Reproductive factors and maternal long-term mortality

Frode Halland
Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2020
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Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 20.03.2020
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Year: 2020
Title: Reproductive factors and maternal long-term mortality

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Print: Skipnes Kommunikasjon / University of Bergen
Scientific environment

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Norwegian Institute of Public Health
Acknowledgements

When I started to work at The Women’s Clinic in Bergen in 2009, Nils-Halvdan was appointed as my supervisor. He was supposed to help facilitate my clinical progress. He did not, instead he lured me into research. We were both on call when he gave me an offer I could not refuse. It was as if he gave me a degree on a silver plate...

Nils later introduced me to the boss, Rolv Skjærven, and after a couple of strong beers and bicycle talk, I was approved for research. With Rolv it’s much about being a good listener… The two of them tailored a position for me and I slipped through the narrow needle eye and became a PhD candidate at UIB. Obviously, the three of us could not pull this off on our own, and Kari Klungsøyr was appointed as my third supervisor.

In addition to being «the man» in registry based reproductive epidemiology and statistics, my main supervisor, Rolv Skjærven, has this unique curiosity combined with a creative mind. He loves new ideas and encourages thinking, re-thinking and debunking of established knowledge. This has been truly inspiring and maybe the most important lesson learned. Rolv sees opportunities were others see obstacles, and luckily for us he refuses to retire.

Nils-Halvdan has a strong encouragement and delivers enthusiastic supervision. He is positive, structured and have both clinical expertise and scientific knowledge. He has kept me together and pushed me in the right direction whenever I drifted. Nils is both a «tusseladd» and a «nisse», and I am proud to be called the same, by Rolv, after our collaboration.

Kari Klungsøyr has kept the three of us in line. I am grateful for your patience, guidance, punctuality and thoroughness. Thank you for sharing your experience in perinatal epidemiology and your profound understanding and application of the medical birth registry.

Rolv is a superstar when it comes to research and I have had the privilege of being introduced to leading researchers in different countries. The collaboration with Allen Wilcox at the NIEHS has been very inspiring and fruitful for the research group. Wilcox has this unique ability to decipher complex problems, to focus the main findings and finally to express it in a clear and understandable manner. I had the privilege of discussing preliminary results and thoughts on his porch in North Carolina. With his overview, humble approach and ability to listen he demonstrated how collaboration with others can thrive research.
My base has been at the Departement of Global Public Health and Primary Care in the Research group of Registrybased studies of familial risks. My extended thanks goes to the friendly and helpful administrative staff. I am truly grateful to the members of the research group. All knowledge, inspiring and friendly fellow PhD candidates and seniors: Lorentz Irgens, Kjell Haug, Lisa deRoo, Liv Grimstvedt Kvalvik, Linn Marie Sørbye, Hilde Engjom and Aleksandra Pirnat. Thank you for your contribution, support and all the fun!

I am grateful for the everlasting support from my friends and fellow clinicians. Especially, I want to thank Ingeborg Bøe-Engelsen for pushing me when I rather wanted to ski, bike, run or pretty much anything other than finishing this thesis: «Bare få det gjort Frode! ».

I would like to express my gratitude to my family. My parents, Inger and Martin Halland, have always believed in me and supported me. Already at young age, they trusted me to make my own decisions and I can thank them for my independence and stubbornness. Finally, I am deeply grateful to Siri, and our three children. Your love, your encouragement and support, your laughter, your pranks, your annoyance and lack of understanding, has distracted me enough to keep me going.

Thank you!
Abstract

Background: Reproductive epidemiological studies are, at large, based on cross-sectional data focusing on the first pregnancy. Reproductive factors are found to affect maternal longevity and especially cardiovascular health. Present knowledge is limited by broad assumptions, insufficient follow-up and poor understanding of causation.

Objectives: We wanted to examine the association between number of births and maternal long-term mortality (paper I). Here we used paternal mortality by number of children to contrast maternal mortality. The second objective was to investigate reproductive patterns in mothers with perinatal losses (paper II). Finally, the third aim was to study the association between perinatal losses and maternal long-term mortality (paper III). In all papers we wanted to evaluate how maternal education (a proxy for socioeconomic status) modified the associations. We did the analyses in two strata of education; low (<11 years) and high (≥11 years).

Methods: The main data source was The Medical Birth Registry of Norway (1967–2009, papers I – III) with linkage to The Cause of Death registry (papers I and III) and the National Education database (papers I - III). The mothers’ unique national identification numbers were used to link all births to a given mother into sibling files. Only mothers with complete birth records were included (except analyses on the inter-pregnancy interval in paper II).

Results: Mothers with one birth, compared to mothers with two births and high education (reference), had increased mortality; cardiovascular mortality: low education, hazard ratio (HR) 4.0, 95% confidence interval (CI) 3.3 to 4.8, high education, HR 1.9, 95% CI 1.5 to 2.4; non-cardiovascular mortality: low education, HR 2.3, 95% CI 2.2 to 2.4, high education, HR 1.4, 95% CI 1.3 to 1.5.

For mothers with low education, cardiovascular mortality increased linearly with each additional birth above one (p-trend 0.02), for non-cardiovascular mortality there was no association. In contrast, for mothers with high education, cardiovascular and
non-cardiovascular mortality declined with additional births (p-trend 0.045 and <0.01, respectively). Paternal mortality followed similar trends when stratified on mothers’ education.

Of the 652,320 mothers, 29 per 1000 had one or more perinatal loss. Of the mothers with perinatal losses, only 6.2 percent had more than one loss. Perinatal losses increased the fertility in affected mothers. The fertility rate for mothers without losses was 2.22. For mothers with one loss the fertility rates was 3.19 (high education: 3.24, low education: 3.14). The inter-pregnancy interval was significantly shortened when the index birth was a perinatal loss compared to a surviving child. Mean difference in months with 95% CI; 1\textsuperscript{st} to 2\textsuperscript{nd} birth 17.7 (17.1 – 18.2), 2\textsuperscript{nd} to 3\textsuperscript{rd} birth 28.2 (27.3 – 29.2) and 3\textsuperscript{rd} to 4\textsuperscript{th} birth 26.3 (24.5 – 28.0). A perinatal loss in the first birth, and no subsequent loss, reduced the inter-pregnancy interval between the 2\textsuperscript{nd} and the 4\textsuperscript{th} birth from 40.2 months to 28.4 months. Risk of having a loss in the last birth increased with sibship size and previous perinatal losses.

Mothers with no surviving children and one perinatal loss, compared to one child-mothers without perinatal losses (reference), had excess mortality; cardiovascular mortality: low education HR 2.7 (1.4 – 4.3), high education HR 0.9 (0.13 – 6.5); non-cardiovascular mortality: low education HR 1.6 (1.3 – 2.2), high education HR 1.8 (1.1 – 2.9). Increased mortality in mothers with one perinatal loss and surviving children was only found in mothers with low education; cardiovascular mortality: two surviving children HR 1.7 (1.2 – 2.4), three or more surviving children HR 1.6 (1.1 – 2.4); non-cardiovascular mortality: one surviving child HR 1.2 (1.0 – 1.5), two surviving children HR 1.2 (1.1 – 1.4). In these analyses the reference category was mothers without losses and number of births equal to number of surviving children.

**Conclusions and implications:** Mothers with only one birth, compared to mothers with two, had increased long-term mortality. This applied both to women with low and high education. For mothers with low education, cardiovascular long-term mortality increased with increasing number of births above one. This increase was not observed for mothers with high education. The mortality pattern among fathers
was similar to that of mothers. A mother’s first birth, higher number of births and low
education was associated with perinatal loss. Perinatal losses increased fertility and
significantly shortened the inter-pregnancy interval. Selective fertility is a more
prominent factor in more recent times. Childless mothers with a perinatal loss had
excess long-term mortality. Among mothers with surviving children and one perinatal
loss, only mothers with low education had increased long-term mortality.

By examining long-term mortality in mothers with fixed shibships we have obtained
new knowledge and demonstrated heterogeneities in risk. We have also highlighted
that attained education, a proxy for socio-economic status, is strongly linked to
pregnancy complications and is a substantial modifying factor on associations
between reproductive factors and long-term maternal mortality.
List of publications


II: Halland F, Morken NH, Klungsøyr K, Skjærvén R. *Reproductive Patterns in Mothers with Perinatal Losses – Selective Fertility* (unpublished work)


In this thesis the papers will be addressed with the roman numbers listed above.

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1. Definitions and abbreviations

Birth number/order  The ordinal number of a specific birth relative to all previous births to a woman.


Gestational age  The duration of a pregnancy estimated from the last day in the last menstrual period or, from 1999, derived from ultrasound measurements in the first trimester of the pregnancy.

Early neonatal mortality  Death of a live-born baby before the 7th day of life.

Fertility rate  The average number of children born of a woman in her lifetime within a population. In this thesis, defined as the average number of registered births per mother in the Medical Birth Registry of Norway.

Inter-pregnancy interval  In this thesis, defined as the interval, in months, between a birth and conception of the next pregnancy (conception measured by ultrasound or if missing last menstrual period).

MBRN  Medical Birth Registry of Norway.

Neonatal deaths  Death of a live-born baby within the first 28 days of life.

Non-cardiovascular mortality  Mortality by other causes than cardiovascular (see cardiovascular mortality).
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Parity</td>
<td>The total number of viable pregnancies for a woman. In MBRN, the number of births of a woman from 16 weeks of gestation.</td>
</tr>
<tr>
<td>Perinatal death/ loss</td>
<td>Fetal losses from 22 weeks of gestation, stillbirths and neonatal deaths in the first week after birth. In this thesis, from 16 weeks of gestation.</td>
</tr>
<tr>
<td>Perinatal mortality rate</td>
<td>Perinatal deaths, per 1000 births.</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Development of hypertension with proteinuria or edema, or both, due to pregnancy or the influence of a recent pregnancy; it usually occurs after the 20th week of gestation.</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>Delivery before the end of the 37th week of gestation (&lt; 259 days).</td>
</tr>
<tr>
<td>Recurrence</td>
<td>In this thesis (paper II), defined as two or more perinatal losses.</td>
</tr>
<tr>
<td>Selective fertility</td>
<td>A tendency for a woman to replace a perinatal loss.</td>
</tr>
<tr>
<td>Sibship</td>
<td>A group of individuals born of the same parents. In this thesis defined as a group of individuals with the same mother.</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>A fetus or baby born without vital signs after 22 weeks of gestation (WHO 28 weeks of gestation). In this thesis, counted after 16 weeks of gestation (In the MBRN 0.2% of all births were late miscarriages, &lt;22 weeks).</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>Infants whose weight is &lt; the 10th percentile for gestational age.</td>
</tr>
</tbody>
</table>
Surviving child  In this thesis, defined as a child surviving the first week after birth.

**Statistical abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>MD</td>
<td>Mean difference</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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2. Reproductive and life course epidemiology

Reproductive health: “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and its functions and processes. Reproductive Health, therefore, implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when, and how often to do so. It also includes sexual health, the purpose of which is the enhancement of life and personal relationship, and not merely counselling and care related to reproductive and sexually transmitted diseases.” (Defined by the WHO, Cairo conference in 1994)

Reproductive epidemiology does not traditionally cover all aspects listed in the definition above, but focus determinants of diseases related to reproduction in human populations. Main topics are fecundity, pregnancy, birth and early markers of child health (1).

Following the “Barker hypothesis”, of early life influence on chronic disease, life course epidemiology evolved. Life course epidemiology is the study of long-term biological, behavioural, and psychosocial processes that link adult health and disease risk to physical or social exposures during gestation, childhood, adolescence, adulthood, and between generations (2). A branch of life course epidemiology is based on the hypothesis that reproductive factors can trigger dormant disease or cause physiological alterations that lead to chronic disease in a mother and effect long-term morbidity and mortality.

The importance of population-based registries in studies on associations between reproductive factors and long-term mortality

A women’s later-life mortality risk can be derived by predisposing factors and exposures in life. Especially in developed countries where women have long lifespans, the reproductive window is relatively short and makes competing risk a major challenge when evaluating associations between reproductive exposures and longevity (Figures 1 & 2). Population-based registries, with extensive follow-up,
provide large data sets that enable studies of weak and time-limited exposures such as reproductive factors.

Figure 1

Risk exposure during a lifespan

**Lifespan**

- Birth
- Reproductive window
- Death

Exposure

Competing risk

Figure 2

Competing risk during a lifespan

**Competing risk:**

- Physical health
- Reproductive exposures
- Lifestyle
- Maternal longevity
The predictive value of a woman’s reproductive history – the fixed sibship approach

Most reproductive epidemiological studies are based on cross-sectional data. To avoid bias by repeated observations one common method is to study the first pregnancy only. Another approach is to include repeated pregnancies and adjust for parity, thereby treating the pregnancies as independent events. Many researchers seem to neglect that women who stop reproducing after one pregnancy have increased mortality compared to mothers with two or more pregnancies (3, 4).

Given the fact that adverse pregnancy outcomes are related and effect the sibship size of a given mother (5) a “longitudinal” method of analysis has been applied intermittently since the late 1960ies (6, 7). In 1979, Bakketeig and Hoffman (B&H) reported perinatal mortality by birth order and sibship size (8). In contrast to previous cross-sectional studies (9, 10), they found that perinatal mortality decreased with increasing parity. This led to a controversy fronted by Jean Golding (11) and Nathan Mantel (12). The study was denounced because of accusations of bias, and in the following the longitudinal method was characterized as a blind alley. However, the discussion continues, and one important focus in reproductive epidemiology is the weaknesses of conventional analysis where standard adjustments of parity, or restricting to 1st births only, are the chosen strategies (13-18).

The B&H data covered the period from 1967 to 1973, and included mothers with one, two, three or four singleton pregnancies. Absolute numbers were: 96,705, 67,297, 11,828 and 1,050 mothers, respectively, with corresponding percentages: 54.7, 38.0, 6.7, and 0.6. Using our current data, we reconstructed the B&H material utilizing the same study population (women with first births in 1967 to 1973), but now with follow-up until 2009. With complete sibship data, we got the following corresponding percentages: 14.5, 49.7, 28.3, and 7.5.

