Generations, reproduction and birth outcome

A registry-based cohort study in Norway 1967-2006

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Introduction

Intergenerational studies are studies in which relations between characteristics of family members from two or more generations are explored.[1] In many ways, intergenerational studies represent new territory in research. However, a few intergenerational papers were produced in the mid-20th century [2-6]. Intergenerational studies are used in life-course epidemiology [7-9] to investigate primary research hypotheses and to explore mechanisms underlying established associations.[1] In this thesis, we explored the intergenerational association between mothers and their offspring and fathers and their offspring.

Intergenerational studies include studies in which the recurrence of the same characteristic across generations is examined. This refers not only to phenotypes, but also to socioeconomic and behavioural characteristics. Intergenerational studies also include studies in which characteristics in one generation are related to different characteristics in another generation. So far, substantially more studies have examined associations down the maternal line than down the paternal line.

Family members across generations share genes, but they also share environmental, behavioural and socioeconomic characteristics. Intergenerational associations may be driven by one of these factors, or by a combination of them.[1]

Our aim was to describe associations between birth outcomes across two generations. Hypotheses were proposed about how genetic and environmental, behavioural and socioeconomic factors may affect reproduction and birth outcomes through generations. However, distinguishing between these influences, besides determining actual genetic mechanisms, were not necessarily possible based on the present data. Maternal-paternal comparisons did, however, help us to investigate these mechanisms.

Founded in 1967, the Medical Birth Registry of Norway (MBRN) is a unique source for reproductive epidemiologic research over generations.[10] Men and women born in 1967 are now more than 40 years old, which means that, for the first cohorts in the registry, we have close to complete reproduction.

Abstract

Aims. Our aim was to describe associations between birth outcomes across two generations. Hypotheses were proposed about how genetic and environmental, behavioural and socioeconomic factors may act on reproduction and birth outcomes through generations.

Methods. Population-based cohort studies for two generations. Data were derived from the Medical Birth Registry of Norway (MBRN) based on all births in Norway between 1967 and 2006 (*Paper I* 1967-2004), more than 2.3 million births. Births were linked to the mother's and father's own birth records by their national identification numbers, thus providing generation files with birth records on mothers and their offspring and fathers and their offspring.

Results. In *Paper I*, we investigated intergenerational recurrence of breech delivery and found that both men and women delivered in breech at term contribute to increased risk of breech delivery in their offspring. The highest risk of recurrence of breech delivery was observed for first-born men and women delivered at term (odds ratios (ORs) 2.2, 95% confidence interval (C.I.) 1.8 to 2.7 and 2.2, 1.9 to 2.5, for men and women, respectively). For men and women born preterm, we essentially observed no recurrence between generations. Since recurrence through the father was as strong as recurrence through the mother, it seems reasonable to attribute the observed pattern of familial predisposition to term breech delivery to genetic inheritance, predominantly through the fetus.

In *Paper II*, we examined the associations between parents' gestational age and birth weight and perinatal mortality in their offspring. Perinatal mortality in offspring was not significantly associated with paternal gestational age or birth weight. In contrast, we found a strong inverse association between maternal gestational age and perinatal mortality in their offspring. A threefold increased risk in perinatal mortality was found among offspring of mothers born at 28-30 weeks of gestation compared with the offspring of mothers born at term (37-43 weeks) (relative risk (RR) 2.9, 95% C.I. 1.9

to 4.6). There was also a clear increase in perinatal mortality risk as maternal birth weight decreased. The highest perinatal mortality risk was found for offspring whose mother's birth weight was < 2000 g (crude RR 1.5, 95% C.I. 1.1 to 1.9) compared with mothers whose birth weight was 3500-3999 g. However, confined to mothers born at ≥ 34 weeks of gestation, the birth weight association was not significant, indicating that maternal immaturity rather than birth weight itself may be the important factor. The contrast between the maternal and paternal associations indicates that preterm delivery in females, but not in males, is linked to increased perinatal mortality risk in the next generation. Among preterm mothers, a larger proportion of offspring deaths were preterm births compared with mothers born at term. One possible explanation for the association between maternal gestational age and offspring perinatal mortality could thus be genetic factors, predominantly through maternal genes, relating to preterm delivery. Fetal genes seem to be less important since the association between paternal gestational age and offspring mortality was lacking. Increased perinatal mortality through the maternal line may also reflect environmental factors associated with preterm birth and correlated across generations.

In *Paper III*, we investigated intergenerational birth weight associations by mother's birth order, with the emphasis on possible mechanisms behind the findings. Maternal birth weight increased steadily with increasing birth order, while, in contrast, offspring birth weight showed a reverse trend. First-born mothers tended to be older, to have higher education, to more often be married or cohabit and to smoke less than later-born mothers at the time of their first pregnancy. We suggest that first born mothers have the same biological potential for achieving similar sized offspring as later-born mothers, and that social factors account for the reduction in the mean birth weight of the offspring of later-born mothers.

Conclusions. Intergenerational recurrence of various outcomes, i.e. the same characteristics, and intergenerational associations between the parents' own birth characteristics and different outcomes in their offspring were studied for both mothers and fathers. We found similarities, but also apparent dissimilarities, between the parents' relative contribution to predictors of adverse birth outcomes in their offspring.

The comparison between maternal and paternal intergenerational relations provided important new insight that may help when focusing on possible causal mechanisms. The results from all three papers may also have clinical relevance.

List of publications

The thesis is based on three papers, which will be referred to by Roman numerals as follows:

I. Nordtveit TI, Melve KK, Albrechtsen S, Skjaerven R. **Maternal and paternal contribution to intergenerational recurrence of breech delivery: population based cohort study.** BMJ 2008; 336; 872-876.

II. Nordtveit TI, Melve KK, Skjaerven R. **Maternal and paternal birth characteristics and perinatal mortality in their offspring: a population based cohort study.**

III. Nordtveit TI, Melve KK, Skjaerven R. **Intergenerational birth weight associations by mother's birth order - The mechanisms behind the paradox: A population-based cohort study.** Early Human Development 85 (2009) 577–581.

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II Notification form for the Medical Birth Registry of Norway 1999-2006.

