates.

Self-reported chronic conditions include asthma, arthritis, chronic hypertension, diabetes mellitus, endometriosis, epilepsy, hypo/hyper thyroids, ovarian cyst and myoma, and pregnancy complications were gestational hypertension, preeclampsia, placental abruption, placental previa, preterm.

Table S1: Pregnancy characteristics by previous mode of delivery, The Norwegian Mother, Father and Child Cohort (1999–2008) linked with the Medical Birth Registry of Norway, N=42,379

Characteristics	Total n (%)	Previous vaginal delivery n (%)	Previous cesarean delivery n (%)
All women	42379	37226	5153
Time to pregnancy (months)			
< 12	39164 (92.4)	34519 (92.7)	4645 (90.1)
≥ 12	3215 (7.6)	2707 (7.3)	508 (9.9)
Maternal age at previous delivery (years)			
< 25	9128 (21.5)	8208 (22.1)	920 (17.9)
25-34	31416 (74.1)	27516 (73.9)	3900 (75.7)
≥ 35	1835 (4.3)	1502 (4.0)	333 (6.5)
Maternal education (years)			
≤ 13	14023 (33.1)	12230 (32.9)	1793 (34.8)
>13	28193 (66.5)	24859 (66.8)	3334 (64.7)
Missing	163 (0.4)	137 (0.4)	26 (0.5)
Smoking			
Non-smoker	31154 (73.5)	27404 (73.6)	3750 (72.8)
Quit smoking in the current pregnancy	7275 (17.1)	6368 (17.1)	907 (17.6)
Current smoker	3198 (7.6)	2789 (7.5)	409 (7.9)
Missing	752 (1.8)	665 (1.8)	87 (1.7)
Pre-pregnancy body mass index (kg/m^2)			
<18.5	1052 (2.5)	945 (2.5)	107 (2.1)
18.5-24.9	26265 (62.0)	23504 (63.1)	2761 (53.6)
25-29.9	9882 (23.3)	8516 (22.9)	1366 (26.5)
≥30	4226 (10.0)	3425 (9.2)	801 (15.5)
Missing	954 (2.3)	836 (2.3)	118 (2.3)
Chronic conditions [a]			
None	34947 (82.5)	30961 (83.2)	3986 (77.4)
One or more	7432 (17.5)	6265 (16.8)	1167 (22.6)
Complications in the previous pregnancy [b]			
None	36427 (86.0)	32684 (87.8)	3743 (72.6)
One or more	5094 (12.0)	3787 (10.2)	1307 (25.4)
Missing	858 (2.0)	755 (2.0)	103 (2.0)
Parity (previous births)			
One	28607 (67.5)	24682 (66.3)	3925 (76.2)
Two or more	13772 (32.5)	12544 (33.7)	1228 (23.8)

[a]Self-reported chronic conditions: asthma, arthritis, chronic hypertension, diabetes mellitus, endometriosis, epilepsy, hypo/hyper thyroids, ovarian cyst and myoma.

[b] Gestational hypertension, preeclampsia, placental abruption, placental previa, preterm.

2. Table S2: Cesarean delivery in the previous birth and fecundability ratio (FR) in the pregnancy registered in the Norwegian Mother, Father, and Child Cohort Study, N=42,379