Thus, the original B&H data was extremely biased in terms of lifetime number of pregnancies due to lack of follow-up. To have 4 pregnancies during a 7 year period is
extreme, and obviously, to achieve that, the distances between pregnancies have to be very short.

Due to the above, it may be hazardous to rely on results based on a fixed sibship size analytical strategy as a prediction model when data are based on incomplete reproduction. However, with sibship data covering the included women’s complete reproduction, the selection bias is reduced or even eliminated, and valid interpretations are possible.

It is recognized that repeated pregnancies are dependent events, and strong associations between pregnancy complications in the first and second pregnancy have been reported in several studies (19-24). The predictive value of looking at reproductive exposures by the mothers’ total reproduction within the reproductive period is limited, as it is impossible for a clinician to foresee a mother’s final number of pregnancies. However, retrospective studies of mothers with completed reproduction can have great value in risk assessment and differentiation when the outcome, i.e. long-term maternal morbidity and mortality, occur after the closure of the reproductive window. A pregnancy is a stress test that may reveal dormant or future risk of disease (25, 26), and successful intervention to reduce mortality associated with reproductive factors depends on accurate risk assessment. In life course epidemiology, applying the longitudinal method with complete birth records, compared to the cross-sectional (1st birth), has the potential to prevent invalid conclusions and generalized risk assumptions and could facilitate targeted intervention.
3. Physiological changes in pregnancy

The old saying, “a child, a tooth” (women with more children having fewer teeth) illustrates a long-standing concern about the physical cost of childbearing. A study of identical female twins found that the twin with more children indeed had fewer teeth (27). The disposable soma theory builds on the idea of a trade-off between reproduction and longevity (28, 29). The theory predicts that high physical demands in females (young age at first birth and high parity) will shorten their post reproductive lifespan.

Some studies have, however, shown beneficial effects of pregnancies on maternal longevity. A historical dataset from Britain found a positive association between higher age at first and last birth and longevity in aristocratic women (30). High age at last birth was also correlated with a long lifespan in historical Sami mothers (31) and in an Old Order Amish community (32). More recent cohort studies, also indicate that increased longevity is associated with late births (33-36). A population-based study of Norwegian middle-aged mothers found that mortality was highest for the childless and next highest for the mothers with one child compared with those with two children. Having more than two children was found to be protective (3). Another Norwegian population-based study found that male and female cancer patients had increased survival if they had children (37).

The sum of physiological changes in a mother following a pregnancy and postpartum resolution depends on; the preconceptional physiological status, the pregnancy itself and health status during and after pregnancy (diet, weight gain/ loss, smoking and physical activity). Repeated pregnancies may accumulate physiological changes in a mother. The sum of alterations may be harmful, balanced or beneficial (Figure 3).
To ensure fetal growth and development, the circulatory system of the mother undergoes dynamic physiological changes. In a normal pregnancy, cardiac output is increased and peripheral vascular resistance (PVR) is reduced along with a decrease in blood pressure (Figures 4 & 5) (38). The haemodynamic changes are similar to those seen with physical training and exercise (39). Weight retention (40) and long-term declines in high density lipoprotein (HDL) after pregnancy (41) may adversely affect long-term risk of cardiovascular disease.
Figure 4

Cardiac Output and PVR before, during and after pregnancy

PVR: peripheral vascular resistance.

Figure 5

Serial Blood Pressures before, during and after pregnancy

Systolic, diastolic and mean arterial pressure. (Figure 4 and 5, reproduced with permission from American Heart Association, Wolters Kluwer Health Inc. License Number: 4466530438282. Sanghavi & Rutherford, Circulation. 2014;130:1003-1008.)
Rejuvenating effects on the pregnant mother

As the organs age there is a reduction in the regenerative capacity of the tissue (42). Scientists now speculate if pregnancy could have rejuvenating effects on the mother. Recent studies on old mice have found that pregnancy can restore the regenerative capacity of the liver (43) and enhance the capacity to repair demyelination in the CNS (44). A rat model demonstrated pregnancy-induced regeneration after cardiac ischemic injury (45). Another study on myocardial infarction found improved contractile function in the heart after treatment with stromal cells derived from placental tissue (46). Substantial regression of cardiac hypertrophy in old mice was found after exposure to the circulation of young mice, heterochronic parabiosis (Figure 6). The same study identified a circulating factor (GDF 11) in young mice, which had the same effect as parabiosis when used as treatment in old mice (47). Validation studies on the effect of GDF 11 has not been able to reproduce this finding (48). Pregnancy is akin to a natural mix of blood circulations between a young and an old individual and fetal cells are present in the maternal circulation in all human pregnancies (microchimerism) (49). A liver biopsy from a woman with hepatitis C showed tissue regeneration and the hepatocytes had a male fetal origin (50). However, it is not clear whether persisting fetal cells in mothers are a random finding, are pathogenic (induce autoimmune disease) or act as regenerative stem cells (51). One theory is that fetal cells in mothers explain why women live longer than men. The present knowledge indicates that different pathways and mechanisms may play an important role.
Regeneration of myocardial hypertrophy in old mice by heterochronic parabiosis or GDF 11 – therapy. (Reproduced with permission from Elsevier, Inc. License Number 4270111185956. Growth Differentiation Factor 11 Is a Circulating Factor that Reverses Age-Related Cardiac Hypertrophy, Cell. doi.org/10.1016/j.cell.2013.04.015.)
4. Reproductive factors associated with maternal mortality

Infant health has long been the primary focus in relation to pregnancy complications, but gradually there has been an increasing interest in pregnancy outcomes and implications for maternal longevity (26, 52-55). One might assume that factors being beneficial for the health and survival of the fetus would prove beneficial for the mother as well. However, it is important to recognize that the fetus resembles a parasite and the mother a host. For a woman with severe preeclampsia, an early perinatal loss versus a surviving child with higher gestational age, may actually be protective because of reduced strain on her circulatory system. Uncomplicated and complicated pregnancies differ in their prediction of future health. Sattar and Greer have suggested that pregnancy act as a stress test to reveal subclinical vascular and metabolic disease (25).

In 2011, the American Heart Association listed preeclampsia, gestational diabetes mellitus, preterm birth, and birth of a child small for gestational age as pregnancy related risk factors for maternal cardiovascular disease (56). The different factors will, in the following, be briefly presented according to the literature.

Preeclampsia

A review from 2007, found that women with preeclampsia had increased later-life risk of vascular disease, relative risks (RR) (95% confidence interval): hypertension 3.70 (2.70 to 5.05), ischaemic heart disease 2.16 (1.86 to 2.52), stroke 1.81 (1.45 to 2.27) and venous thromboembolism 1.79 (1.37 to 2.33). Overall mortality after preeclampsia was 1.49 (1.05 to 2.14) (54). Another review from 2013, reported a doubling in risk of future cardiovascular and cerebrovascular events in mothers with preeclampsia compared to unaffected mothers (55). The mechanisms behind the association of preeclampsia and later life cardiovascular disease are not fully established and the generalized long-term mortality risk of mothers with preeclampsia
was debunked by Skjærven et al. in 2012 (57). In contrast to most studies on maternal health, who used information from the first pregnancy only, they assessed mortality of mothers with complete reproductive histories. The increased risk of cardiovascular death associated with preeclampsia was primarily found in mothers who never had another delivery (figure 7).

**Figure 7**

[Graph showing CVD mortality by preeclampsia (term/ preterm) and number of pregnancies. Skjaerven et al., BMJ, 2012]

**Gestational diabetes mellitus**

Of mothers with gestational diabetes, approximately 50% develop type-2 diabetes mellitus within 5 years (58), and a high generalized risk was described in an extensive review (59). Having gestational diabetes, compared to a normo-glycemic pregnancy gave a seven-fold increased risk of future type-2 diabetes mellitus (59) and a 70% increased risk of later cardiovascular disease (60).
Preterm birth and birth of a child small for gestational age

Two systematic reviews from 2014 (61) and 2016 (62) on the association between preterm birth and maternal cardiovascular mortality reported a doubling of risk compared to term birth. A population-based study from Sweden reported a significant interaction between preterm birth and fetal growth on mothers’ risk of cardiovascular disease. Mothers with infants very small for gestational age (approximately 2 SD below the mean) had adjusted hazard ratios (HR) of cardiovascular disease at 1.38 (95% confidence interval 1.15-1.65) and 3.40 (2.26-5.11) if infants were term and very preterm, respectively (63). It is well-established that offspring birth weight is inversely correlated to maternal cardiovascular disease risk, the lower birth weight the greater the risk (26, 64, 65). However, a Norwegian population based study from 2018, reported increased maternal cardiovascular mortality in mothers having large preterm babies, HR 1.5 (1.03-2.2) (66).

The American guidelines does not include perinatal loss as a maternal risk factor for cardiovascular disease. The long-term effect on maternal mortality associated with perinatal loss is understudied and complex because of bereavement. One cohort study, from the Jerusalem Perinatal study, compared mothers with at least one stillbirth, with mothers with only live births and found increased mortality, hazard ratio 1.40 (95% confidence interval 1.02-1.77) (67). Stillbirth was especially associated with increased mortality from cardiovascular causes. A recent Danish population based follow-up study found that mothers with a perinatal loss had increased mortality, and especially from cardiovascular disease, adjusted hazard ratio 2.29 (95% confidence interval 1.48-3.52) (68).

There is an ongoing debate whether pregnancy complications (preeclampsia, preterm birth, small for gestational age etc.) are manifestations of dormant, pre-existing cardiovascular disease or mediators of cardiovascular risk or both.
5. Determinants of health and disease

The social determinants of health (SDH) are the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems (69).

Socioeconomic inequalities in health in high-income countries

All high-income countries have substantial inequalities in health within their populations. It is a general understanding that socioeconomic position should be derived from individual-level indicators like highest level of completed education, occupation or income (70). In high-income countries, mortality and morbidity rates usually increase with a stepwise decrease in socioeconomic position (71). It is assumed that social inequalities affect the health of nearly everybody, as a gradient, emphasizing that explanations should be pursued in factors acting across society (72). Higher mortality with relative inequalities are found at all ages, but the association is strongest in early middle age (73). However, because of rising average mortality rates at older ages, absolute inequalities tend to increase with age. Throughout Europe, mortality is found to be higher in people with low education, but varies substantially among countries (Figure 8) (74). In Norway, the reported relative index of inequality for women with lowest education was 2, indicating twice the mortality risk of women with highest education. Mortality rates of the higher educated are comparable in different high-income countries. This implicates that the relative difference in inequality between countries is driven by variation among the least educated. One reported explanation for this is that the lower educated are more susceptible to unfavourable national conditions (75).
Relative inequalities in mortality by level of education in 16 European countries, 1990s. Inequalities between women with the lowest level of education and those with the highest. (Reproduced with permission from (N Engl J Med, Mackenbach JP et al. 2008;358:2468-2481), Copyright Massachusetts Medical Society.)

**Trends**

Despite a growing understanding of social inequalities and a general decline in mortality rates, mortality differences between socioeconomic groups in European countries have increased during the twentieth century (76-78). One possible explanation, is a difference in mortality decline/ increase between socioeconomic groups. In times of economic and social development, the higher socioeconomic groups experience a faster mortality decline, especially for cardiovascular disease, than the lower groups (79). In times of recession, mortality rates tend to rise faster in lower socioeconomic groups than in higher (80). In both settings, the changes in mortality are not equally shared and the gap between socioeconomic groups widens. Differences in life expectancy, between the lowest and the highest socioeconomic groups, have been reported to increase in more recent time in several European countries (71). Differences of inequality between countries are manifested in both total and cause-specific mortality (73, 74). For the Nordic countries and the United Kingdom, especially large inequalities were reported for cardiovascular mortality and
ischaemic heart disease (81, 82). After the Second World War, there was a substantial increase in ischaemic heart disease mortality, especially in the Nordic countries, probably caused by changes in health-related behaviours (smoking, diet and physical exercise). During the 1970s, ischaemic heart disease mortality started to decline in the population as a whole. In the 1950s and 1960s, the highest mortality was found in the higher socioeconomic groups (manager’s disease), but as the mortality declined there was a shift towards a higher mortality in the lower socioeconomic groups (83, 84). This gradient is now the current association in northern Europe and is due to different timing and speed of the decline in mortality in socioeconomic groups.

**Mechanisms explaining health inequalities between socioeconomic classes**

Causal pathways partly explain social inequalities of health. Material, psychosocial and behavioural risk factors are listed as the three major contributors (70).

**Material factors**

Financial resources are at large unevenly distributed between social classes. People with financial disadvantage are exposed to psychosocial stress linked to risk-taking behaviour and have limited access to health-promoting services and products. In countries with large income inequalities, the average life expectancy is lower and mortality rates are higher than in countries with a more even distribution of wealth (85, 86). Material factors associated with low income and poor health are occupational health risks (chemicals, accidents, strenuous work, etc.), bad housing and environmental risks (pollution, noise, etc.) (87).

**Psychosocial factors**

Low socioeconomic position is associated with psychosocial stressors: personal loss, financial strain, every-day challenges, unfavourable effort-reward balance, lack of control, etc. (88). In addition, disadvantaged persons have smaller networks, less social support (89), and less effective coping styles (90). Negative psychosocial factors generate unhealthy behaviour (smoking, drug and alcohol abuse, lack of
physical training, etc.) and induce biological adverse effects. Long-term stressors are associated with neural, endocrine, and immune system changes which increase the risk of developing a range of diseases (91).

**Health-related behaviours and life-course perspective**

Smoking is one of the most important determinants of health problems and inequalities. Over all, the highest prevalence of smoking is in the low socioeconomic groups. Comparative studies have found that especially in northern Europe disadvantaged people smoke more than people in higher socioeconomic groups and the difference was even greater in women (92, 93). In Norway, the prevalence of smoking during pregnancy decreased in all education groups from 1999-2000, but the relative risk between the groups increased significantly (Figure 9) (94). This suggests that smoking is an even stronger determinant of health problems and inequalities today.