Papers I-III

1. Definitions and abbreviations

Birth order	The ordinal number of a given birth in relation to all previous births by the same woman. See parity below.
Breech presentation	A longitudinal fetal position with the head at the uterine fundus. All births delivered in breech presentation are considered to be breech delivery, irrespective of the mode of delivery, thus including both elective and emergency caesarean section (*Paper I*).
CS	Caesarean section
Congenital anomaly	A congenital anomaly may be viewed as a physical, metabolic, or anatomic deviation from the normal pattern of development that is present at birth. Diagnosed at birth by paediatric examination at the birth clinic and, since 1999, also during the stay at the neonatal ward for infants transferred to such units. Recorded in the MBRN in accordance with the International Classification of Diseases (ICD); ICD-8 (8th revision) for the years 1967-98 and ICD-10 (10th revision) thereafter. Classified as major and minor anomalies on the basis of definitions used by Eurocat (European Surveillance of Congenital Anomalies, www.eurocat.ulster.ac.uk).
Early neonatal death	Refers to the death of a live-born neonate between zero and six completed days after birth.
Fetal death	Stillbirth. See below.
Gestational age	The duration of pregnancy estimated from the first day of the last normal menstrual period or since 1999 on the basis of ultrasound measurements during pregnancy.
Low birth weight (LBW)	Birth weight less than 2500 g.
MBRN	Medical Birth Registry of Norway.
Parity	Number of children previously born to a woman. In the MBRN, we count children as any pregnancy from 16 weeks' gestation, including late abortions and stillbirths.
Perinatal mortality	All registered stillbirths from 16 weeks' gestation plus live births who die within the first week of life divided by the total number of births (live and still).

Preterm delivery	Delivery before 37 completed weeks of gestation (less than 259 days).
Small for gestational age (SGA)	Birth weight less than the 10th (*Paper I*) or the 2.5th percentile (*Paper II-III*) for a given gestational age.
Stillbirth	The absence of signs of life at or after birth. In this thesis we count stillbirths from 16 weeks' gestation. Terminations of pregnancy due to serious birth defects are defined as stillbirths (*Paper II*).

Statistical abbreviations

C.I.	Confidence interval
OR	Odds ratio
RR	Relative risk / risk ratio
SD	Standard deviation
SE	Standard error

2. Intergenerational studies

The importance of intergenerational studies to the field of reproduction

Acknowledging and understanding intergenerational reproductive associations is important for several reasons. Firstly, such associations may add new knowledge to the aetiology of adverse birth outcomes.[1] They may reflect the presence of persistent environmental, socioeconomic and behavioural causes, and they may suggest shared genetic causes, being good candidates for future molecular genetic studies. Secondly, such analyses may be relevant to public health and clinical practice.[1] In order to avoid adverse pregnancy outcomes, information about a previous generation may be valuable to clinicians working in antenatal care when evaluating an ongoing pregnancy. Understanding intergenerational associations will be helpful in defining deviation from the expected and thus in identifying high-risk pregnant women. Finally, recognising intergenerational associations will be important for understanding results from other family studies, e.g. sibling studies.[1]

Data sources for studies of intergenerational birth outcomes

Cohort studies usually require large data sets, because the outcomes of interest are often relatively rare. This is also true for generational cohort studies. In Norway, there is a long tradition for standardised collection of health data, for instance through population-based registries. The MBRN is a registry based on mandatory reporting of births over a 40-year period, with almost 100% coverage of all births in the country.[10] Different databases/registries can be linked to each other by means of unique identification numbers assigned to all Norwegian citizens at birth. More important for the present studies, birth records from the first periods of the MBRN's existence can be linked to subsequent births by the same subjects, forming generational data sets.

Intergenerational causes and exposures

Emanuel defined intergenerational factors in reproductive problems as 'those factors, conditions, exposures, and environments experienced by one generation that relate to the health, growth and development of the next generation'.[11] As stated above, family members across generations share genes, but they also share environmental, behavioural and socioeconomic characteristics. Approximately 50% of the fetal genes are passed on from the mother and the other 50% from the father, which should theoretically produce associations of similar magnitude for father-offspring and mother-offspring.[1 12-15] Genomic imprinting means unequal transcription of parental alleles, i.e. the expression of the alleles is dependent upon the sex of the parent from which they are inherited.[16-18] Imprinted genes appear to be relatively rare.[19] Maternal genes may be viewed as genetic factors expressed in daughters and acting on the female capability to carry a pregnancy, e.g. physical characteristics of the mother that are influenced by genes.[1 12-15] Furthermore, mitochondrial genes, located in the cell's cytoplasm outside the nucleus, are transmitted through the maternal line and contribute to recurrence from mother to offspring (mother to son or mother to daughter).[13 18] This thesis has not taken account of imprinting or mitochondrial effects.

Environmental, behavioural and socioeconomic exposures operate through both parents, but for daughters they may be more strongly associated with the mother than the father. In addition, as people tend to find their partners within the same socioeconomic strata, as is suggested by the high correlation in educational attainment between spouses,[20] mothers and fathers are likely to share socioeconomic environments and often have the same behavioural pattern.[21] For instance, paternal smoking will most likely affect the pregnancy through a high correlation between paternal and maternal smoking habits, and not through exposure to passive smoking.[22] Other factors such as parenting, which certainly influence the health of offspring, may have consequences across more than one generation.[23 24]

Maternal line

The mother provides (slightly more than) half of the genes to the fetus. The additional effect of mothers on the fetus is the result of the intrauterine environment, which is influenced by maternal genes, the mother's health, behaviour and social conditions. The effect on the offspring through the mother may also be a consequence of the mother's own experience as a fetus. For instance, low gestational age and low birth weight (LBW) due to an adverse intrauterine environment may produce long-term physiological changes in the female infant, i.e. the growth and form of her body and reproductive organs, and its structures, functions and metabolism, which in turn increase her future risk of unfavourable pregnancy outcomes.[15 21 25] Intrauterine exposure to adverse environmental factors may have harmful consequences on later reproduction, perhaps particularly for the female fetus.[26]

Paternal line

The father provides the other half of the fetal genes.[13] He also provides behavioural and social factors that have an impact on the mother and the intrauterine environment. Fathers' and offspring's birth characteristics can be associated via an intrauterine mechanism if there is assortative mating, i.e. couples self-select each other on the basis of having similar birth characteristics.[18 27] Assortative mating is unusual, however,[28] and, besides, it is unlikely to alter estimates by more than 10%.[29] Finally, exposure of a male fetus to an adverse intrauterine environment could have long-term effects on sperm quality.[21] Some authors claim that, if the father was exposed to a toxin at the fetal stage, teratogenesis could result in an association between the father's and offspring's birth characteristics.[30]

3. Previous intergenerational studies

In this section, we will describe a selection of intergenerational studies. The focus will be on the recurrence of the same characteristic from parents to offspring and associations between characteristics in parents and other characteristics in their offspring. Studies on mothers are more frequent, despite increased interest in understanding father-offspring associations.