Group	Fecundability ratio			
	Adjusted FR [a] (95% CI)	Adjusted FR [b] (95% CI)	Adjusted FR [c] (95% CI)	Adjusted FR [d] (95% CI)
Previous mode of delivery				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	0.90 (0.88-0.93)	0.90 (0.87-0.92)	0.90 (0.88-0.92)	0.90 (0.88-0.92)
Previous mode of delivery				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Planned cesarean delivery	0.91 (0.86-0.95)	0.90 (0.86-0.94)	0.90 (0.86-0.95)	0.92 (0.88-0.96)
Emergency cesarean delivery	0.90 (0.87-0.93)	0.90 (0.87-0.92)	0.90 (0.87-0.93)	0.89 (0.86-0.91)
Mode of delivery				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery in the prior delivery	0.90 (0.87-0.92)	0.89 (0.87-0.92)	0.90 (0.87-0.92)	0.88 (0.86-0.91)
Cesarean delivery in earlier delivery	0.95 (0.90-0.99)	0.95 (0.90-1.00)	0.95 (0.90-0.99)	1.04 (1.00-1.09)
Time interval restricted to less than 3 years				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	0.90 (0.88-0.93)	0.90 (0.87-0.93)	0.90 (0.87-0.93)	0.89 (0.87-0.92)
Time interval restricted to 3 to 7 years				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	0.88 (0.83-0.93)	0.88 (0.83-0.93)	0.87 (0.82-0.93)	0.89 (0.84-0.93)
Parity (previous births)				
One				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	0.90 (0.87-0.93)	0.89 (0.87-0.92)	0.90 (0.87-0.93)	0.90 (0.88-0.93)
Two or more				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	0.93 (0.88-0.98)	0.92 (0.87-0.98)	0.93 (0.87-0.98)	0.94 (0.90-0.99)

[a] Main model, adjusted for maternal age and pregnancy complications at previous birth, maternal education, smoking and chronic conditions, accounting for women participating with several pregnancies.

[b] Analysis restricted to women below the age of 35 only, model adjusted for same factors as [a].

[c] Excluding pregnancies where the women responded "3 months or more" of trying to conceive without specifying the exact duration, model adjusted for same factors as [a].

[d] Analysis including both planned and unplanned pregnancies, model adjusted for same factors as [a].

3. Table S3: Cesarean delivery in the previous birth and relative risk (RR) of infertility in the pregnancy registered in the Norwegian Mother, Father, and Child Cohort Study, N=42,379

Group	Relative risk of infertility			
	Adjusted RR [a] (95% CI)	Adjusted RR [b] (95% CI)	Adjusted RR [c] (95% CI)	Adjusted RR [d] (95% CI)
Previous mode of delivery				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	1.21 (1.10-1.33)	1.21 (1.10-1.34)	1.22 (1.11-1.34)	1.23 (1.12-1.35)
Previous mode of delivery				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Planned cesarean delivery	1.20 (1.01-1.42)	1.19 (1.00-1.43)	1.23 (1.04-1.46)	1.18 (1.00-1.39)
Emergency cesarean delivery	1.21 (1.09-1.35)	1.22 (1.09-1.37)	1.21 (1.09-1.35)	1.24 (1.12-1.39)
Mode of delivery				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery in the prior delivery	1.23 (1.12-1.36)	1.23 (1.11-1.37)	1.24 (1.12-1.37)	1.27 (1.16-1.41)
Cesarean delivery in earlier delivery	1.11 (0.93-1.33)	1.09 (0.90-1.32)	1.12 (0.94-1.34)	0.99 (0.83-1.18)
Time interval restricted to less than 3 years				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	1.20 (1.06-1.34)	1.20 (1.06-1.36)	1.21 (1.07-1.36)	1.23 (1.09-1.38)
Time interval restricted to 3 to 7 years				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	1.36 (1.13-1.64)	1.36 (1.12-1.64)	1.38 (1.15-1.66)	1.36 (1.13-1.63)
Parity (previous births)				
One				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	1.20 (1.07-1.34)	1.21 (1.08-1.35)	1.20 (1.08-1.34)	1.20 (1.08-1.33)
Two or more				
Vaginal delivery	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cesarean delivery	1.17 (0.96-1.43)	1.15 (0.93-1.42)	1.20 (0.98-1.45)	1.15 (0.95-1.39)

[a] Main model, adjusted for maternal age and pregnancy complications at previous birth, maternal education, smoking and chronic conditions, accounting for women participating with several pregnancies.

[b] Analysis restricted to women below the age of 35 only, model adjusted for same factors as [a].

[c] Excluding pregnancies where the women responded "3 months or more" of trying to conceive without specifying the exact duration, model adjusted for same factors as [a].

[d] Analysis including both planned and unplanned pregnancies, model adjusted for same factors as [a].