**Figure 9**

Smoking at the beginning of pregnancy in educational groups in the years 1999–2014, in Norway. (Reproduced with permission from Nicotine & Tobacco Research, Grotvedt et al. 10.1093/ntr/ntw313, License Number: 4466540997672, Copyright Oxford University Press.)
In alcohol-consuming adults, having lower education compared to the highest level of education gave an almost three times increased risk of excess alcohol consumption (95, 96). Financial problems and low social support partly explained the association, but education was described as an independent significant marker. A follow-up study on drug and alcohol abuse in Danish men reported that deprived social conditions at young age and poor school performance seemed to correlate with substance abuse in adult life (97). Physical inactivity is also found to be strongly related to low educational attainment (98). Especially perceived control and material factors were key indicators of educational differences. In 1989, an extensive review on the relation between socioeconomic status and obesity reported contrasting patterns in developed and developing countries (99). In developed societies, a consistently inverse association for women was observed, with a higher probability of obesity with lower socioeconomic status (negative association). In developing societies, a higher likelihood of obesity was correlated with higher socioeconomic status (positive association).

In 2007, McLaren published an update to the original review (100). The aim was to study obesity patterns across societies (different socioeconomic development settings) and to focus associations of obesity and specific indicators for socioeconomic status. In general, the social variations related to obesity were stronger for women compared to men. The negative association between socioeconomic status and higher body weight for women in highly developed countries were strongest for the indicators education and occupation, but in general somewhat weaker than the previous review reported. In developing countries, the reversed positive association was strongest for the indicators income and material status. So, even in an on-going obesity epidemic, where virtually all social groups were affected, the original findings of Sobal and Stunkard (99) were validated. However, McLaren argued that trends related to globalization (diet changes in different socioeconomic groups, introduction of western media etc.) gradually would shift the burden of obesity to groups of low socioeconomic status also in developing countries.
In European populations, the association of increasing likelihood of obesity with lower socioeconomic status is consistent (101). The rise in obesity is a major contributor to the epidemic of type 2 diabetes mellitus and women with diabetes mellitus have a substantially increased risk of myocardial infarction and stroke (102).

The weathering hypothesis implies that health deteriorates in early adulthood because of aggregation of negative socioeconomic factors (103). A life-course perspective has been used to explain accumulation of risk in disadvantaged persons (104, 105). Higher long-term mortality rates in low socioeconomic groups are seen as a result of socially patterned exposures acting at different times in a lifespan. One disadvantage increases the likelihood of another at a later point in time. Chains of events can also reinforce each other and induce a downward social mobility (106). Low socioeconomic status may translate into health disadvantages and facilitate an even lower social position later on.

**Socioeconomic position and reproductive patterns**

Low educational attainment is associated with young maternal age. In later life, early motherhood is associated with several adverse social outcomes, including failing partnerships, high parity and poorer housing conditions (107). In addition, teenage motherhood is found to increase the risk of psychiatric morbidity in adulthood. In Canada, it is estimated that as many as one third of all pregnancies may be unintended (108). The women with unintended pregnancies were characterised as younger, less educated, had a lower income and were more likely in unstable relationships. Among the mothers with unintended pregnancies, the only significant predictor of not using any form of contraception was low educational attainment.

Mothers with low compared to high education more frequently experience complicated pregnancies (109-113). In a life-course perspective, reproductive factors may induce social mobility, raising a child with a mental or physical disability, or just raising many children can compromise social involvement, educational attainment.
and a career. Even with the extensive evidence of socioeconomic inequalities in health, researchers seem to underestimate the association between low education and pregnancy complications and adverse outcomes.

The mechanisms explaining the excess mortality risk associated with higher parity are not established. Some insight have been provided by analysing the association of paternal mortality and number of children. If the association was similar in mothers and fathers, a causal explanation linked to the pregnancy itself would be unlikely and would rather indicate that social confounding was causing the effect. Cardiovascular mortality in fathers have been analysed and those who had the highest number of children had increased risk (114-116). Adjusting for lifestyle factors, most commonly education, weakened the associations of mortality and parity/number of children in both mothers and fathers (116, 117). These results suggest that the association of parity and mortality in mothers may at large be explained by socioeconomic status.

The need to belong

«No man is an island, entire of itself; every man is a piece of the continent, a part of the main. If a clod be washed away by the sea, Europe is the less, as well as if a promontory were, as well as if a manor of thy friend's or of thine own were. Any man's death diminishes me because I am involved in mankind; and therefore never send to know for whom the bell tolls; it tolls for thee. »

Poem by John Donne, Meditation 17.

Lack of attachments is strongly linked to material, psychosocial and behavioural risk factors in disadvantaged persons. It is a fundamental human motivation to build interpersonal attachments. In a far-reaching review, Baumeister and Leary consolidate that belongingness is critical for human development (118). Hence, low educational attainment and early motherhood may be an obstacle for personal growth.
6. Socioeconomic position and reproductive patterns in Norway

In 1913, following the Grand Duchy of Finland, Norway was the second country in Europe to grant universal woman’s suffrage, and equal rights for women and men were gradually obtained. After the Second World War, Norway gradually evolved into a social democracy with vast financial resources derived from oil reserves (from the 1970s). The strong Norwegian welfare state is based on gender equality and encourages and supports education, career building and, importantly, pregnancies at the same time.

Since the 1960s, Norway has progressively overcome the conflict between childbearing and rearing and pursuing a career. It is now an ideal to combine a career with having children. Women enter long education tracks prior to- or in parallel to having children. Employees who become pregnant are protected by strict rules that regulate employment, dismissal and maternity leave. Both studying and working pregnant women get financial support through stately welfare programs. This setting builds stability and encourages women to have their desired number of children in addition to pursuing a career. The increase in female education rate was a major trend in the 20th century (Figure 10). Normativity changed from having low education (<10 years) to high education (11 or more years). The Norwegian cohort is therefore a reference population containing a high number of educated and uneducated mothers with both high and low parities. Analyses of demographic data from 26 countries found a consistent association between higher education and lower fertility (119). Previous studies on parity and mortality may be biased because educated mothers tend to have few children (low parity) while uneducated mothers tend to have more children (higher parity). Investigation of the 1964 birth cohort of women in Norway, suggested that early childbearing was a strong marker for leaving or not entering a long education track (120). This led to the hypothesis that in Norway, childbearing impeded education more than education restricted childbearing. If this is the case,
early motherhood could be an early marker for both future accumulation of negative lifestyle factors and higher parities.

**Figure 10**

Women's educational attainment in years in Norway during the 20th century. F. Halland (unpublished)
7. Aims of the work

Our aim was to describe associations between birth outcomes and long-term maternal mortality. We wanted to provide more accurate risk assessments by examining women with completed reproduction. We hypothesised that current generalized risk assessments of maternal long-term mortality and reproductive factors could be biased because of inappropriate handling of social factors as well as by analysing only first pregnancies. We wanted to disentangle this problem by analysing data stratified on level of education and to use paternal mortality to contrast maternal mortality. We used sibling data from the MBRN for the period 1967 to 2009.

Research objectives

Paper I. To investigate the association between number of births and maternal long-term mortality by socioeconomic factors. We hypothesised that the parity effect would be dependent on the mothers’ educational level.

Paper II. To investigate reproductive patterns in mothers with perinatal losses. We hypothesised that a perinatal loss would increase a mother’s fertility and that the association would be modified by the mothers’ educational level.

Paper III. To investigate the association between perinatal losses and maternal long-term mortality. We hypothesised that the impact of perinatal losses would be modified by additional surviving children and the mothers’ educational level.
8. Materials and methods

Data sources

The studies were based on linked data from The Medical Birth Registry of Norway (MBRN) and the Cause of Death Registry with data from 1967 to 2009, as well as with the National Education Database which provided educational level as registered in 2009.

Medical Birth Registry of Norway

The MBRN, established by the Directorate of Health in 1967, is the world’s first national medical birth registry. Registration is legally mandated for all births from 16 weeks of gestation and counts approximately 3 million births in 2019. The original purpose of the registry was: “epidemiological surveillance of birth defects and other perinatal health problems in order to detect, as soon as possible, any future increase in rates” (121). The registry prospectively collects data on maternal health before and during pregnancy, any complications during pregnancy or birth, and birth outcomes. This includes information about labour interventions, birth complications, maternal complications after birth, vital status of the baby at birth, and neonatal diagnoses in the child including congenital anomalies. Since 1999, information about maternal smoking habits, medication use in pregnancy and use of folic acid before and during pregnancy, as well as ultrasound based estimation of gestational age has been included. In addition, mandatory reporting to the MBRN from all neonatal intensive care units for infants transferred to such units after birth was introduced in 1999. The extensive registry with its long follow-up is especially useful when studying rare exposures and to test epidemiological hypothesis.

In Norway almost every child is delivered in a hospital (>99%) (122). The Norwegian maternity units are responsible for notifying deliveries to the MBRN, using a standard notification form, one form per child. The notification forms are sent continuously, and at the latest one week after discharge. The first notification form, virtually unchanged from 1967 to 1998, was a paper form mainly based on free text
specifications to questions about the mother’s health before and during pregnancy (including pregnancy complications), induction of labour, interventions during delivery and birth outcomes (Appendix A). Free text was coded at the MBRN using the International Classification of Diseases (ICD), 8th version. In December 1998, a new MBRN notification form was introduced, based on check boxes, and, as mentioned above, including some new information (Appendix B). Information provided by free text has since 1999 been coded using ICD-10. From 2005, electronic notification to the MBRN was gradually introduced, and completed by 2007 (Appendix C). This notification is based on extraction from the medical records filled out at the delivery units. Information about the pregnancy is collected from a standard antenatal chart, which the woman carries with her to the delivery unit, and/or by interview.

In Norway, the National Registry provides unique national identification numbers (personal ID numbers) to each live born individual after birth, as well as to immigrants coming to live in the country. The MBRN is routinely linked with the National Registry, and through this linkage, the birth registry receives national identification numbers for fathers and children, and ascertains the mothers’ ID numbers (included on the birth notification forms). In addition, marital status for mothers, and all dates of death and emigration for mothers, fathers and children are included from the National Registry. The routine linkage also ensures complete registration of all live born children in the MBRN, as births in the National Registry that have not been reported to the MBRN, are specifically requested from the delivery units.

Due to the mandatory reporting and several quality tasks performed at the MBRN, there are few missing births in the registry, especially livebirths (121). Further, since the MBRN uses the unique national identification numbers (which includes birth dates) as identifiers for all mothers, fathers and children, maternal age is complete for all women with national identification numbers. Dates of death for mothers, fathers and children are included from the National Registry, and will not have missing data for individuals living in the country. Parity and infant birthweight have very little
missing data (<1%), while the proportion of missing gestational age at delivery has varied throughout the registry period, increasing from around 4% during the first decades to above 8% in the late 90s, and then dropping to less than 1% after 1999 when ultrasound based estimation was included in the registry.

The MBRN has undergone extensive quality control throughout its history and has been validated with medical records for a number of outcomes, such as diabetes and asthma (123), rheumatoid arthritis (124), preeclampsia (125, 126), obstetric sphincter tears (127), uterine ruptures (128), offspring oral cleft (129) and Down syndrome (130), most with satisfying results. The validity of MBRN data on diagnosis of unexplained antepartum fetal death was found sufficient for future large-scale epidemiological studies. Compared with clinical and autopsy data, the sensitivity and specificity were 78% and 88%, respectively (131).

**Record linkage**

As mentioned, the national identification numbers, provided from the National Registry, are included in the MBRN. They are critical for identifying individuals in the MBRN and facilitate linkage of birth records to create family units. All registered births to a given mother can be linked in sibling files (maternal sibships). This allows analyses on mothers with complete reproductive histories. Up to 2015, there are registered more than 1.4 million maternal sibships in the MBRN.

The ID number is also used to link the MBRN data to other data sources, including other population based registries in Norway. In the present project, the MBRN data were linked to the Cause of Death Registry for causes of death and the National Education database for maternal educational level. The Norwegian Cause of Death Registry records and dates every death and contains information on causes of death. Causes of deaths are coded using the ICD (7th revision for years 1967-68, 8th revision for years 1969-85, 9th revision from 1986-95 and 10th revision from 1996). The National Education Database, Statistics Norway, contains individual information on all education received in Norway (132). All Norwegian inhabitants from 16 years
of age are covered and the registry is routinely updated every year. The data are categorized, based on number of completed years of education.

**Study design and study populations**

*Population-based sibling data*

The three studies in the present thesis are population-based retrospective cohort studies, utilizing registry-based data. The main file used for analyses contained all births in Norway from 1967 to 2009. All births were linked to their mothers by means of the mothers’ national identification numbers, providing sibling files with the mother as the observation unit. Mothers with complete reproductive histories were analysed – utilizing a fixed sibship approach.

*Confounding by social factors*

To control for confounding by social factors we did stratified analyses by education in years (low: less than 11 years and high: 11 or more years). It is common to categorize education into three levels: low (< 11 years), middle (11 - 14 years) and high (≥ 15 years). In the preliminary analyses we recognized that the difference in effect was between low, and middle and high education. This justified the dichotomization, and our second level (high) contained both middle and high education.

*Exclusions*

In paper I-III we excluded mothers born outside Norway. In paper II and III we further exclude mothers with plural pregnancies and mothers missing information on education. These differences, along with different approaches to ensure follow-up time in paper I, and paper II and III, explain the discrepancies in the study populations (listed below).
**Paper I**

In paper I, we investigated age specific (40 to 69 years) maternal mortality (cardiovascular and non-cardiovascular) in relation to the total number of births. A total of 527,964 mothers with 1,258,075 births were included. Of the total, 283,912 mothers had low education and 242,402 had high education (1,650 mothers missing information on education, 0.3%). Fifteen percent of the mothers had one birth, 46% had two, 29% had three, 8% had four, and 3% had five or more. There were 16,664 maternal deaths. Only mothers with complete reproduction within the registry period (1967 to 2009) were eligible. To ensure that the women had completed their reproduction, mothers with a first birth after 1990 were excluded. The mothers then had at least 19 years follow-up time to complete their reproduction. Of mothers with 5 children, approximately 90% completed their reproduction within 19 years. In a sensitivity analysis, we expanded the sample to include mothers with births before and after 1967, partly based on self-report. To contrast maternal mortality we analysed paternal mortality in relation to their total number of children. A total of 427,688 fathers were included. The reduced number (compared to mothers) reflects that information on fathers were missing for approximately 2%, but more importantly we only included men who were registered as father for all of the children to a given mother.