Intergenerational recurrence of phenotypes

Birth weight

A number of intergenerational studies have investigated the association between maternal and offspring birth weight.[25 31-41] Studies reporting a direct association between parents' and offspring birth weight often suggest a genetic effect on birth weight. The proportion of total variability due to genetic variability has been reported to be between 0 and 70%.[42] A study by Carr-Hill et al. comparing the birth weights of 505 young mothers and their offspring estimated the effect of genetic factors to be less than 20%, thus concluding that genes only have a minor effect on birth weight.[32] A recent very large study from the MBRN estimated that fetal genes and maternal genes explained 31% and 22%, respectively, of the variation in offspring birth weight.[36]

Most of these studies were carried out in developed countries. However, one small study from Guatemala found that for every 100 gram (g) increase in maternal birth weight, offspring birth weight increased by an average of 29 g.[43]

Hackman et al. reported a significant partial correlation between maternal and offspring birth weight after controlling for a number of potential confounders.[25] However, offspring birth weight was not adjusted for offspring gestational age, and, since analysis indicated an association between maternal birth weight and offspring gestational age, it is unclear whether maternal birth weight is associated with offspring intrauterine growth, offspring gestational age, or whether it is probably a combination

of both. The authors suggested that the mechanism behind the mother-offspring birth weight correlation could be explained by reduced maternal birth weight interfering with the development and growth of reproductive or endocrine organ systems. Klebanoff et al. found that maternal birth weight did not significantly affect offspring gestational age or preterm birth, but reported a significant effect on both offspring birth weight and the risk of LBW.[34] However, very low birth weight mothers had offspring with relatively normal birth weight and were not at increased risk of having LBW offspring, because these mothers were almost certainly preterm.

A few studies have investigated the relationship between paternal and offspring birth weight.[28 35 37 40 44] In studies involving both parents, paternal birth weight had a much weaker association with offspring birth weight than maternal birth weight.[45] An association with the father suggests an effect of fetal genes, although environmental, behavioural and socioeconomic factors may also be part of such an association.[13] For both mothers and fathers, some of the referred studies did not include preterm or low birth weight infants[35] or those who died,[28 37-39] thus increasing the strength of any associations by excluding some of the smallest and most preterm infants.

Paradoxically and in contrast to the above studies, a low correlation is found between birth weights of mothers and offspring in studies of mothers who are twins. Twin mothers have offspring as large as or even larger than mothers who are singletons, even though they are generally smaller at birth.[46-48] Similarly, although first-born mothers themselves generally have the lowest mean birth weights, their offspring have a higher mean birth weight than those of later-born mothers.[39 49]

Gestational age

The recurrence of preterm delivery is generally low across generations.[39] Klebanoff reported that women who were preterm at birth were not at increased risk of giving birth to either preterm or SGA infants.[50] Lie et al. found that both mothers and fathers who were themselves the result of pregnancies of long duration tended to have offspring with pregnancies of long duration, although the tendency was strongest for

the mothers.[51] The authors assumed that fetal and maternal genes play equally important roles in determining the time of delivery, since the effect from the mothers, being the sum of maternal and fetal genes, was stronger than the effect from the fathers, where only fetal genes are involved.[13] Unexpectedly, fathers who had high birth weights were at increased risk of having preterm offspring compared with fathers with lower birth weights, while this association was not found for the mothers.[51] This finding was further explored by Klebanoff, who found that, when the mother was born small, increasing paternal birth weight was associated with an increased risk of preterm birth, indicating a fetus growing faster than the mother can adapt.[52] Klebanoff's study had several limitations, most importantly a small sample size and missing information on paternal gestational age.

Wilcox et al. explored the effect of maternal and fetal genes on preterm delivery risk by creating a two-generational cohort from the MBRN comprising mothers and fathers and their first-born offspring.[15] Mothers and fathers born preterm had an RR for preterm delivery in their offspring of 1.54, 95% C.I. 1.42 to 1.67 and 1.12, 95% C.I.1.01 to 1.25, respectively. The authors claimed the weaker association for fathers born preterm as an argument against a major contribution by fetal genes, and the increased risk among preterm mothers was consistent with maternal genes that confer maternal susceptibility to preterm delivery, e.g. physical characteristics of the mother that trigger preterm delivery. However, other plausible explanations of recurrence risk through the maternal line could be physiological changes in a female baby born preterm predisposing her to deliver her own babies prematurely, and environmental factors being more likely to be shared between mothers and their daughters. The findings were confirmed by Swamy et al., who found that preterm women but not men were at increased risk of having preterm offspring.[53]

Birth weight by gestational age

Several Scandinavian studies have shown that mothers who were themselves SGA were up to three times as likely to have SGA offspring compared with mothers who

were AGA or LGA.[40 50 54-56] For instance, among Swedish women, Klebanoff found that those who were SGA at birth were at more than twice the risk of giving birth to an SGA infant, and there was an even greater increase in the risk of giving birth to a preterm infant.[50] Jaquet et al. found that, if the mother or the father had been SGA themselves, the risk of their offspring being SGA was 4.7 and 3.5 times greater, respectively, compared with mothers and fathers who had been AGA.[57] When both parents were SGA, the risk of their offspring being SGA was 16.3 times greater. As the recurrence through the father was almost as strong as the recurrence through the mother, this suggested a fetal genetic component in the determination of fetal growth. It was a methodological weakness of this study that the sample size was small and that information on parents' birth weight and gestational age was based on recall and questionnaires.