4. Table S4: Characteristics of study population by pregnancy planning status registered in the Norwegian Mother, Father, and Child Cohort Study

Characteristics	Pregnancies in women with previous birth		Pregnancies in women without previous caesarean delivery	
	Planned	Unplanned	Planned	Unplanned
Total	42379	9953	74025	18480
Mode of delivery [a]				
Vaginal delivery	37226 (87.8)	8782 (88.2)	65434 (88.4)	16283 (88.1)
Cesarean delivery	5153 (12.2)	1171 (11.8)	8591 (11.6)	2197 (11.9)
Time to prior pregnancy (months)				
<12 months	39164 (92.4)	9762 (98.1)	65987 (89.1)	18100 (97.9)
≥12 months	3215 (7.6)	191 (1.9)	8038 (10.9)	380 (2.1)
Maternal age (years) [a]				
< 25	9128 (21.7)	2607 (26.2)	8560 (11.6)	4692 (25.4)
25-34	32225 (74.0)	6720 (67.5)	56373 (76.2)	11069 (59.9)
≥35	1917 (4.4)	626 (6.3)	9092 (12.2)	2719 (14.7)
Maternal education (years)				
≤13	14023 (33.1)	4459 (44.8)	21856 (29.5)	8394 (45.4)
>13	28193 (66.5)	5426 (54.5)	51878 (70.1)	9956 (53.9)
Missing	163 (0.4)	68 (0.7)	291 (0.4)	130 (0.7)
Smoking				
Non-smoker	31154 (73.5)	6645 (68.0)	53268 (72.0)	10976 (59.4)
Quit smoking in the current pregnancy	7275 (17.2)	1761 (18.0)	14473 (19.6)	4497 (24.3)
Current smoker	3198 (7.6)	1373 (14.0)	5056 (6.8)	2717 (14.7)
Missing	752 (1.8)	174 (1.8)	1228 (1.6)	290 (1.6)
Pre-pregnancy body mass index (kg/m^2)				
<18.5	1052 (2.5)	334 (3.4)	2076 (2.8)	817 (4.4)
18.5-24.9	26265 (62.0)	5929 (59.6)	48290 (65.2)	11682 (63.2)
25-29.9	9882 (23.3)	2199 (22.1)	15813 (21.4)	3617 (19.6)
≥30	4226 (10.0)	1160 (11.7)	6411 (8.7)	1765 (9.6)
Missing	954 (2.3)	331 (3.3)	1435 (1.9)	599 (3.2)
Chronic conditions [b]				
No	34947 (82.5)	7971 (80.1)	60548 (81.8)	14750 (79.8)
One or more	7432 (17.5)	1982 (19.9)	13477 (18.2)	3730 (20.1)
Pregnancy complications [a c]				
No	36427 (86.0)	8549 (85.9)	65579 (88.6)	16237 (87.9)
One or more	5094 (12.0)	1123 (11.3)	7802 (10.5)	2053 (11.1)
Missing	858 (2.0)	281 (2.8)	644 (0.9)	190 (1.0)
Parity (previous births)				
Nulliparous	0	0	35369 (47.8)	9392 (50.8)
One prior birth	28607 (67.5)	4196 (49.4)	26222 (35.4)	4577 (24.8)
Two or more prior birth	13772 (32.5)	5037 (50.6)	12080 (16.3)	4410 (23.9)
Missing	0	0	354 (0.5)	101 (0.6)

[a] Measured at the time of previous pregnancy in the pregnancies in women with previous birth, and at the time of index pregnancy in pregnancies in women without previous caesarean delivery.

[b] Self-reported chronic conditions: asthma, arthritis, chronic hypertension, diabetes mellitus, endometriosis, epilepsy, hypo/hyper thyroids, ovarian cyst and myoma.

[c] Includes gestational hypertension, pre-eclampsia, placental abruption, placental previa, preterm.

5.