**Paper II**

In paper II, we retrospectively studied reproductive patterns in mothers with perinatal losses. A total of 652,320 mothers were included, 311,374 mothers had low education and 340,946 had high education. Of the mothers, 2.9% experienced perinatal losses (18,636). To ensure long enough follow-up for all mothers to have almost complete reproductive histories, we truncated the data to include only women who had at least 7 years follow-up after their last pregnancy. This would allow time for women to have an additional registered pregnancy by 2009 (95% of women in Norway have their second birth within 7 years of the first). The data used for analyses on the inter-pregnancy interval was not truncated, because it was no indication to do so.
**Paper III**

In paper III, we investigated age specific (40 to 69 years) maternal mortality (cardiovascular and non-cardiovascular) in relation to perinatal loss. During follow-up there were 16,490 maternal deaths. The study population was the same, and we applied the same truncation to ensure follow-up, as for paper II. As most mothers (94 percent) had only one perinatal loss in their reproductive history, this group of mothers was our main focus.

**Variables**

*Mothers age at first birth.* The mothers age, in years, at the time of her first registered birth in the Medical Birth Registry of Norway (MBRN).

*Number of births (number of children).* Refers to the total number of births registered in the MBRN. Births were counted from 16 weeks of gestation. A twin pregnancy is registered as two births.

*Sibship.* The total number of births registered in the MBRN, from 16 weeks of gestation, to the same mother.

*Last birth.* The last registered birth in the MBRN to a given mother.

*Inter-pregnancy interval.* In this present thesis defined as the period, in months, between birth of a child and conception of the subsequent pregnancy registered in the MBRN. Conception was derived from ultrasound or if missing from last menstrual period.

*Stillbirths.* In the present thesis defined as a fetus/ baby born at or after 16 completed weeks of gestation and showing no signs of life at birth.

*Perinatal deaths.* In the present thesis defined as a stillbirth (as defined above) or an early neonatal death (death of a child during the first week after birth).
Overall mortality. Death due to all causes in the Cause of Death Registry. Causes of death were based on complete data from the Cause of Death registry.


Non-cardiovascular mortality. Defined as deaths other than cardiovascular deaths. Causes of death were based on complete data from the Cause of Death registry.

Statistical analysis

Statistical analyses were done utilising SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA) versions 20.0-22.0.

Long-term maternal mortality was the main outcome in paper I and III. In paper II, we analysed reproductive patterns in mothers with perinatal losses. In all papers, the analyses were based on mothers with completed reproduction. We analysed age specific mortality (40 to 69 years), most mothers have completed their reproduction at the age of 40 years. From analysing the data there was a tendency that associations between pregnancy factors and maternal mortality faded as the mothers reached higher age. We therefore studied premature death, which today are deaths that should be prevented, and the upper age limit was set to 69 years at time of death.

Hazard ratios. The main statistical approach in paper I and III was to study time to death (mortality). Mothers and fathers were followed from time of their own birth to either death or censoring. We applied Cox proportional hazard models to calculate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

Odds ratios. In paper II, the main statistical approach was to study risk of a perinatal loss by birth order and by having a perinatal loss in the last birth, stratified by sibship
size. We applied logistic regression analyses to calculate adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

**Trends.** In paper I, we used regression models to evaluate linear trends (p-trend) in mortality risk by increasing number of births above one.

**Effect modification/Interactions.** Interaction on the multiplicative scale was tested by inclusion of an interaction term in the multivariate analyses. Paper I: we estimated whether level of education modified the association between number of births and mortality (education * parity). Paper III: we evaluated whether education modified the association between a perinatal loss and maternal mortality (education * loss).

**Stratification.** The interaction terms mentioned above were statistically significant, and we therefore did stratified analysis by educational level, low (<11 years) and high (≥11 years) (all papers).
9. Ethical considerations

All papers were based on anonymised, compulsory data and individual consent was not necessary. The studies were approved by the internal review board of the Medical Birth Registry of Norway (2009/1868).
10. Review of papers

Paper I


Objective. Present knowledge indicates a positive association between increasing number of births and especially cardiovascular risk in mothers. There is uncertainty about the mechanisms behind the association. We wanted to investigate whether number of births was correlated to long-term maternal mortality (death at 40 to 69 years) and modifications by socioeconomic factors (level of education).

Materials and methods. The sibling data used were from the MBRN, with births registered from 1967 to 2009. The data were linked to the Cause of Death Registry and the National Education Database. In total, 527,964 mothers were eligible, and 16,664 died during follow-up. To evaluate the effect of social versus biological factors on the association between mortality risk and number of births, we did stratified analyses by mothers’ education (low: <10 years and high: ≥11 years). We also carried out interaction analyses, using a multiplicative model, to evaluate modification by maternal education on the association between number of births and maternal mortality. Using a regression model we evaluated linear trends in the association between mortality and number of births above one. In a sensitivity analyses we also included mothers with self-reported births before the start of the registry (1967) and within the registry. To explore unmeasured social confounding we analysed paternal mortality risk by number of children in strata of spouses’ education.

Results. Independent of number of births, mothers with low compared to high education had increased mortality risk; cardiovascular: HR 2.62, 95% CI 2.34 to 2.93, non-cardiovascular: HR 1.67, 95% CI 1.62 to 1.73. There was a significant interaction between number of births and educational level for cardiovascular and
non-cardiovascular mortality (p<0.01 and p=0.02, respectively). Mothers with one birth, compared to mothers with two births and high education, had a high mortality risk; cardiovascular: low education, HR 4.0, 95% CI 3.3 to 4.8, high education, HR 1.9, 95% CI 1.5 to 2.4, non-cardiovascular: low education, HR 2.3, 95% CI 2.2 to 2.4, high education, HR 1.4, 95% CI 1.3 to 1.5. Hazard ratios for cardiovascular mortality among mothers with low education increased linearly with increasing number of births from two to five or more (same ref. as above); (p-trend=0.02) HR 2.4, 95% CI 2.0 to 2.8 (two births) to 3.1, 95% CI 2.2 to 4.5 (five or more births). In contrast, for mothers with high education, cardiovascular mortality risk declined with increasing number of births from two to five or more (p-trend=0.045). Risk for non-cardiovascular mortality was not associated with number of births above one in low educated mothers (p-trend=0.11), but again in high educated mothers there was decreasing risk with increasing number of births above one (p-trend=<0.01). Father’s mortality followed the same pattern, as for mothers, when we stratified on maternal education.

Conclusions. Mothers with only one birth, compared to mothers with two, had increased long-term mortality. Only in mothers with low education, and for cardiovascular causes, did we find an association between increasing number of births and maternal mortality. Higher number of births in mothers with high education was associated with decreased mortality. Fathers’ mortality followed the same pattern.

Paper II

Reproductive Patterns in Mothers with Perinatal losses – Selective Fertility.
Halland F, Morken NH, DeRoo LA, Klungsøyr K, Skjærvén R

Objective. Present knowledge, based on historical data, indicates that perinatal loss increase fertility and shorten the inter-pregnancy interval. We wanted to reevaluate whether perinatal losses alter reproductive patterns, and to identify differences by mothers’ attained education.
Materials and methods. The sibling data used were from the MBRN, with births registered from 1967 to 2009. The data were linked to the National Education Database. A total of 652,320 mothers with 1,465,023 births were eligible. There were 19,923 perinatal losses and 18,636 mothers experienced one or more perinatal losses. Only 6.2 percent of mothers with perinatal loss had more than one loss. In the mothers, we estimated occurrence of having one or more perinatal losses by sibship size, and occurrence of number of perinatal losses from one to six and recurrence rate. By number of perinatal losses, we assessed mothers by number of surviving children, and we calculated fertility and surviving children rates. We analysed perinatal mortality, stratified by sibship size, by birth number. We estimated OR’s for having a perinatal loss in the last birth by sibship size and previous perinatal losses. Finally, we analysed differences in the inter-pregnancy interval in mothers with a perinatal loss compared to mothers with a surviving child. In two strata of the mothers’ attained education, we evaluated differences in effect of perinatal loss (low <11 years, high ≥11 years).

Results. Occurrence and recurrence of perinatal loss was associated with low maternal education (low education: 34 and 66, high education: 24 and 55 per 1000). Mothers without losses had a fertility rate of 2.25 and mothers with one loss had a rate of 3.19. First born siblings had the highest perinatal mortality in all sibship sizes. There was a strong association with increasing risk of perinatal mortality and higher parity. For each birth number the perinatal mortality rate increased with sibship size above one. The perinatal mortality rates for the second birth were, for mothers with two births 3.2 per 1000 and for mothers with five births 51.7. For all sibship sizes the last sibling had the lowest perinatal mortality rate, but the rate increased with higher sibship sizes. Risk of perinatal loss in the last birth increased with sibship size above one and previous perinatal losses (reference, sibship size two and no previous perinatal loss): sibship size two and one previous loss OR (95% CI) 15.0 (12.1 to 18.6), sibship size three; no previous loss 1.6 (1.5 to 1.8), one previous loss 5.9 (4.9 to 7.1), two previous losses 35.9 (20.5 to 63.0). The inter-pregnancy interval, between the 1st and the 2nd birth, after a perinatal loss, compared to a surviving child,
decreased substantially (12.5 and 30.2 months, respectively. Mean difference (95% CI) 17.7 (17.1 – 18.2).

Conclusions. Perinatal losses significantly modify reproductive patterns by increasing fertility and by shortening the inter-pregnancy interval. A first birth, previous perinatal losses and low education increase the risk for perinatal loss.

Paper III


Objective. Present knowledge indicates a positive association between perinatal loss and mortality risk in mothers. We wanted to investigate whether perinatal loss was associated with long-term maternal mortality (death at 40 to 69 years), and whether surviving children and attained education modified the associations.

Materials and methods. The sibling data used were from the MBRN, with births registered from 1967 to 2009. The data were linked to the Cause of Death Registry and the National Education Database. In total, 652 320 mothers were eligible, and 18,636 experienced one or more perinatal losses. Of the total number of mothers, 16,490 died during follow-up and of these deaths, 769 had a history with a perinatal loss. We analysed age-specific (40-69 years) cardiovascular and non-cardiovascular mortality. We calculated crude mortality in mothers with perinatal losses compared to mothers without and evaluated modifications on the crude ratios by level of education and surviving children. Stratifying by number of births, we analysed mortality in mothers with one and two or more losses, compared to mothers without losses. In strata of mothers’ attained education (low <11 years, high ≥11 years), we did the following analyses. For mothers with only one birth, we analysed mortality in those with a perinatal loss compared to mothers without. We further estimated mortality in mothers with one perinatal loss by number of surviving children relative mothers.
without losses and number of births corresponding to number of surviving children. Finally, in strata of education, we compared mortality in mothers with two or more births whether there was a loss in the first or in the last birth. Here the reference group was mothers with two births and no perinatal loss. We also carried out interaction analyses, using a multiplicative model, to evaluate whether educational level modified the association between a perinatal loss and maternal mortality.

**Results.** Overall, crude mortality in mothers with one perinatal loss was increased; cardiovascular: HR 1.8, 95% CI 1.5 to 2.1, non-cardiovascular: HR 1.3, 95% CI 1.2 to 1.4. Maternal educational level modified these associations, and in mothers with high education, the excess mortality associated with a perinatal loss was almost eliminated. Having no surviving children gave a two-fold increase in the crude estimates. Surviving children attenuated the risk. Having increasing number of births in mothers with one perinatal loss weakened the mortality risk in an almost linear fashion. In mothers with more than four births there was no longer a significant excess mortality risk. Having two or more losses compared to one loss gave increased hazard, but also here increasing number of births attenuated the risk. Childless mothers with one perinatal loss had excess mortality compared to mothers with one child and no loss; cardiovascular: low education, HR 2.7, 95% CI 1.7 to 4.3, high education, HR 0.91, 95% CI 0.13 to 6.5, non-cardiovascular: low education, HR 1.6, 95% CI 1.3 to 2.2, high education, HR 1.8, 95% CI 1.1 to 2.9. In mothers with surviving children and one perinatal loss, excess mortality was only found in mothers with low education; cardiovascular: two surviving children, HR 1.7, 95% CI 1.2 to 2.4, three or more surviving children, HR 1.6, 95% CI 1.1 to 2.4, non-cardiovascular: one surviving children, HR 1.2, 95% CI 1.0 to 1.5, two surviving children, HR 1.2, 95% CI 1.1 to 1.4. In mothers with two or more births we found no significant differences in mortality whether the loss was in the first or in the last birth. Few mothers had a loss in the last birth compared to a loss in the first birth. There was a significant interaction between perinatal loss and education for cardiovascular mortality (p=0.027).
Conclusions. Childless mothers with a perinatal loss have excess long-term mortality, especially of cardiovascular causes. In mothers with one perinatal loss and surviving children, increased mortality was only found in mothers with low education (however this excess risk decreased by increasing number of surviving children).
11. Discussion of methods

Internal validity

Internal validity refers to the degree of systematic error in a study. To what extent a causal conclusion is warranted depends on minimization of systematic errors. The main systematic errors are classified as selection bias, information bias and confounding.

Selection bias / selection of individuals

Selection bias is present when the study population differs from the population you want to study. More precisely, you have selection bias when the association between an exposure and an outcome varies in the study population and the background population (133).

The source population, in this thesis, is based on all births in Norway, with a close to 100 percent coverage in the MBRN. Since this population based registry is based on mandatory reporting of all births in the country, including stillbirths from 16 gestational weeks, selection bias is not a systematic error of major concern in our studies.