Preeclampsia

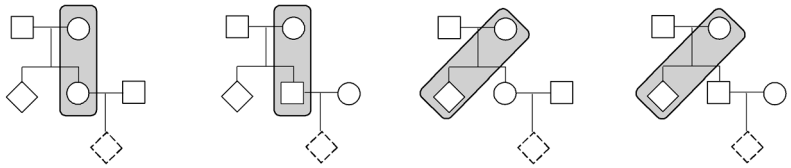
Several researchers have used familial patterns of recurrence of preeclampsia to assess the impact of maternal and fetal genes, a shared environment, or a combination, on the risk of preeclampsia.[13] A population-based case-control study from Utah showed that men and women who were themselves born after preeclamptic pregnancies contributed to a two and three times increased risk of preeclampsia in the next generation, respectively.[58] The authors suggested a genetic predisposition to preeclampsia transmitted through both the mother and the father. The methods used in this study need further discussion, however. Firstly, the accuracy of the recorded diagnosis of preeclampsia should be questioned, since the study was based on birth certificate records and not medical records. Many of the women could in fact have had gestational hypertension. Moreover, in the analyses of men, information was not available about preeclampsia in the mothers of their partners. Secondly, the associations were adjusted for 15 possible confounding variables, but maternal factors known to be associated with preeclampsia, such as body mass index (BMI) prior to pregnancy, smoking and a history of preeclampsia in previous pregnancies, were not among them.

Nilsson et al. found that full sisters and mother-daughters were more similar with respect to preeclampsia and gestational hypertension than both maternal and paternal half-sisters, emphasising a genetic component in the development of these conditions.[59] The importance of maternal genes to the liability of developing preeclampsia was estimated to be 30%, while the contribution of paternal genes was not analysed. The study was limited by underreporting of gestational hypertension. However, with a population of 1.2 million births between 1987 and 1997 and their parents, this study from Sweden was the largest until then concerning the relative importance of genes and environment in the aetiology of preeclampsia and gestational hypertension.

Lie et al. found that, if a woman became pregnant by a man who had already fathered a preeclamptic pregnancy in another woman, her risk of developing preeclampsia was almost twice as great compared to a woman who became pregnant by a man who had not fathered a preeclamptic pregnancy in another woman, strongly suggesting that fetal genes from the father contribute to the increased risk.[60]

In a recent study, Skjaerven et al. showed that both the mother and the fetus carry heritable characteristics that contribute to an increased risk of preeclampsia.[14] They found that both men and women delivered after a preeclamptic pregnancy contributed to an increased risk of preeclampsia in the next generation. The recurrence through the mother was stronger than the recurrence through the father, presumably because mothers carry maternal genes and also pass on fetal genes to their offspring, while the fathers only pass on fetal genes to their offspring.[13] However, unaffected sisters of affected persons had almost as great an excess risk in their own pregnancies as their affected sisters, indicating a strong maternal effect as unaffected sisters are less likely to be carrying fetal genes (Figure 1 page 23, adapted from [14]. ○; female, □; male, ◊; female or male, dotted diamond; pregnancy at risk for preeclampsia).

Figure 1



OR (95% C.I.)	2.2 (2.0 to 2.4)	1.5 (1.3 to 1.7)	2.0 (1.7 to 2.3)	1.1 (0.9 to 1.4)

One study from Iceland investigated familial predisposition and patterns of genetic inheritance of eclampsia and preeclampsia through four generations. The prevalence of both eclampsia and preeclampsia were significantly higher in daughters of women with a history of preeclampsia or eclampsia than in daughters-in-law. Also, granddaughters were much more likely to develop preeclampsia than granddaughters-in-law. The authors suggested that the results could be consistent with single recessive and dominant gene inheritance. [61]

Congenital malformations

In a cohort of half a million females and half a million males in the MBRN, Skjaerven et al. and Lie et al. studied survival and reproduction in females and males with birth defects, and their risk of transmitting the same defect or a dissimilar birth defect to their offspring.[62 63] Both females and males with birth defects had higher mortality and were less likely to reproduce compared with females and males without birth defects (see Figure 3 on page 47). The authors do not discuss possible explanations for the reduced fertility rate among men and women with birth defects. The overall recurrence risk of birth defects from father to offspring was significantly higher than from mother to offspring, indicating that affected fathers contribute more birth defects to the next generation than affected mothers, and that the general recurrence risk of birth defects is probably not affected by maternal genes.[13] However, both studies give rise to questions. Most importantly, only birth defects that were recognised within five days

after birth were considered. Furthermore, only a small proportion of mothers and fathers were followed until the age of 30 years.

A few studies are restricted to recurrence of the same birth defect carried by the mother or the father. By using data from the MBRN linked to clinical data on virtually all oral cleft patients treated in Norway over a 35-year period, Sivertsen et al. found that the intergenerational recurrence risk of oral clefts was high and equally high when transmitted through fathers and mothers.[64] This lack of difference between mothers and fathers indicates that fetal genes, rather than maternal genes, make the major contribution to the recurrence risk. Two other studies found that mothers were at higher risk than fathers of passing on a heart defect to their offspring.[65 66] Similarly, a study of spina bifida revealed that mothers of offspring affected by spina bifida more often had a family history of spina bifida than fathers did.[67] This could be evidence of preferential transmission of some birth defects through the female line, although the studies may be biased by more complete reporting by mothers. A recent Danish study investigated the contribution of genetic and environmental factors to familial aggregation of hypospadias.[68] Hypospadias was found to have a strong familial component, with a similar recurrence risk ratio for twin brothers and brothers and sons of a hypospadias case. The inheritance was transmitted equally through the maternal and paternal sides of the family. The findings documented genetic rather than intrauterine environmental factors in the development of hypospadias. However, the study was biased by underreporting of the milder forms of hypospadias and misclassification of the diagnosis in some subgroups.

Menarche, menopause

Two studies have shown that age at menarche recurs from mothers to daughters, and one of them reported that half of the variation was due to genetic factors.[69 70] A potential source of bias may be recall bias as the data were collected retrospectively. Similarly, age at menopause is found to be passed on from mothers to daughters, suggesting genetic effects.[71]

Intergenerational recurrence of socioeconomic and behavioural characteristics

Smoking, age at birth, family size

The tendency for socioeconomic position to be transferred from one generation to the next [72] is important in explaining the intergenerational recurrence of many birth outcomes. A Swedish study aimed at comparing smoking habits in two generations found a doubled risk of smoking among daughters if the mothers smoked during pregnancy.[73] Moreover, age at first pregnancy recurs across generations from mothers to daughters, and this is especially true for teenagers.[74 75] Interestingly, repetition of age at first parenthood has also been found between mothers and their sons.[74] A study from Finland showed that the probability of a daughter being multiparous was higher if her mother was multiparous at the time when the daughter was born than if she was not.[69] Total family size has also been found to be repeated across generations.[69] This probably reflects shared biological, social and behavioural factors between generations. It is interesting to note that the recurrence of such reproductive outcomes as menarche, menopause and family size persists despite secular changes in the prevalence of these outcomes.[69 70 76]

Caesarean section (CS)

CS rates have increased all over the world, e.g. in Norway for nulliparous women from 3.4% in 1967-76 to 15.6% in 1996-2004.[77] Two studies have examined the recurrence of CS across generations. Varner et al. found that mothers born by CS had a 40% excess risk of delivering by CS themselves.[78] Consistent with this, a more recent study from the MBRN reported that mothers born by CS had a 55% increased risk of delivering their first child by CS.[79] In contrast, this did not apply to fathers born by CS. The authors suggested two possible mechanisms behind the mother-daughter findings: biological inheritance through genes, predominantly maternal genes that are important for outcomes that may predispose to a CS, and/or environmental or social influence, through habits and learning.