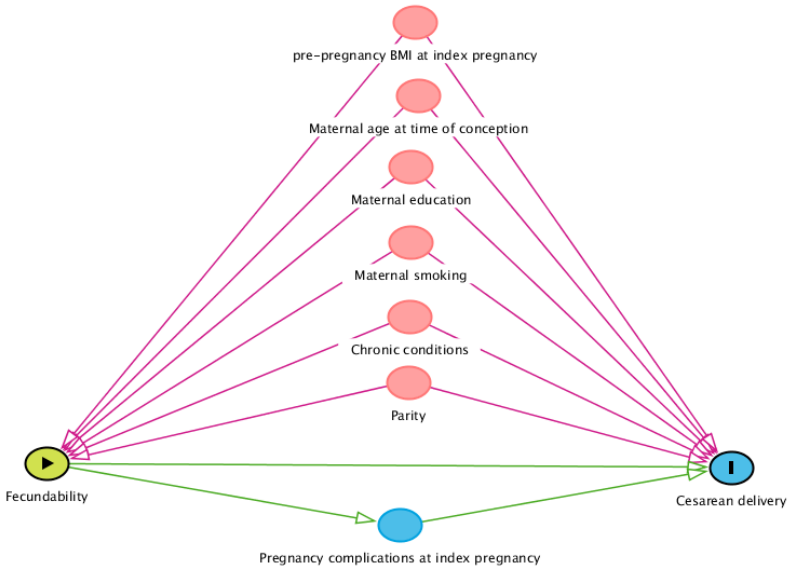

Figure S2. Directed acyclic graph illustrating the associations between our exposure (fecundability), outcome (caesarean delivery) and covariates.

Self-reported chronic conditions were asthma, arthritis, chronic hypertension, diabetes mellitus, endometriosis, epilepsy, hypo/hyper thyroids, ovarian cyst and myoma, and pregnancy complications were gestational hypertension, preeclampsia, placental abruption, placental previa, preterm.

6. Table S5. Pregnancy characteristics by time to pregnancy registered in the Norwegian Mother, Father, and Child Cohort Study, N= 74,025

Characteristics	Total n (%)	< 12 months n (%)	≥ 12 months n (%)
All women	74025	65987	8038
Mode of delivery			
Vaginal delivery	65434 (88.4)	58810 (89.1)	6624 (82.4)
Cesarean delivery	8591 (11.6)	7177 (10.9)	1414 (17.6)
Maternal age at the start of trying to conceive the index pregnancy (years)			
< 25	8560 (11.6)	7399 (11.2)	1161 (14.4)
25-34	56373 (76.1)	50435 (76.4)	5938 (73.9)
≥35	9092 (12.3)	8152 (12.4)	940 (11.7)
Maternal education (years)			
≤13	21856 (29.5)	18977 (28.8)	2879 (35.8)
>13	51878 (70.1)	46749 (70.9)	5129 (63.8)
Missing	291 (0.4)	261 (0.4)	30 (0.4)
Smoking			
Non-smoker	53268 (72.0)	47768 (72.4)	5500 (68.4)
Quit smoking in the current pregnancy	14473 (19.6)	12767 (19.4)	1706 (21.2)
Current smoker	5056 (6.8)	4348 (6.6)	708 (8.8)
Missing	1228 (1.7)	1104 (1.7)	124 (1.5)
Pre-pregnancy body mass index (kg/m^2)			
<18.5	2076 (2.8)	1837 (2.8)	239 (3.0)
18.5-24.9	48290 (65.2)	43595 (66.1)	4695 (58.4)
25-29.9	15813 (21.4)	13950 (21.1)	1863 (23.2)
≥30	6411 (8.7)	5300 (8.0)	1111 (13.8)
Missing	1435 (1.9)	1305 (2.0)	130 (1.6)
Chronic conditions [a]			
None	60548 (81.8)	54823 (83.1)	5725 (71.2)
One or more	13477 (18.2)	11164 (16.9)	2313 (28.8)
Complications in the current pregnancy [b]			
None	65579 (88.6)	58903 (89.3)	6776 (84.1)
One or more	7802 (10.5)	6587 (10.0)	1215 (15.1)
Missing	644 (0.9)	497 (0.8)	147 (1.8)
Parity (previous births)			
Nulliparous	35369 (47.8)	30309 (45.9)	5104 (63.9)
One	26222 (35.4)	24126 (36.6)	2088 (26.2)
Two or more	12080 (16.3)	11248 (17.1)	791 (9.9)
Missing	354 (0.5)	304 (0.5)	50 (0.6)

[a] Self-reported chronic condition: asthma, arthritis, chronic hypertension, diabetes mellitus, endometriosis, epilepsy, hypo/hyper thyroids, ovarian cyst and myoma.