If a longitudinal approach is applied, as the fixed sibship size method, short follow-up time will systematically place mothers in lower sibship groups (8). It is hazardous to rely on results based on a fixed sibship size analytical strategy as a prediction model when data are based on incomplete reproduction. However, with sibship data covering the included women’s complete reproduction, this selection bias will be marginalised, and valid interpretations emerge. In the papers I-III, we have extensive follow-up and the analyses are based on complete reproduction.

When the exposure is related to reproduction and the outcome is maternal morbidity/mortality, inadequate follow-up time is a significant concern. The largest previous population-based study on the association between parity and later-life maternal
cardiovascular disease had a median follow-up time of 9.5 years starting from the age of 50 (4). This approach is robust and selection bias is less likely. In contrast, the largest previous study of perinatal loss and maternal mortality should be interpreted with caution because of potential selection bias (68). There were few deaths (1.06 percent) and pregnancy related deaths were included (only mothers who died the same calendar day that they gave birth were excluded). The mean age of death was 37 years in the exposed group (perinatal loss) and 41 years in the unexposed. Median follow-up time was 15 years from exposure (perinatal loss). Truncation of deaths to younger ages will tend to elevate the estimated mortality risk (57).

The maternal mortality ratio (MMR; number of maternal deaths per 100 000 livebirths) varies substantially between regions. The definition of maternal death, in this setting, is the death of a woman while pregnant or within 42 days of termination of pregnancy (The World Health Organisation). In 1990, the worldwide estimate was 283, in developing countries 318 and in developed countries 25. In Norway the ratio was 5.9 (134). Subsequent pregnancies accumulate maternal mortality risk in an additive manner.

In contrast to most studies on reproductive factors and maternal mortality we analysed long-term mortality, defined as age specific mortality at 40 to 69 years. By doing this, mothers with pregnancy related deaths, haemorrhage, sepsis, thromboembolic or cardiac disasters etc., were close to excluded from the study population (only 1.9% of mothers in the MBRN are 40 years or more at delivery). In developed countries pregnancy related deaths are mainly caused by pre-existing conditions and evidently increasing age is a risk factor (135). Including these deaths when analysing long-term mortality will tend to distort the results, especially if the follow-up time is limited (clustering of maternal deaths at time of birth and in the postpartum period). In paper I, all mothers had at least 19 years of follow-up time after their first birth. In paper II and III, the mothers had at least 7 years of follow-up time from their last birth. The median follow-up time from birth of the mother to death or censoring was in paper I and III 54 and 52 years, respectively. This is to our knowledge the longest follow-up times in register-based studies of maternal mortality.
and reproductive factors. Even with this substantial follow-up time selection bias can be present, but the aim in paper I and III was to study premature death. A significant correlation between an exposure and mortality depends on differences in life expectancy in the exposed and unexposed group.

The variation in hazard by follow-up time (mother’s age at death) is demonstrated below (Figure 11, unpublished results). The figure displays maternal CVD mortality risk by preeclampsia (term or preterm) in the first birth and total number of births (one versus two or more) in five age-at-death groups. As follow-up increases, more mothers of higher age will be included. Deaths due to other causes will be prevalent, and mortality risk by preeclampsia will be reduced.

**Figure 11**

![Preeclampsia and CVD death](image)

Mothers with missing information on education were excluded (0.3 percent). In general, this small group of mothers had excess mortality risk and could therefore represent a cluster of mothers with low/no education. However, this small group of
mothers are not likely to distort our results and when left out we would, if anything, expect a conservative estimate for mothers with low education.

We had selection by design. In all the studies we only included mothers born in Norway and therefore the results are not applicable for first generation immigrants. The exclusion was done to ensure a more equal socioeconomic background in the study population. We used education as a proxy for socioeconomic status and this method would not apply equally well for immigrants. For example, immigrants with high education from their home country would appear as having missing or no education in our data. In papers II and III we excluded mothers with plural pregnancies. Prevalence of perinatal mortality in mothers with plural pregnancies was 10 percent (in our data), contrasting 2.9 percent in mothers without plural pregnancies. The causal relation between higher plurality and perinatal mortality was the reason for this exclusion.

**Information bias/ misclassification**

In epidemiology, information bias is defined as bias arising from measurement error, misclassification (133). Misclassification can either be non-differential or differential. Non-differential information bias is when all categories of a variable have the same probability (same error rate) of being misclassified for all study subjects (136). Differential information bias arise when the probability (error rate) of being misclassified differs between groups of study subjects. If non-differential misclassification is present the effect will be biased towards the null value. If differential misclassification is present the effect will tend to be exaggerated or underestimated.

**Social class and health determinants.** Mothers’ attained education was used as a proxy variable for socioeconomic status (70). We used two levels of education: low (less than 11 years) and high (eleven or more years). The mothers included in the study population were evenly distributed between the two groups (paper I: low 54, high 46 percent, Paper II and III: low 48, high 52 percent). The difference in percentages between the papers was because of different inclusion criteria. Mean year
of birth for mothers in paper I was 1954, and in papers II and III 1957. Having low education was more common for mothers in the 1960s and 1970s. So the association between low education and low socioeconomic status was less consistent at that time. As a consequence, older mothers were more likely to be misclassified as having low socioeconomic status and they were also the ones at highest risk of dying during follow-up time. The current association between negative health determinants and low education emerged during the 1970s (83, 84). Before this time period, negative health determinants (smoking, diet, physical exercise, obesity etc.) were more evenly distributed between low and high education mothers. This further adds uncertainty to the use of education as a proxy for socioeconomic status for the older mothers. In our analyses, we tried to control for this bias by adjusting for the mothers’ year of birth.

Paternal mortality by number of children was estimated in strata of the spouses’ education (high and low). As we only used fathers’ mortality to explore the role of unmeasured social confounding in mothers, the misclassification of socioeconomic status in mothers would be similar in fathers and hence not affect the comparison.

**Paper I.** In a sensitivity analysis, mothers with self-reported births before 1967 and births in the MBRN were included. We did this to include more mothers at the cost of potential misclassification of parity. As we included mothers with perinatal losses, a mother’s parity based partly on self-report may have been underestimated in some cases. Some mothers could neglect perinatal losses, especially early losses, when reporting number of births before 1967. Even though this tendency to “forget” previous losses might theoretically be higher in mothers who later die prematurely than in mothers who do not, this differential misclassification will not likely distort the results significantly, as perinatal losses were rare events (overall occurrence 2.9 percent). We found the same trends in the sensitivity analysis as in the major analysis.

**Confounding**

A confounder is a causal concept. You have bias by confounding when a variable effects both the independent variable (exposure) and the dependent variable (outcome), thus representing a common cause (133, 137, 138). In this work, we
evaluated possible confounders based on the hypothesis of common causes. In all papers, we adjusted for the mothers’ or fathers’ birth year, using a linear term. We did this to handle effect differences by calendar time. To handle social differences, we stratified the analyses by education, low and high. In paper II and III we also adjusted for mothers’ age at first birth. Both young age (<20 years) and older age at first was associated with increased risk of perinatal loss. The adjustments were significant, but the results were not substantially changed. The stratified analyses gave contrasting results.

**Paper I.** The association of parity and long-term maternal mortality was analysed in strata of education. To evaluate residual social confounding in each strata we evaluated paternal long-term mortality by number of children. Any association in fathers would be unrelated to the physiological events of pregnancy. We found similar patterns for maternal and paternal mortality by number of births/children. This indicates that the differences in maternal mortality risk by parity in part is biased by residual social confounding.

**Effect modification/ moderation (interaction)**

An interaction, or effect modification, may be found when evaluating the relationship between three or more variables. When the simultaneous influence of two variables on a third is not additive there is an interaction (133). Most frequently, interactions are considered in the context of regression analyses. Interaction on the multiplicative scale was tested by inclusion of an interaction term in the multivariate analyses. We found significant interactions by mothers’ level of education on the association between parity and long-term mortality, and on the association between perinatal loss and long-term cardiovascular mortality. Consequently, analyses were stratified on maternal education, low and high.
**External validity**

External validity refers to the extent to which the results of a study can be generalized to different situations and people (133). Internal validity is a requirement for external validity. The Norwegian cohort of mothers is an ideal population even compared to other populations in developed countries.

In paper I we conclude that social differences are the most likely explanation to the diverging mortality risk by parity above one between levels of maternal education. Cultural differences in different societies are likely to influence the estimates somewhat. However, we demonstrate that a biological explanation is less plausible. This is generalizable as the physiology of pregnancy is more or less independent of cultural differences.

**Precision**

The precision in estimated associations is reduced by random errors. Higher precision can be achieved by increasing the study population and by optimizing the study design. In epidemiological studies, increasing the sample size is the principle way of increasing precision (133).

In the present work, the large population-based study sample and the compulsory registration of data provided a high level of precision in most estimates, demonstrated by narrow confidence intervals. However, we studied rare events (premature maternal deaths) in strata of mothers’ attained education, and for some analyses the precision was week (few cases and few deaths).
12. Discussions of the results

Paper I

Most studies on maternal longevity and number of births find that mortality is highest for those with the highest parities. In the recent Swedish study, the conclusion was that risk of future cardiovascular disease followed a J-shaped risk-pattern. Mothers with two births had the lowest risk and mothers with five or more had the highest risk (4). We identified this pattern also in the Norwegian overall data, but only for cardiovascular mortality (Figure 12A).

Most studies on reproductive factors and maternal mortality recognize that social factors play a role, and adjust for education. Due to the significant interaction by mothers’ level of education on the association between parity and long-term mortality adjusting is not warranted. We therefore stratify the analyses by maternal education, low (<11 years) and high (≥11 years) (Figure 12B).

Figure 12

Maternal cardiovascular mortality by number of births, overall (A) and stratified by the mother’s education in years (B). Norwegian-born women, first birth after 1966 and before 1991. Adjusted for the mothers’ birth year. HR, hazard ratio; CI, confidence interval; ref, reference.
The stratified results were striking and contrasted the current understanding. Only in mothers with low education (<11 years) did we find the J-shaped pattern. In mothers with high education (≥11 years), there was no increasing risk of cardiovascular long-term mortality with higher number of births.

In 2017, Skjærven, published a follow-up study using updated data with maternal deaths to the end of 2014, thus including five additional years (Figure 13) (139). The original results were confirmed, in fact strengthened. In the high education group, cardiovascular mortality was significantly reduced in mothers with three and four births compared to mothers with two. The J-shaped association in the low education group was weakened. However, in this updated analysis, the highest number of births was four or more.

Figure 13

This is similar to the original findings for non-cardiovascular mortality (Figure 14 A and B). Mortality was in general higher for mothers with low education, but there was no evidence of increasing mortality with higher number of births above one (Figure 14B).

Figure 14

Maternal noncardiovascular mortality by number of births, overall (A) and stratified by the mother’s education in years (B). Norwegian-born women, first birth after 1966 and before 1991. Adjusted for the mothers’ birth year. HR, hazard ratio; CI, confidence interval; ref, reference.

Mortality is strongly linked to lifestyle factors, especially death of cardiovascular causes. The most plausible explanation to the diverging stratified curves (Figure 12B, pg. 57) is residual social confounding. The association between higher parity and lifestyle factors may be contradictory in the two education groups (the weathering hypothesis). Higher cardiovascular mortality associated with increasing parity in mothers with low education may be caused by accumulation of negative lifestyle factors, and the reverse association in mothers with high education may be explained by accumulation of beneficial social factors. For example, among women with high education, having many children may represent a deliberate choice, with a selection of the healthiest women in the high-parity groups. Among women with low education, having many children may more often represent random happenings, and
be associated with an opposite selection in the high parity groups. We evaluated smoking patterns in higher parity mothers to test the hypothesis of accumulation of positive health determinants in the high education group and negative in the low education group. In the MBRN, smoking is recorded from 1999. Prevalence of smoking in the second birth was the outcome and we compared mothers with two births to mothers with three or more births. Among mothers with high education, the smoking prevalence decreased with 19 percent (from 5.1 percent to 4.3 percent). In mothers with low education, we found the opposite pattern: Here the prevalence increased with 9 percent (from 25.1 to 27.6 percent).

When comparing mortality in mothers and fathers we found that the two groups were fairly similar. Fathers tended to have the same relative mortality as the mothers by education and parity. This finding supports the theory that educational level and parity combined are important determinants for risk due to social factors.

Rich-Edwards et al. presented three possible mechanisms to explain the observed increase in cardiovascular mortality in relation to higher number of births: 1) accumulation of physiological change in repeated pregnancies, 2) unhealthy lifestyle, and 3) selection bias, women with high cardiovascular risk choose to have many children (26).

We cannot rule out the possibility of accumulation of physiological effects by repeated pregnancies. If so, our results indicate protective effects, contrasting previous theory. A beneficially altered physiology in mothers with higher parities, may be outweighed by accumulation of negative social factors in mothers with low education and higher parities.

It is important to emphasize that the Norwegian cohort of mothers, in contrast to most other populations, benefit from a system that encourages having children without compromising education and career building. In our cohort of mothers, parity is evenly distributed between the two education groups. We fear that this is not the case in many other populations. Studies on parity and mortality will then be biased
because of selection - mothers with higher parity will predominantly have low education.

Giving birth to many children does not seem to negatively affect longevity. Our results actually suggest the opposite - that a high number of births may increase longevity in mothers (139). Again, this may partly be due to the mentioned selection of healthy women choosing to have more children. In a world where fertility rates are dropping and educated women choose not to have children, this is an encouraging finding.

The modal family size in the study population, irrespective of education, was two or three children (75 percent of mothers). A small group of mothers ended up with only one birth (15 percent). This suggests that mothers with only one birth are more likely to suffer from secondary infertility. Severe pregnancy complications may preclude successive births and neonatal outcomes may discourage further pregnancies. After deciphering the J-shaped association between parity and mortality, the one-birth mothers constitutes a particular high-risk group. Mortality in one-birth mothers, compared to two-birth mothers, was similar in both strata of education, cardiovascular mortality 80 percent increased and non-cardiovascular mortality 40 percent increased. Also for one-birth mothers there was a strong social gradient, two-fold increased mortality risk in low compared to high education mothers. Subfertility is associated with impaired maternal and paternal health (male and female factors) (140, 141), and unfavorable prepregnat lipid values is associated with having none or only one child (142). Interestingly, we found increased mortality also in fathers with only one child. The strong association between long-term mortality and having only one birth, irrespective of education, implies that reduced fertility may be a biological marker for reduced longevity both for mothers and fathers.