Associations between exposures in parents and outcomes in their offspring

An increasing number of studies have shown that the mother's own intrauterine experience and development, and her childhood growth and environment may influence her capacity to reproduce as an adult.[4 72 80 81]

Fertility

As described above, both girls and boys with birth defects were significantly more likely to die than those without birth defects, not just during the perinatal period and infancy, but until young adulthood. In addition, among those who survived, the proportion of men and women with birth defects who had children was lower than that among men and women without birth defects.[62 63] Ekholm et al. found that women born with very low birth weight had reduced reproduction, whereas women born preterm were not affected.[82] Hack et al. found that women, but not men, with a very low birth weight had lower pregnancy rates.[83] Both studies were hampered, however, by small sample sizes.

This lower reproduction may be in line with other studies showing reduced quality of life among individuals resulting from complicated pregnancies. Bartley showed that males with low birth weight were more likely to experience socioeconomic disadvantage in childhood and adolescence.[84] Phillips found that men with low birth weight had lower social class and income and were less likely to marry.[85] Swamy et al. investigated long-term consequences among survivors of preterm birth by using data from the MBRN. Both men and women born preterm had much lower rates of reproduction than men and women born at term.[53] However, follow-up among the index cohort was incomplete, i.e. those born in recent years had not yet had the opportunity to reproduce. As expected, both men and women born preterm were more likely to have a low education than men and women born at term. In another study from Norway, Moster et al. followed children with a wide range of gestational ages until adulthood by linking compulsory national registries.[86] Decreasing gestational age at birth was associated with increasing risk of medical and social disabilities in adulthood, including lower rates of reproduction. Furthermore, low birth weight and

preterm birth seem to be the most important risk factors for impairments and anomalies, e.g. cryptorchidism, which, for males, may be related to a higher risk of infertility.[62 87]

Infant outcomes

Studies from different populations have shown an inverse association between mother's birth weight and several infant outcomes, e.g. LBW, very low birth weight, moderately low birth weight, preterm delivery, SGA, stillbirth, perinatal and infant mortality (described more fully below), and respiratory distress syndrome.[25 34 39 88 89] Some of these authors suggested that the reduced birth weight may be related to organ system growth disturbance, including the reproductive and/or endocrine systems.[25] A direct association has been found between maternal birth weight and maternal weight gain during pregnancy, indicating that a mother's birth weight also has long-term physiological consequences.[25 90] Moreover, women who were SGA, preterm or had low weight at birth were at particularly high risk of hypertension or preeclampsia as adults.[91-93] One of these studies was conducted as a case-control study, and the control and case participation rates were 50% and 85%, respectively. In addition, birth weight was self-reported with a potential risk of recall bias, and gestational age at birth was unknown so that the authors were not able to separate the effect of low birth weight due to being preterm from low birth weight due to being growth restricted.[91]

Stillbirth, perinatal and infant mortality

Associations have been found between maternal birth weight and mortality in offspring,[25 34 90] but some of these studies were based on small numbers without significant results. In a study by Skjaerven et al. based on data from the MBRN from 1967 to 1994, mothers with a birth weight < 2000 g were twice as likely to lose a baby in the perinatal period as mothers with a higher birth weight. Moreover, the survival of an offspring was strongly affected by its birth weight relative to its mother's birth weight.[81] Swamy et al. found that mothers born preterm were at increased risk of

stillbirth and infant death (< 1 year) in their offspring compared with mothers born at term. However, the results were only statistically significant for mothers born at 28-32 weeks of gestation. For preterm fathers, only those born at 33-36 weeks of gestation were at increased risk of infant mortality in their offspring. Fathers born ≥ 43 weeks were at increased risk of stillbirth in their offspring. The small sample size of subgroups and possible misclassification of gestational age were limitations of this study.[53]

Critical period

Early gestation is the critical period for organ and tissue development and some researchers claim that this is the period when intergenerational effects originate. Lumey et al. examined the effects of maternal intrauterine undernutrition on offspring birth weight in a cohort of women born between 1944 and 1946 in the Netherlands.[94] Mothers exposed to undernutrition in utero during the first trimester of pregnancy had offspring whose birth weight was lower than expected, while there were no long-term effects on offspring birth weights as a result of maternal undernutrition in late pregnancy. The authors concluded that a mother's own growth in the early gestational period was critical to her future reproductive success.

Similarly, first-born infants generally have lower birth weight than later-born infants,[95-97] probably due to differences in intrauterine growth late in pregnancy. [98 99] Paradoxically, first-born mothers tend to have offspring with a higher mean birth weight than the offspring of later-born mothers.[39 49] Finally, twins have the same growth pattern as singletons until late in gestation,[100] but have babies whose mean birth weight is similar to or even greater than those of singleton mothers.[46 47]

4. Aims of the work

Our aim was to describe associations between birth outcomes across two generations. Hypotheses were proposed about how genetic and environmental, behavioural and socioeconomic factors may act on reproduction and birth outcomes across generations. We used generational data from the MBRN, 1967-2006 (*Paper I* 1967-2004), a generational data set where the first birth cohorts have now nearly finished their reproductive careers.

Research objectives

Paper I. To investigate the intergenerational recurrence of breech delivery, with a hypothesis that both women and men delivered in breech contribute to increased risk of breech delivery in their offspring.

Paper II. To investigate the associations between parents' gestational age and birth weight and perinatal mortality in their offspring, with particular focus on the paternal relations.

Paper III. To investigate intergenerational birth weight associations by mother's birth order, with the emphasis on possible mechanisms behind the findings.