[b] Include gestational hypertension, preeclampsia, placental abruption, placental previa, preterm

7. Table S6: Fecundability and relative risk (RR) of cesarean delivery in the pregnancy registered in the Norwegian Mother, Father, and Child Cohort Study, N=74,025

	Relative risk of cesarean delivery				
Group	Adjusted RR [a] (95% CI)	Adjusted RR [b] (95% CI)	Adjusted RR [c] (95% CI)	Adjusted RR [d] (95% CI)	Adjusted RR [e] (95% CI)
All women					
< 3 cycles	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3-6 cycles	1.09 (1.04-1.15)	1.09 (1.03-1.15)	1.08 (1.02-1.14)	1.07 (1.02-1.12)	1.07 (1.02-1.13)
7-11 cycles	1.11 (1.03-1.19)	1.08 (1.00-1.17)	1.11 (1.03-1.19)	1.09 (1.01-1.17)	1.08 (1.00-1.16)
≥ 12 cycles	1.55 (1.46-1.64)	1.54 (1.44-1.63)	1.55 (1.46-1.64)	1.51 (1.43-1.59)	1.44 (1.36-1.52)
Parity (previous births)					
Nulliparous					
< 3 cycles	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3-6 cycles	1.02 (0.97-1.09)	1.01 (0.95-1.08)	1.00 (0.94-1.08)	1.01 (0.96-1.07)	1.02 (0.96-1.08)
7-11 cycles	1.00 (0.92-1.09)	0.99 (0.90-1.08)	1.00 (0.92-1.09)	0.99 (0.91-1.07)	0.99 (0.91-1.08)
≥ 12 cycles	1.27 (1.19-1.36)	1.27 (1.18-1.36)	1.27 (1.19-1.36)	1.26 (1.19-1.33)	1.23 (1.15-1.31)
One					
< 3 cycles	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3-6 cycles	1.02 (0.92-1.14)	1.05 (0.94-1.18)	1.02 (0.90-1.16)	1.03 (0.94-1.14)	1.02 (0.92-1.13)
7-11 cycles	1.01 (0.85-1.20)	0.95 (0.78-1.16)	1.01 (0.85-1.20)	1.07 (0.91-1.26)	1.01 (0.85-1.19)
≥ 12 cycles	1.45 (1.26-1.65)	1.47 (1.26-1.71)	1.44 (1.26-1.65)	1.45 (1.27-1.64)	1.36 (1.20-1.56)
Two or more					
< 3 cycles	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3-6 cycles	1.10 (0.94-1.29)	1.22 (1.00-1.49)	1.09 (0.91-1.32)	1.06 (0.92-1.23)	1.06 (0.91-1.25)
7-11 cycles	0.93 (0.70-1.22)	1.01 (0.71-1.43)	0.93 (0.70-1.22)	0.91 (0.70-1.18)	0.91 (0.69-1.20)
≥ 12 cycles	1.50 (1.20-1.86)	1.57 (1.19-2.06)	1.49 (1.20-1.85)	1.43 (1.17-1.75)	1.41 (1.14-1.75)

[a] Main model, adjusted for maternal age (at the time of trying to conceive) and pregnancy complications at the index pregnancy, maternal education, smoking and chronic conditions, accounting for women participating with several pregnancies.

[b] Analysis restricted to women below the age of 35 only, model adjusted for same factors as [a].

[c] Excluding pregnancies where the women responded "3 months or more" of trying to conceive without specifying the exact duration, model adjusted for same factors as [a].

[d] Analysis including both planned and unplanned pregnancies, model adjusted for same factors as [a].

[e] Main model adjusted for complications in the index pregnancy and same factors as [a].

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230847336 (print)
9788230861066 (PDF)