**Paper II and III**

Perinatal losses seem to influence the long-term health in mothers. A recent Danish study reported 80 percent increased overall mortality and 130 percent increased cardiovascular mortality in mothers with perinatal loss compared to mothers without
This study, or to our knowledge any other study, did not account for the reproductive history of the mother following a loss. Was the loss her only birth, did she experience a consecutive loss or did she have one or more successful succeeding pregnancies? Stillbirths are difficult to predict, 30 to 50 percent are unexplained and only 10 percent are associated with maternal medical conditions (143). Is a perinatal loss a random unfortunate event or a result of inherent biological conditions in the embryo or the mother? Perinatal losses have multifactorial causation with great heterogeneity. Even so, generalized risk assumptions of perinatal loss and maternal mortality are made. By doing this, a mother with severe preeclampsia and a mother with a fetus with a trisomy are placed in the same group when evaluating the association of perinatal loss and maternal mortality risk.

As we concluded in paper II, pregnancies are dependent events and a perinatal loss altered the reproductive pattern in most mothers. The normal response, shortly after a perinatal loss, was to give birth to a “replacement child”. This effect, called selective fertility, was found irrespective of education. However, the effect was more consistent in mothers with high education (higher continuation rate, shorter inter-pregnancy interval). Occurrence of a perinatal loss increased with higher parity and was more frequent in socially disadvantaged mothers (40 percent increased risk in mothers with low versus high education). In general, mothers with low versus high education had increased mortality: overall mortality 170 percent, cardiovascular mortality 400 percent increased. We found a significant interaction between perinatal loss and education for cardiovascular mortality (p=0.027). In other words, low education (associated with higher prevalence of obesity, smoking etc.) seems to be a common pathway for both risk of experiencing a perinatal loss and long-term maternal mortality, and especially for cardiovascular causes. When we analysed mothers with a perinatal loss and surviving children, excess mortality was only found in mothers with low education. One possible explanation is that these mothers constitute a sub-group, within the low education group, of more disadvantaged mothers.
Of the mothers with one perinatal loss, less than six percent ended up as childless (low and high education: 6.7 and 5.0 %). Compared to mothers with one birth without perinatal loss, childless mothers with a perinatal loss had excess non-cardiovascular mortality. Cardiovascular mortality was only significantly increased in mothers with low education. Interestingly, this is in accordance with historical data from Norway where childless mothers had the highest long-term mortality risk followed by mothers with one child, compared to mothers with two children. (3) The MBRN does not include women without pregnancies. Could the excess mortality in childless mothers with a perinatal loss be similar to mortality risk in women without pregnancies? Obviously several factors are involved - a woman must desire children, she must have a partner (historically) and she must be fertile. The first two conditions are likely to be present in mothers with a perinatal loss. On the other hand, primary infertility is likely to be more closely linked to compromised health than secondary infertility. The new knowledge on selective fertility, as a modifier, suggests that secondary infertility plays a role in childless mothers with a perinatal loss. In this unfortunate group, low and high educated mothers had the same excess risk of non-cardiovascular mortality. However, we found contrasting patterns of causes of death in the two groups. In the high education group, we found indication of a causal association between exposures, leading to deaths, and compromised fertility. Of the deaths, 50 percent were caused by cancer (69 percent in reproductive organs), 32 percent experienced traumatic injuries and 13 percent had diseases not linked to life-style factors. The proportion of life-style related deaths was only 6.5 percent. In contrast, in the low education group causes of death were strongly linked to social factors, 41 percent, and half of these were alcohol or drug related. This gradient implies different causation for infertility in the two groups - biological limitations in mothers with high education and negative lifestyle factors in mothers with low education.

There was only one death of cardiovascular causes among childless mothers with high education and a perinatal loss. Although we didn’t have statistical power to evaluate the risk, the fact that we didn’t have deaths indicates a week association between perinatal loss and later mortality. If a perinatal loss was a causal factor we
would expect to find a strong relation in mothers with high education (less competing risk). However this was not the case.
13. Conclusions

A woman’s reproductive history is affected by time trends, social factors and fertility (including pregnancy outcomes and health status). Repeated pregnancies should therefore not be treated as independent events. By recognizing the simple fact - that social factors are linked to both a mother’s education and parity, we have tried to disentangled historical concerns, a tooth for a child and the disposable soma theory, about multiparity and later life mortality. Giving birth to many children does not seem to reduce longevity (paper I).

Selective fertility is not a new term, but it has not been incorporated in reproductive terminology. We demonstrate the chain of effects set of by a perinatal loss in a mother. The inter-pregnancy interval is dramatically shortened, her fertility increases and she finishes with a surviving child. By recognizing the normal reproductive pattern following a perinatal loss, we could detect the mothers who responded atypically and identify potential risk groups (paper II). Irrespective of education, excess maternal mortality was found in childless mothers with a perinatal loss. Higher mortality in mothers with a perinatal loss and surviving children was only present in low educated mothers, indicating a relationship driven by accumulation of negative social factors (paper III).

Mothers with only one birth, with or without a perinatal loss, had the highest long-term mortality risk, especially for cardiovascular causes (papers I and III). The high risk in one birth mothers is in accordance with previous findings, but in the light of our interpretation of the association of parity and mortality our results stand out (no evidence of a J-shaped relation). Even though we find a social gradient (doubling of risk in low education mothers), this was found irrespective of education. The ratio between cardiovascular mortality risks for mothers with one birth versus four births (RR) was 2.8 in mothers with high education and 1.4 in mothers with low. The difference in the ratios between the two education-strata (two-fold, 2.8/1.4=2, in high-education mothers) points towards a biological causation explaining the high
mortality found in one birth mothers and supports the hypothesis that reduced fertility is associated with increased mortality, especially of cardiovascular causes.

Our results are relevant for public health and clinical practice as well as for future studies. We have applied a longitudinal approach and looked at fixed sibships, a method denounced as a blind alley. When estimating risk later in life, after the closure of the reproductive window, this method can help identify mothers at risk and hopefully initiate targeted intervention to prevent future disease.

This thesis also leaves a question mark. What is the applicability for future risk assessment based on cross-sectional studies looking at first pregnancies only, or studies that treat repeated pregnancies as independent events? As a clinician, I will be cautious to present generalized risk assessments concerning a mother’s future health based on the outcome of her first pregnancy only.
14. Future implications

Cardiovascular disease (CVD) is one of the major contributors to maternal mortality. It is estimated that one out of three women dies of CVD (144, 145). Ischaemic heart disease is also listed as one of the leading causes of death in 2030 (145). Cardiovascular disease presents itself differently in men and women. It is estimated that as many as two out of three cardiovascular deaths in women occur without previously recognised symptoms (146).

Most previous studies on reproductive factors are limited by reliance on information from the first pregnancy, overlooking information from later pregnancies. We have demonstrated that examining long-term mortality in mothers with complete pregnancy histories enables the identification of heterogeneities in risk. We have also highlighted the strong relation between low socioeconomic status, pregnancy complications and excess later life mortality. The focus forward would be to disentangle generalized risk estimates of reproductive outcomes (preeclampsia, preterm birth, gestational diabetes, fetal growth) and later life mortality, especially of cardiovascular causes. Impaired fertility as a common cause in mothers with adverse pregnancy outcomes and few children would be one of the main hypotheses.

We should analyze mothers with complete birth records. If an interaction is present between maternal education and a reproductive exposure, stratification is warranted. To estimate residual confounding we should compare maternal and paternal mortality. To test the hypothesis that pregnancy complications may have direct long-term effects, the risk in sisters with and without a history of pregnancy complications should be compared.

Reproduction indeed seems to be a stress test, especially for later life CVD risk. The Medical Birth Registry of Norway now has the power to shed light on complex associations related to childbearing. If done properly, this could off-set early identification of mothers at risk, especially for CVD, and inform disease prevention strategies for women.
15. References


69. WHO. Commision on Social Determinants of Health (CSDH). 2013.


16. Appendix


Vennligst benytt skrivemaskin ved utfylling av blanketten

Medisinsk registerering av fødsel

Statens Helsetilsyn
Postboks 9132 Dep. 0033 OS-O

Menig: Det skal fylles ut blanketten for hvert barn (født). Der bør det etter fødselen, skal det også fylles ut i legenæringen om detaljer, og skjer detaljens melding til skriveren (leveransmen).
Appendix C: Electronic birth notification, The MBRN (2005 - )
17. Papers I-III
Long-term mortality in mothers with perinatal losses and risk modification by surviving children and attained education: a population-based cohort study

Frode Halland,1 Nils-Halvdan Morken,1 Lisa A DeRoo,2 Kari Klungsøy,3 Allen J Wilcox,4 Rolv Skjaerven5

ABSTRACT

Objective: To assess the association between perinatal losses and mother’s long-term mortality and modification by surviving children and attained education.

Design: A population-based cohort study.

Setting: Norwegian national registries.

Participants: We followed 652,320 mothers with a first delivery from 1967 and completed reproduction before 2003, until 2010 or death. We excluded mothers with plural pregnancies, without information on education (0.3%) and women born outside Norway.

Main outcome measures: Main outcome measures were age-specific (40–69 years) cardiovascular and non-cardiovascular mortality. We calculated mortality in mothers with perinatal losses, compared with mothers without, and in mothers with one loss by number of surviving children in strata of mothers’ attained education (<11 years low), ≥11 years high).

Results: Mothers with perinatal losses had increased crude mortality compared with mothers without; total: HR 1.3 (95% CI 1.3 to 1.4), cardiovascular: HR 1.8 (1.5 to 2.1), non-cardiovascular: HR 1.3 (1.2 to 1.4). Childless mothers with one perinatal loss had increased mortality compared with mothers with one child and no loss; cardiovascular: low education HR 2.7 (1.7 to 4.3), high education HR 0.91 (0.13 to 6.5); non-cardiovascular: low education HR 1.6 (1.3 to 2.2), high education HR 1.8 (1.1 to 2.9). Mothers with one perinatal loss, surviving children and high education had no increased mortality, whereas corresponding mothers with low education had increased mortality; cardiovascular: two surviving children HR 1.7 (1.2 to 2.4), three or more surviving children HR 1.6 (1.1 to 2.4); non-cardiovascular: one surviving child HR 1.2 (1.0 to 1.5), two surviving children HR 1.2 (1.1 to 1.4).

Conclusions: Irrespective of education, we find excess mortality in childless mothers with a perinatal loss. Increased mortality in mothers with one perinatal loss and surviving children was limited to mothers with low education.

INTRODUCTION

The long-term effects of perinatal losses on maternal mortality are unclear. A recent Danish population-based study found increased mortality in mothers with perinatal losses.1 A body of studies indicates that grieving a lost child can induce poor physical and mental health and increase later-life mortality.2–5 However, pre-existing risk factors, genetic and lifestyle induced, can represent shared pathways for a perinatal loss and excess mortality in later life.6–8 Of all perinatal losses, stillbirths account for more than 50%, and between 30% and 50% of the stillbirths remain unexplained.7 8 Only 10% of stillbirths are associated with maternal medical conditions, predominantly hypertension and diabetes.9 The most important risk factors for stillbirths in developed countries are nulliparity, obesity and advanced maternal age, obesity and smoking being the highest-ranking modifiable risk factors.
In general, low educational attainment is highlighted as a major stressor affecting women during pregnancy and childbirth, increasing the likelihood of adverse outcomes like perinatal loss.\textsuperscript{10} 11

The normal response to losing a child is to have a new child.\textsuperscript{13} 14 Studies on the effects of a replacement-child on the grieving process show diverging results. Morbid grief reactions\textsuperscript{13} and severe anxiety\textsuperscript{16} 17 have been reported. On the other hand, replacing a loss with a subsequent child is found to alleviate the grief\textsuperscript{18} 19 and is associated with less depression.\textsuperscript{20} 21

The aim of the study was to assess the association between perinatal losses and long-term maternal mortality and the modifying effects of surviving children and attained education.

**MATERIALS AND METHODS**

We conducted a population-based cohort study on long-term mortality of mothers with perinatal losses registered in the Medical Birth Registry of Norway from 1967 to 2003. Perinatal deaths were in this study defined as fetal losses from 16 weeks of gestation, stillbirths and neonatal deaths in the first week after birth. Surviving children were defined as children surviving the perinatal period. The Medical Birth Registry of Norway has recorded delivery data since 1967, with registration legally mandated for all births from 16 weeks of gestation. The Medical Birth Registry includes data on demographics, maternal diseases and detailed pregnancy and delivery information, as well as infant outcomes. The Medical Birth Registry of Norway is routinely matched with the Central Person Register, which provides every live-born infant in Norway with a unique national identification number. Mothers are registered with their unique identification numbers, which enables all births to a given mother to be linked in sibling files with the mother as the observation unit. Causes of death came from the Norwegian population-based Cause of Death Registry. Cardiovascular causes of death were defined as ischaemic heart diseases, I20–I25 (International Classification of Disease, 10th Revision (ICD-10)), 410–414 (ICD-8 and ICD-9) and cerebrovascular diseases (stroke), I60–I69 (ICD-10), 430–438 (ICD-8 and ICD-9). Non-cardiovascular causes of death were defined as all other than cardiovascular (ICD-8, ICD-9 and ICD-10). For information on maternal educational level, the data were linked to the National Education Database. The educational system in Norway is organised in primary school (7 years), lower secondary school (3 years), upper secondary school (3 years) and higher education. The first 10 years are mandatory.

All births in the Medical Birth Registry of Norway were included, of which 0.2\% were late miscarriages (16–21 weeks). To analyse mothers with complete birth records, we included women with first births from 1 January 1967 and last births until 31 December 2002 (providing 7 years of follow-up to 31 December 2009—the end of observation for maternal deaths). About 97\% of mothers have their second child within 7 years after their first birth if they chose to have another. We excluded women with plural pregnancies, women born outside Norway and mothers without information on education (0.3\%).