5. Materials and methods

Data sources – Medical Birth Registry of Norway

The studies were based on data up to 2004 (*Paper I*) and 2006 (*Papers II* and *III*) from the MBRN, a population-based, compulsory registry of all births in Norway since 1967. The registry was established by the Directorate of Health. Its particular aim was 'epidemiological surveillance of birth defects and other perinatal health problems in order to detect, as soon as possible, any future increase in rates'.[10] Used to generate and test hypotheses, the MBRN is especially useful for research questions that need large study samples. All live births and stillbirths of at least 16 weeks of gestation (since 2002, from 12 weeks) are registered in the MBRN, which contained more than 2.3 million births in 2006.

Almost all births in Norway take place in a hospital (> 99%).[101] A standardised notification form comprising the demographic data of the parents, maternal health before and during pregnancy, complications and interventions during delivery, as well as the condition of the newborn, is filled in by the midwife or doctor attending the birth. The notification form was unchanged from 1967 until 1998 (Appendix 1), when a new form based on checkboxes was introduced (Appendix 2). The new notification form introduced information on maternal smoking habits, the use of multivitamins and folic acid and gestational age estimation based on ultrasound. Furthermore, since 1999, the MBRN receives a separate notification form for all infants transferred to a neonatal intensive care unit, with specification of birth defects and other neonatal diagnoses made during their stay.

The validity of variables registered in the MBRN varies, but for outcomes such as birth weight and other measurements at birth, it is considered to be high,[10] although validation of most of the variables has not been performed. Validation studies have been performed for certain birth defects (Down's syndrome,[102 103] cleft lip and palate,[104] and gastroschisis[105]) and for maternal diabetes,[106] obstetric sphincter tears,[107] unexplained antepartum death[108] and rheumatic disease,[109] all showing satisfactory results (ascertainment from 70% to more than 90%). The validity of infant death is

considered to be high since all deaths among live-born individuals are recorded in the Central Population Registry, and routine record linkage has been established between the Central Population Registry and the MBRN.

Record linkage

In Norway, parallel civil registration of births in the *Central Population Registry* provides national identification numbers to each individual soon after birth. By means of the mother's identification number (recorded on the birth notification form), record linkage is routinely established between the MBRN and the Central Population Registry to obtain the infant's and father's identification numbers, and for information on all dates of death. This routine record linkage also enables the identification of any missing birth notifications for live births, so that they can be actively sought from the birth clinics. Furthermore, there is routine record linkage with the *Cause of Death Registry* run by *Statistics Norway* for causes of infant deaths. These routine record linkages thus ensure near complete ascertainment of all births in the country, as well as all infant deaths (including causes of death). Very few records are not routinely matched, and the solving of unmatched records has had high priority throughout the history of the MBRN. Non-matches between the MBRN and the civil registration of births are mainly due to refugees and foreign citizens giving birth in Norway before receiving a Norwegian identification number, and they account for around 100 to 200 births annually. In the present studies, the national identification numbers were used to link parents (first generation) with their own offspring (second generation).

Data on educational level were obtained from the National Education Database, Statistics Norway.[110] This register covers all Norwegian inhabitants of at least 16 years of age and is continuously updated. Data on maternal educational level were based on the highest number of completed years of education as registered in 2002 and categorized as low (< 11 years), medium (11-14 years), and high (> 14 years) in accordance with national recommendations.[110]

Study design and study populations

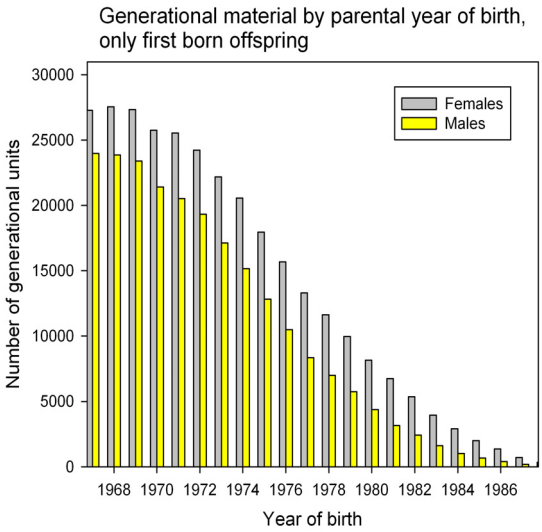
Population-based generational data. The three studies are population-based historical cohort studies, utilising registry-based data. The main analytical files used were generational files based on all births in Norway from 1967 to 2006 (*Paper I* 1967-2004). Births were linked to the mother's and father's own birth records by their national identification numbers, thus providing generation files with birth records on mothers and their offspring and fathers and their offspring. We also linked mother, father and offspring records (trios) to study the effect on offspring birth outcome when both parents were affected by the same birth outcome (*Paper I*).

Paternal half-siblings. In order to specifically study effects transmitted through the fathers, we used the MBRN records to identify paternal half-siblings, i.e. siblings with the same father and different mothers (*Paper I*).

Standard unlinked data file. A standard data file with the infant as the observation unit, covering all births in Norway from 1967 to 2004, was used to describe proportions of birth outcomes and proportions of individuals in the first generations who reproduced.