Initially, we analysed crude mortality in mothers with perinatal losses compared with mothers without losses. We evaluated modifications on the crude mortality ratios by mothers’ education, low or high, and by having or not having surviving children. Low education was defined as <11 years and high education as \( \geq 11 \) years. Further stratification on education did not provide additional information.

In strata of education (low and high), we first assessed mortality in childless mothers with one perinatal loss relative to mothers with one child and no loss. Second, we estimated mortality in mothers with one perinatal loss by having surviving children, one to three or more. Here, we used mothers without losses and number of births corresponding to number of surviving children as strata-specific references. In repeated analyses, we included mothers with surviving children from zero to three or more, and used mothers without losses and two births as a common reference category.

**Subanalyses:** Irrespective of education, we evaluated the association between perinatal losses (one and two or more, separately) and maternal mortality in strata of number of births from one to five. Mothers without losses were used as strata-specific references. By low and high education for mothers with two or more births, we evaluated whether having a loss in the first or in the last birth affected mortality. Finally, we evaluated if mortality differed in mothers by having a loss in the last birth before the age of 30 years, compared with at 30 or more years.

In sensitivity analyses, we evaluated differences in the crude mortality estimates by the mothers’ birth year (before 1950 and in 1950 or later). To control for potential bias, we repeated the main analyses excluding mothers who lost children aged 2 weeks to 7 years. We also evaluated the contribution of pre-eclampsia and preterm births on the association between perinatal losses and mortality.

We used Cox proportional hazard regression models (SPSS for Windows, V22, http://www.spss.com) to calculate age-specific (40–69 years) HRs for total, cardiovascular and non-cardiovascular mortality. The underlying time variable in the Cox model was the mothers’ birth year. In order to handle effect differences by calendar time, we adjusted for the mothers’ birth year using a linear term. We further adjusted for the mothers’ age at first birth. We applied a multiplicative model to evaluate interactions between perinatal losses and education for maternal mortality. To calculate rates (per 1000), in **tables 2–4**, we used a standard life-table approach.
RESULTS
Of the 652,320 mothers, 16,490 died during follow-up (table 1). The median follow-up time from birth of the mother to death or censoring was 52 years (IQR 45–59 years) and from first delivery 27 years (IQR 27–35). Overall occurrence of perinatal losses was 2.9%.

Mothers with low education, age at first birth <20 years or >34 years had the highest occurrence, 3.4%, 3.8% and 3.0%, respectively. Less than 6% of the mothers with a perinatal loss ended up childless. Occurrence of a perinatal loss increased with increasing number of births from 9 per 1000 in mothers with one or two births to 156 per 1000 in mothers with five or more births (table 2).

Of the mothers with losses and more than one birth, 50% had a loss in the first birth and only 14% had a loss in the last birth.

Crude mortality in mothers with a perinatal loss: modifications by education and surviving children
Mothers with a perinatal loss had higher mortality than mothers without losses; crude HRs (95% CIs), total: 1.3 (1.3 to 1.4), cardiovascular: 1.8 (1.5 to 2.1), non-cardiovascular: 1.3 (1.2 to 1.4) (table 3).

The crude results were significantly modified by the mothers’ level of education. For mothers with low education, the HRs were similar to the crude estimates, but for mothers with high education, the associations almost disappeared. We found a significant interaction between perinatal loss and educational level for cardiovascular mortality (p=0.0027). There were not significant interactions for overall or non-cardiovascular mortality (p=0.084 and p=0.40, respectively). Modification by no or any surviving children also gave significant differences in mortality. Childless mothers with one perinatal loss had a doubled risk compared with mothers with one loss and surviving children (table 3).

Mortality in childless mothers with one perinatal loss
Figure 1A–D illustrates the increased mortality risk in childless mothers with one perinatal loss, compared with mothers without losses and two children. Having a perinatal loss as the only birth was 1.7 times more common and cardiovascular deaths in mothers were 10 times higher if maternal education was low rather than high (table 4).

Comparing cardiovascular mortality for childless mothers with a loss to mothers with only one birth and no loss gave a HR of 2.7 (1.7 to 4.3) for mothers with low education and 0.91 (0.13 to 6.5) for mothers with high education. The corresponding figures for non-cardiovascular mortality were: low education HR 1.6 (1.3 to 2.2) and high education HR 1.8 (1.1 to 2.9).

Mortality in mothers with surviving children and one perinatal loss
Mortality in mothers with high education, one perinatal loss and surviving children did not differ significantly from mothers without losses, although CIs were wide (table 5 and figure 1B,D). In contrast, for mothers with low education and one loss, we found significant differences in mortality risks (table 5 and figure 1A,C).

Cardiovascular mortality risk was increased in mothers with two and three or more surviving children (HR 1.7

### Table 1: Baseline characteristics of the mothers by education in years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Less than 11</th>
<th>11 or More</th>
<th>Less than 11:11 or more ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers: N, (% row)</td>
<td>652,320 (100)</td>
<td>311,374 (48)</td>
<td>340,946 (52)</td>
<td>0.9</td>
</tr>
<tr>
<td>Mothers with perinatal losses: n, (% of N)</td>
<td>18,636 (2.9)</td>
<td>10,586 (3.4)</td>
<td>8,050 (2.4)</td>
<td>1.4</td>
</tr>
<tr>
<td>Mothers with one perinatal loss (% of n)</td>
<td>17,491 (94)</td>
<td>9,883 (93)</td>
<td>7,608 (95)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mothers with two or more perinatal losses (% of n)</td>
<td>11,45 (6.1)</td>
<td>703 (6.6)</td>
<td>442 (5.5)</td>
<td>1.2</td>
</tr>
<tr>
<td>Medium age at death (IQR)</td>
<td>52 (47–58)</td>
<td>53 (47–58)</td>
<td>52 (46–58)</td>
<td>–</td>
</tr>
<tr>
<td>Median age at first birth (IQR)</td>
<td>24 (21–27)</td>
<td>22 (20–25)</td>
<td>25 (22–28)</td>
<td>–</td>
</tr>
<tr>
<td>Total no. of deaths: X (% of N)</td>
<td>16,490 (2.5)</td>
<td>11,703 (3.8)</td>
<td>4,787 (1.4)</td>
<td>2.7</td>
</tr>
<tr>
<td>Total no. of deaths in mothers with perinatal losses (% of X)</td>
<td>769 (4.7)</td>
<td>603 (5.2)</td>
<td>166 (3.4)</td>
<td>1.5</td>
</tr>
<tr>
<td>Cardiovascular deaths: x1, (% of N)†</td>
<td>1,895 (0.3)</td>
<td>1,499 (0.5)</td>
<td>396 (0.1)</td>
<td>5.0</td>
</tr>
<tr>
<td>Cardiovascular deaths in mothers with perinatal losses (% of x1)†</td>
<td>115 (6.1)</td>
<td>104 (6.9)</td>
<td>11 (2.8)</td>
<td>2.5</td>
</tr>
<tr>
<td>Non-cardiovascular deaths: x2, (% of N)‡</td>
<td>14,595 (2.2)</td>
<td>10,204 (3.3)</td>
<td>4,391 (1.3)</td>
<td>2.5</td>
</tr>
<tr>
<td>Non-cardiovascular deaths in mothers with perinatal losses (% of x2)‡</td>
<td>654 (4.5)</td>
<td>499 (4.9)</td>
<td>155 (3.5)</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Data are presented for age-specific deaths, 40–69 years.
†Cardiovascular causes of death: ischaemic heart disease and cerebrovascular disease combined (see the Materials and methods section).
‡Non-cardiovascular causes of death: all other causes than cardiovascular causes (see the Materials and methods section).
### Table 2  
Mortality, ages 40–69, by number of births and number of perinatal losses, in 652,320 mothers  
Mothers stratified by number of births, and then number of losses  
<table>
<thead>
<tr>
<th>Number of births and number of losses</th>
<th>Cardiovascular mortality</th>
<th></th>
<th>Non-cardiovascular mortality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (per 1000)</td>
<td>Deaths (per 1000)</td>
<td>(HR 95% CI)*</td>
<td>N</td>
</tr>
<tr>
<td>One birth (18%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>115,603</td>
<td>550 (4.8)</td>
<td>1.0 (ref)</td>
<td>117,123</td>
</tr>
<tr>
<td>No loss</td>
<td>114,595 (991)</td>
<td>531 (4.6)</td>
<td>2.5 (1.6 to 4.0)</td>
<td>116,091</td>
</tr>
<tr>
<td>One loss</td>
<td>1008 (9)</td>
<td>19 (19)</td>
<td></td>
<td>1036</td>
</tr>
<tr>
<td>Two births (49%)</td>
<td>315,517</td>
<td>797 (2.5)</td>
<td>1.0 (ref)</td>
<td>318,513</td>
</tr>
<tr>
<td>Total</td>
<td>312,694 (991)</td>
<td>775 (2.5)</td>
<td>2.1 (1.4 to 3.3)</td>
<td>315,629</td>
</tr>
<tr>
<td>No loss</td>
<td>2730 (9)</td>
<td>20 (7.0)</td>
<td>5.0 (1.2 to 20)</td>
<td>2788</td>
</tr>
<tr>
<td>One loss</td>
<td>93 (0)</td>
<td>2 (22)</td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>Two losses</td>
<td>1008 (9)</td>
<td>19 (19)</td>
<td></td>
<td>1036</td>
</tr>
<tr>
<td>Three births (26%)</td>
<td>166,266</td>
<td>404 (2.4)</td>
<td>1.0 (ref)</td>
<td>167,609</td>
</tr>
<tr>
<td>Total</td>
<td>158,471 (953)</td>
<td>358 (2.3)</td>
<td>1.9 (1.3 to 2.6)</td>
<td>159,760</td>
</tr>
<tr>
<td>No loss</td>
<td>7542 (45)</td>
<td>41 (5.4)</td>
<td>5.7 (2.3 to 14)</td>
<td>7593</td>
</tr>
<tr>
<td>One loss</td>
<td>2730 (9)</td>
<td>20 (7.0)</td>
<td></td>
<td>2788</td>
</tr>
<tr>
<td>Two losses</td>
<td>93 (0)</td>
<td>2 (22)</td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>Four births (6%)</td>
<td>37,947</td>
<td>107 (2.8)</td>
<td>1.0 (ref)</td>
<td>38,299</td>
</tr>
<tr>
<td>Total</td>
<td>33,064 (871)</td>
<td>88 (2.7)</td>
<td>1.3 (0.75 to 2.2)</td>
<td>33,361</td>
</tr>
<tr>
<td>No loss</td>
<td>4443 (117)</td>
<td>16 (3.6)</td>
<td>2.0 (0.63 to 6.4)</td>
<td>4487</td>
</tr>
<tr>
<td>One loss</td>
<td>440 (12)</td>
<td>3 (7)</td>
<td></td>
<td>451</td>
</tr>
<tr>
<td>Two or more losses</td>
<td>9711</td>
<td>37 (3.8)</td>
<td></td>
<td>9808</td>
</tr>
<tr>
<td>Five or more births (2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7888 (812)</td>
<td>28 (3.5)</td>
<td>1.0 (ref)</td>
<td>7943</td>
</tr>
<tr>
<td>No loss</td>
<td>1519 (156)</td>
<td>8 (5.3)</td>
<td>1.4 (0.65 to 3.1)</td>
<td>1530</td>
</tr>
<tr>
<td>One loss</td>
<td>440 (12)</td>
<td>3 (7)</td>
<td></td>
<td>451</td>
</tr>
<tr>
<td>Two or more losses</td>
<td>304 (31)</td>
<td>1 (3.3)</td>
<td>0.81 (0.11 to 5.9)</td>
<td>335</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*HR with 95% CI, adjusted for the mothers’ birth year and age at first birth.

### Table 3  
Mortality, ages 40–69, in mothers with one perinatal loss, compared with mothers without, and modifications by mothers’ education and surviving children  
<table>
<thead>
<tr>
<th>Years of education</th>
<th>Childless mothers</th>
<th>Mothers with children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths (per 1000)</td>
<td>HR (95% CI) N=1046</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.8 (1.5 to 2.1)</td>
<td>1.8 (1.5 to 2.3) 0.92 (0.50 to 1.7) 19 (19) 4.1 (2.6 to 6.4) 85 (5) 1.5 (1.2 to 1.9)</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>1.3 (1.2 to 1.4)</td>
<td>1.3 (1.2 to 1.4) 1.2 (1.0 to 1.4) 75 (72) 2.2 (1.7 to 2.7) 525 (32) 1.2 (1.1 to 1.3)</td>
</tr>
</tbody>
</table>

### Table 4  
Maternal mortality, ages 40–69, for mothers with one perinatal loss and no surviving child compared with mothers with one birth without perinatal losses  
<table>
<thead>
<tr>
<th>Education</th>
<th>One birth and no loss</th>
<th>One birth and loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Deaths (per 1000)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>56 198</td>
<td>417 (7.0)</td>
</tr>
<tr>
<td>High</td>
<td>58 382</td>
<td>114 (2.0)</td>
</tr>
<tr>
<td>Ratio low:high</td>
<td>1.0 3.5</td>
<td>1.7 10</td>
</tr>
<tr>
<td>Non-cardiovascular mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>57 263</td>
<td>2547 (44)</td>
</tr>
<tr>
<td>High</td>
<td>58 823</td>
<td>966 (16)</td>
</tr>
<tr>
<td>Ratio low:high</td>
<td>1.0 2.8</td>
<td>1.7 2.1</td>
</tr>
</tbody>
</table>

Analyses stratified on low (<11 years) and high (≥11 years) education level.  
*HR with 95% CI, adjusted for the mothers’ birth year and age at first birth.

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Subanalyses
A high number of births weakened the association between perinatal losses and maternal mortality (table 2). In mothers with one perinatal loss, the point estimates for cardiovascular mortality decreased from HR 2.5 (1.6 to 4.0) in mothers with one birth to HR 1.5 (0.75 to 2.2) in mothers with four births. The same pattern was seen for non-cardiovascular mortality (one birth HR 1.7 (1.4 to 2.2) and four births HR 1.1 (0.79 to 1.6)). Having two or more perinatal losses, relative to one loss, indicated excess mortality, but also here the association weakened with increasing number of births.

In mothers with one loss and surviving children, the increased mortality relative to mothers without losses did not differ significantly by having the loss in the first or the last birth (table 6).

Having a perinatal loss in the last birth before the age of 30 years compared with having a loss in the last birth at the age of 30 or more was associated with increased mortality; cardiovascular: HR 2.3 (1.2 to 4.5), non-cardiovascular: HR 1.6 (1.2 to 2.3).

Sensitivity analyses
The associations between crude maternal mortality and perinatal loss, compared with mothers without losses, by birth year of the mother gave small differences; cardiovascular: before 1950, HR 1.7 (1.4 to 2.2), 1950 or later, HR 1.4 (1.0 to 2.1); non-cardiovascular: before 1950, HR 1.4 (1.0 to 2.1); 1950 or later, HR 1.4 (1.3 to 1.6).

Repeating the main analyses, excluding mothers who lost children aged 2 weeks to 7 years or mothers with pre-eclampsia did not change the associations of mortality with perinatal loss. Mortality in mothers with a preterm loss did not differ from having a term loss.

DISCUSSION
Using linked data from the Medical Birth Registry of Norway, the Cause of Death Register and the National Education Database, we found that childless mothers with one perinatal loss had excess later-life non-cardiovascular mortality. For cardiovascular mortality, the association was only found in mothers with low

Figure 1  Age-specific, 40–69 years, mortality risk in mothers with one perinatal loss by surviving children from zero to three or more. Cardiovascular mortality: Low education (A) and high education (B). Non-cardiovascular mortality: Low education (C) and high education (D). Adjusted for the mothers’ birth year and age at first delivery. CVD, cardiovascular disease; NON-CVD, non-cardiovascular disease; Ref, reference.


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education. Increased long-term mortality in mothers with one perinatal loss and surviving children was limited to mothers with low education. Little is known about the long-term consequences for mothers who experience perinatal losses. A Danish population-based study, with limited follow-up (15 years from first birth) and few deaths, reported that mothers with a perinatal loss had increased mortality, especially of cardiovascular causes.1 The authors aimed at isolating the effect of bereavement by adjusting for cardiovascular disease at the time of delivery. A limitation of this study was the likely inadequate control for predisposing disease, which threatens the ability to isolate the effect of bereavement because manifest chronic disease is rare during the years of childbearing. Predisposing factors like obesity, smoking and familial disposition (genetic factors) were not accounted for22 and nearly two-thirds of the women who suddenly die of cardiovascular disease have no previously recognised symptoms.23 There may also have been inadequate control for social founding because they adjusted for educational level at the time of the first pregnancy and neglected that many mothers will complete their education after giving birth to their first child.

### Crude mortality in mothers with a perinatal loss: modifications by education and surviving children

### Table 5 Maternal mortality, ages 40–69, for mothers with one loss by total number of children surviving the perinatal period compared with mothers with no perinatal losses by number of births

<table>
<thead>
<tr>
<th>Surviving children by education</th>
<th>Mothers with no loss</th>
<th>Mothers with one loss</th>
<th>HR (95% CI)*†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Deaths (per 1000)</td>
<td>N Deaths (per 1000)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56 198 417 (7)</td>
<td>1668 18 (11)</td>
<td>1.2 (0.73 to 1.9)</td>
</tr>
<tr>
<td>2</td>
<td>144 821 593 (4)</td>
<td>4137 34 (8)</td>
<td>1.7 (1.2 to 2.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>94 916 385 (4)</td>
<td>3214 23 (7)</td>
<td>1.6 (1.1 to 2.4)</td>
</tr>
<tr>
<td>High education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58 382 114 (2)</td>
<td>1062 2 (2)</td>
<td>0.59 (0.15 to 2.4)</td>
</tr>
<tr>
<td>2</td>
<td>167 873 182 (1)</td>
<td>3352 7 (2)</td>
<td>1.4 (0.65 to 2.9)</td>
</tr>
<tr>
<td>≥3</td>
<td>104 508 89 (0.9)</td>
<td>2748 1 (0.4)</td>
<td>0.36 (0.05 to 2.6)</td>
</tr>
<tr>
<td><strong>Non-cardiovascular mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>57 263 2547 (44)</td>
<td>1715 112 (65)</td>
<td>1.2 (1.0 to 1.5)</td>
</tr>
<tr>
<td>2</td>
<td>146 791 4534 (31)</td>
<td>4211 182 (43)</td>
<td>1.2 (1.1 to 1.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>96 035 2624 (27)</td>
<td>3255 106 (33)</td>
<td>1.1 (0.90 to 1.3)</td>
</tr>
<tr>
<td>High education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58 823 966 (16)</td>
<td>1073 23 (21)</td>
<td>0.89 (0.59 to 1.4)</td>
</tr>
<tr>
<td>2</td>
<td>168 838 2112 (13)</td>
<td>3382 67 (20)</td>
<td>1.2 (0.94 to 1.5)</td>
</tr>
<tr>
<td>≥3</td>
<td>105 042 1158 (11)</td>
<td>2765 35 (13)</td>
<td>0.99 (0.71 to 1.4)</td>
</tr>
</tbody>
</table>

Analyses stratified on low (<11 years) and high (≥11 years) education level. *HR with 95% CI, adjusted for the mothers’ birth year and age at first birth. †Data are defined: Reference; mothers without losses, strata specific.

### Table 6 Mortality, ages 40–69, for mothers with one perinatal loss in first or last birth, compared with mothers with two births and no loss

<table>
<thead>
<tr>
<th>Education</th>
<th>N</th>
<th>Deaths (per 1000)</th>
<th>Deaths (per 1000)</th>
<th>HR (95% CI)*</th>
<th>N</th>
<th>Deaths (per 1000)</th>
<th>Deaths (per 1000)</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>144 821</td>
<td>593 (4.1)</td>
<td>4466 39 (8.7)</td>
<td>1.8 (1.3 to 2.4)</td>
<td>1250</td>
<td>15 (12)</td>
<td>2.6 (1.5 to 4.3)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>167 873</td>
<td>182 (1.1)</td>
<td>3437 6 (1.7)</td>
<td>1.1 (0.50 to 2.5)</td>
<td>825</td>
<td>1 (1.2)</td>
<td>0.75 (0.11 to 5.4)</td>
<td></td>
</tr>
<tr>
<td>Low/high (rate ratio)</td>
<td>0.9</td>
<td>3.7</td>
<td>1.3</td>
<td>5.1</td>
<td>1.6</td>
<td>1.5</td>
<td>10</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Non-cardiovascular mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>146 791</td>
<td>4534 (31)</td>
<td>4563 234 (51)</td>
<td>1.4 (1.3 to 1.6)</td>
<td>1242</td>
<td>55 (44)</td>
<td>1.3 (0.97 to 1.7)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>168 838</td>
<td>2112 (13)</td>
<td>3465 62 (18)</td>
<td>1.1 (0.82 to 1.4)</td>
<td>824</td>
<td>15 (18)</td>
<td>1.0 (0.61 to 1.7)</td>
<td></td>
</tr>
<tr>
<td>Low/high (rate ratio)</td>
<td>0.9</td>
<td>2.4</td>
<td>1.3</td>
<td>2.8</td>
<td>1.3</td>
<td>1.5</td>
<td>2.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Analyses stratified on low (<11 years) and high (≥11 years) education level. *HR with 95% CI, adjusted for the mothers’ birth year and age at first birth (last line).
results of the Danish study. However, having high education or surviving children almost eliminated the excess risk (table 3). We have recently reported that a high number of births was associated with excess mortality in mothers with low education and reduced mortality in mothers with high education. Perinatal losses were more frequent in mothers with low education relative to mothers with high education (ratio low: high 1.4, table 1) and the occurrence increased with number of births (table 2). Maternal deaths were clustered in mothers with low education and we found a significant interaction between perinatal losses and educational level for cardiovascular mortality. When assessing mortality in mothers with perinatal losses, stratification by educational level and number of surviving children should be applied to avoid bias.

**Mortality in childless mothers with a perinatal loss**

Childless mothers with a perinatal loss were more likely to have low education (ratio low: high 1.7, table 4) and excess cardiovascular risk was restricted to mothers with low education, indicating modification by social factors. However, non-cardiovascular mortality was increased irrespective of education. Of the non-cardiovascular deaths in mothers with low education, 41% died of cancer and 17% of these originated from the reproductive organs (breast, ovary, cervix and uterus). In mothers with high education, 50% died of cancer and here 63% were reproductive cancers. Non-cardiovascular causes of death, other than cancer, were in low-educated mothers, mainly lifestyle related, 69%, and half of these were alcohol or drug induced. In contrast, the proportion of lifestyle-related deaths in mothers with high education was only 13%. Here, the dominating causes of non-cardiovascular deaths, other than cancer, were traumatic injuries, 63%, and diseases not related to lifestyle, 25%. These contrasting patterns for causes of mortality for childless mothers with a loss, suggest that more mothers with high education relative to low experienced restricted fertility by biology (biological infertility). The causation between lifestyle-induced diseases and impaired fertility is relatively weak as reproduction takes place early in life when the alterations in the organs are minor compared to later in life. This implies that factors other than impaired biological fertility, like lack of resources, no partner or instability, may contribute to the reduced fertility to a larger extent in mothers with low compared with high education (social infertility).

**Mortality in mothers with surviving children and a perinatal loss**

Perinatal losses increase fertility. In mothers with high education and a perinatal loss, surviving children neutralised the excess mortality risk associated with the loss. In mothers with low education and a perinatal loss, surviving children reduced the mortality risk, but not completely (table 5). A previous study on the association between pre-eclampsia and later-life cardiovascular mortality also demonstrated that number of births modified the association. Increased later-life cardiovascular mortality was concentrated in mothers with preterm pre-eclampsia and only one birth. Of the mothers with one perinatal loss, 86% had a subsequent birth. A replacement-child prevents complicated grief, but can also indicate good health, stability and resources. Not replacing a perinatal loss at younger age, compared with higher age, significantly increased both cardiovascular and non-cardiovascular mortality. This suggests that younger mothers who fail to replace a loss are more likely to carry predisposing factors associated with reduced fertility and disease later in life.

**Competing risk: biology or social factors**

Subfertility is associated with underlying factors predisposing to cardiovascular disease. We recently reported increased cardiovascular mortality in mothers with one birth, relative to mothers with two births. Having a perinatal loss further increased the cardiovascular mortality in mothers with one birth, but only in mothers with low education (table 4). If a perinatal loss was a biological marker for later-life cardiovascular disease, the contribution to mortality risk should be similar or higher in mothers with fewer additional risk factors (high education mothers). In addition, with a reduced occurrence of perinatal loss in more recent years a condensation of risk would be expected, but we found an indication of reduction of cardiovascular risk over time. The differences in cardiovascular and non-cardiovascular mortality of mothers with perinatal loss between educational groups suggest that reduced fertility outweighs perinatal losses as a risk factor for later-life mortality. Negative lifestyle factors in disadvantaged mothers seem to be a shared pathway for perinatal losses and excess later-life mortality.

**Strengths and limitations**

The strengths of this study are the large population-based material and long follow-up. Registration of number of births, perinatal losses, education and deaths was prospective and virtually complete. The Medical Birth Registry of Norway is the only registry in Scandinavia with compulsory recording of losses from 16 weeks of gestation. Norwegian mothers with a low perinatal mortality rate constitute an ideal population to study the association between perinatal losses and maternal mortality. Modification of risk by education and surviving children should have external generalisability, especially in developed countries where selective fertility is strong. Weaknesses of the study are the lack of data on cardiovascular risk factors such as smoking, alcohol intake and Body Mass Index. The study does not include women without births. When evaluating mortality in childless mothers with a perinatal loss, women without births would have been the ideal reference group. Very few maternal deaths among mothers with high education and perinatal losses are a strong finding by itself, but introduce uncertainty reflected in wide CIs (especially for cardiovascular mortality).
Interpretation
Women with low education have increased risk for perinatal loss and excess long-term mortality. Irrespective of education, we find excess mortality in childless mothers with a perinatal loss. Increased mortality in mothers with one perinatal loss and surviving children was limited to mothers with low education. Our study suggests that lifestyle factors and survivorship outweigh perinatal loss as a risk factor for later-life maternal mortality. Experiencing a perinatal loss should not be used as an indicator for maternal long-term mortality alone.

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Acknowledgements
The authors thank the Medical Birth Registry of Norway for providing the data for this analysis.

Contributors
All researchers had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. FH, N-HM and RS designed and proposed the study. FH and RS analysed the data and prepared the graphs. FH drafted the manuscript. AW, KK, N-HM, LD and RS reviewed the preliminary analyses and the initial draft of the manuscript and provided critical comments. RS is guarantor for data quality.

Funding
This study was supported by the Norwegian Research Council, through the University of Bergen, and in part by the Intramural Program of the National Institute of Environmental Health Sciences, National Institutes of Health.

Disclaimer
The Norwegian Research Council, University of Bergen, and the US National Institute of Environmental Health Sciences had no role in the design and conduct of the study; in the collection, analysis, the interpretation of the data; or in the preparation, review or approval of the manuscript. The authors’ institutions had no role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; or the preparation, review or approval of the manuscript.

Competing interests
All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval
The internal review board of the Medical Birth Registry of Norway and the regional ethics committee, REK Vest, Norway (2009/168).

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
The following sensitivity analyses are commented in the paper but not shown: To control for potential confounding, we excluded mothers who lost children aged 2 weeks to 7 years and repeated the main analyses. The results did not change. In the same way, we excluded mothers with pre-eclampsia and also here the results did not change. In the last sensitivity analysis, we wanted to evaluate whether gestational age of the perinatal loss influenced maternal long-term mortality. We did this by comparing mortality in mothers with a preterm loss with mothers with a term loss. There was no significant difference between the two groups. The data can be provided if needed by Frode Halland, frode.halland@gmail.com.

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