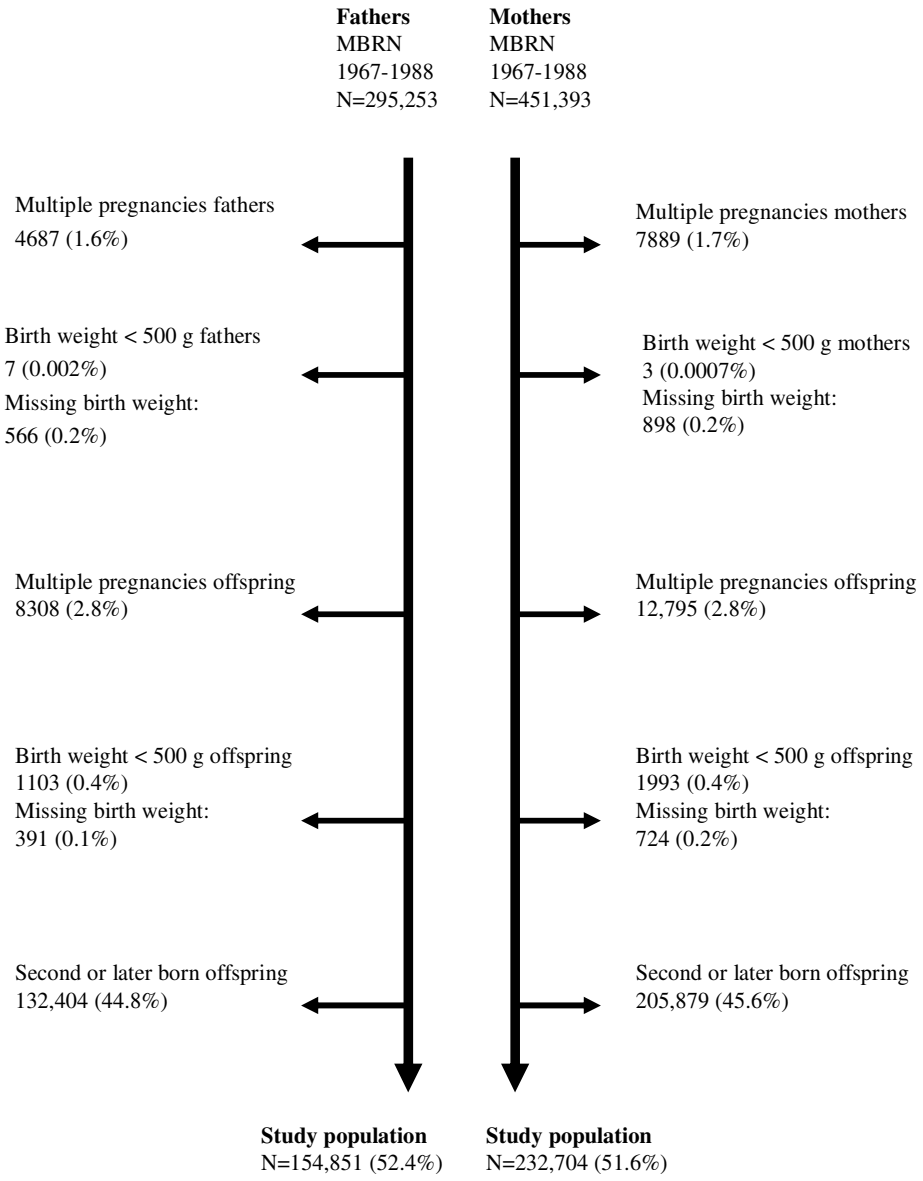
The number of mothers in the MBRN is considerably higher than the number of fathers. Whereas registration of mothers and infants is 100% in our study population, information on fathers is missing for around 2% of births. The father may be missing if mothers who are unmarried or not cohabiting do not provide information about paternity. Fathers are usually of the same age as the mother or older. The main reason for fewer fathers than mothers is that mothers born in the first years of the registry's existence are married to fathers born before 1967, and the fathers' birth records are therefore not available. The amount of generational data, with gradual accumulation as the cohort ages, is shown in Figure 2, which also illustrates that the males reach the level of female reproduction with a delay of two to four years. No generational link is possible for men and women not born in Norway, and births to immigrants can therefore not be part of our study.

Figure 2



Paper I.

In *Paper I*, we had data on 451,393 mother-offspring units and 295,253 father-offspring units. Focusing on intergenerational recurrence of breech delivery, we included singleton pregnancies and birth weights of 500 g or higher in both generations. For all analyses, we restricted the study to first-born offspring in the second generation. This left us with a population of 232,704 mother-offspring units and 154,851 father-offspring units (see the flow chart on the next page). All births delivered in breech presentation were considered to be breech delivery, irrespective of mode of delivery, thus including both elective and emergency CS. The mothers and fathers were born from 1967 to 1988, and more than 98% of the offspring were born during the period 1987-2004. We also linked mother, father and offspring records, yielding 148,692 trio units in order to study the effect on the occurrence of offspring breech delivery of both parents being delivered in breech. We added a special sibship file to further focus on the fetal genetic effect on breech delivery. We identified 35,056 paternal half-siblings where the father had changed partner between his two first births, and both siblings were the first-born offspring of the two mothers.


Fathers
MBRN
1967-1988
N=295,253
Mothers
MBRN
1967-1988
N=451,393
Multiple pregnancies fathers
4687 (1.6%)
Multiple pregnancies mothers
7889 (1.7%)
Birth weight < 500 g fathers
7 (0.002%)
Missing birth weight:
566 (0.2%)
Birth weight < 500 g mothers
3 (0.0007%)
Missing birth weight:
898 (0.2%)
Multiple pregnancies offspring
8308 (2.8%)
Multiple pregnancies offspring
12,795 (2.8%)
Birth weight < 500 g offspring
1103 (0.4%)
Missing birth weight:
391 (0.1%)
Birth weight < 500 g offspring
1993 (0.4%)
Missing birth weight:
724 (0.2%)
Second or later born offspring
132,404 (44.8%)
Second or later born offspring
205,879 (45.6%)
Study population
N=154,851 (52.4%)
Study population
N=232,704 (51.6%)

Paper II.

In *Paper II*, we investigated perinatal mortality risk in offspring in relation to maternal and paternal gestational age and birth weight. Offspring were linked to their mothers and fathers, providing generational data for 546,510 mother-offspring and 394,942 father-offspring units. Singletons in both generations were included, forming 520,794 mother-offspring and 376,924 father-offspring units, which were used for the birth weight analyses. The mothers and fathers were born from 1967 to 1991 and 1967 to 1987, respectively, and the offspring were born from 1981 to 2006. To exclude obviously misclassified gestational ages, births with a birth weight ≥ 4 standard deviations above the mean birth weight for a specific gestational age (birth weight z-scores ≥ 4) were excluded. Parents who were born at ≥ 44 weeks of gestation were also excluded. Data on gestational age were missing for 3.8% and 3.6% of the mothers and fathers, respectively. The final study population left for analyses regarding gestational age thus comprised 487,013 mother-offspring and 353,460 father-offspring units.

Paper III.

In *Paper III*, we investigated the relation between the mother's birth order and the birth weight of her offspring. Singleton mothers were linked to first-born singleton offspring, forming 272,674 mother-offspring units for the analyses. The mothers and their offspring were born in the years 1967 to 1991 and 1981 to 2006, respectively. Twin and triplet mothers were studied separately in a subanalysis (4851 mother-offspring units).

Variables

Breech delivery. Breech presentation is defined as a longitudinal fetal position with the head at the uterine fundus.[111] The prevalence of breech presentation decreases through gestation as the fetus matures; the prevalence of breech presentation is 24% at 28 weeks of gestation and 3-4% at term.[112-116] The proportion of breech delivery

registered in the MBRN increased from 2.5% between 1967 and 1976 to 3.5% between 1997 and 2004. This secular trend may be due to demographic changes, with an increasing proportion of births with low birth order and high maternal age,[112] and to changes in the notification and registration of breech delivery in the MBRN. In *Paper I*, 63% of all breech presenting infants in the second generation were delivered by CS. This increased use of CS could cause a higher proportion of breech delivery since the infant is usually delivered at a lower gestational age.

Prior to 1999, the MBRN notification form did not include direct questions about presentation, but rather questions about complications during delivery. The guidelines accompanying the notification form specified breech delivery as a complication to be notified under this question. From 1999 onwards, a direct question about presentation was included in the notification form, with a separate checkbox for breech delivery. The validity of the data in the MBRN is generally considered to be high, but varies between variables,[10 102-104 106-109 117] and validation of presentation has not been carried out. Norwegian hospital-based studies have reported breech proportions from 3.0% to 3.6 %.[118 119] Data from the MBRN for the same time period indicate a population prevalence of 2.9%, suggesting an adequate ascertainment of breech delivery. Misclassification of presentation is likely to occur at a low level. However, underreporting of breech delivery may be present, especially during the first period of the MBRN's existence. One could also speculate that underreporting of breech delivery may occur in infants delivered by CS. However, in a study by Albrechtsen et al. using data from the MBRN, the proportion of breech delivery was found to increase despite an increasing proportion of CS.[112]

In *Paper I*, all births delivered in breech presentation were considered to be breech delivery irrespective of mode of delivery. Thus, breech delivery also included elective and emergency CS for breech presentation, i.e. women delivered by elective or emergency CS due to a prenatal diagnosis of breech presentation are included among our cases, but not those with successful external cephalic version prior to birth. However, cephalic version has not been a common procedure in breech presentation in Norway.[120]

Gestational age. For most of the study period, gestational age is based on reported menstrual dates, known to be biased by a certain misclassification due to uncertainty about the last menstrual date, bleeding early in pregnancy or registration errors.[10 121 122] Iatrogenic shortening for either medical or psychological reasons (e.g. by CS), more prevalent in the offspring generation, also complicates the interpretation of time trends**.** Preterm birth was defined as delivery before 37 completed weeks of gestation (less than 259 days).[123]

In all three papers, parents' gestational age was based on reported menstrual dates. Offspring gestational age was based on both gestational age and ultrasound dates (for births after 1998). In *Paper I*, gestational age data were missing for 3.6% of the mothers, 3.4% of the fathers and 6.0% and 5.0% of mothers' and fathers' offspring, respectively. In *Paper II*, gestational age was divided into the following categories (completed weeks): 23-27, 28-30, 31-33, 34-36, and 37-43 (reference group). Data on gestational age were missing for 3.8% and 3.6% of the mothers and fathers, respectively.

Birth weight. The quality of the birth weight data is considered to be good in the MBRN, and it is a more accurate and reliable measure than gestational age. Peaks at rounded weights are found (nearest 50 or 100 g). However, this does not constitute a problem for the results. The frequency distribution of birth weight is almost Normal, but with more births in the left tail.[124] In *Paper II*, birth weight (g) was grouped as: < 2000, 2000-2499, 2500-2999, 3000-3499, 3500-3999 (reference group), 4000-4499, and 4500 or more. Birth weight was missing for 0.2% of both mothers and fathers. LBW was defined as a birth weight of less than 2500 g. In *Paper III*, birth weight data were missing for 0.2% of mothers and 0.3% of offspring.

Birth order. This refers to the order in which the individuals were born to their own mother. In *Paper I*, mothers' and fathers' birth order was divided into first-born versus

second or later-born. In *Paper III*, the figure displays results for first to sixth or later-born mothers. In all the tables, birth orders of fourth and higher were merged. Thus, the results are shown for first, second, third and fourth or later-born mothers. In the last category, 61.6% of the mothers were fourth born, and 23.1% and 8.6% were fifth and sixth-born, respectively.

Perinatal mortality. Perinatal mortality was defined as all registered stillbirths from 16 weeks' gestation plus live births that died within the first week of life divided by the total number of births (live and still).

Stillbirth. This was defined as fetal death from 16 weeks' gestation. Whereas there has been a decline in stillbirths with a gestational age of 28 weeks or more and early neonatal deaths, the registration of the earliest stillbirths in the MBRN has improved (16-21 weeks of gestation).[10] Moreover, compared with the early neonatal mortality rate, the stillbirth rate has decreased less over time.[125 126] Thus, the relative contribution of stillbirths to perinatal mortality has increased during recent years.[10] Before 1988, terminated pregnancies were only infrequently notified to the MBRN. In the period from 1988 to 1998, terminations of pregnancy due to serious birth defects were notified as stillbirths on the advice of the Directorate of Health. In 1999, a separate register for late pregnancy terminations (more than 12 weeks' gestation) was established within the MBRN, and since then terminations due to serious birth defects have been included in the MBRN database and can be identified as terminations. In *Paper II*, terminations of pregnancy due to serious birth defects from 1999 onwards were counted as stillbirths.

Early neonatal mortality. This refers to the death of a live-born neonate during the first week of life. The distinction between stillbirth and early neonatal mortality may be difficult to draw in some cases, especially for the smallest infants.[126 127]

Maternal age. Maternal age is complete in the MBRN and part of the national identification number. Many adverse pregnancy outcomes show a U-shaped relationship with maternal age.[128-131] Age at birth (years) was categorised as < 20, 20-24, 25-29, 30-34, and ≥ 35.

Maternal smoking. Smoking was not included in the MBRN until 1999, which is a weakness of the studies. In *Paper III*, smoking habits were categorised as daily smoking and non-smoking. Data on smoking habits were missing for 21.3% of the mothers.

Marital status. Marital status was classified as married / cohabiting and single. Marital status is closely linked to socioeconomic status. Cohabiting was introduced as a separate group in the MBRN in 1982. Previously, cohabitants were therefore part of the 'single' marital status group, with disproportionally many unmarried women in the last years before the change.

Mode of delivery. Caesarean section (CS) rates have increased in Norway for nulliparous women, from 3.4% in 1967-76 to 15.6% in 1996-2004.[77] In *Paper I*, offspring's mode of delivery was classified as vaginal delivery, elective CS or emergency CS. Information on whether or not the CS was planned has been available in the MBRN since 1988. Mode of delivery data were missing for 0.4% and 0.5% of mothers' and fathers' offspring, respectively.

Birth weight by gestational age / z-scores of birth weight by gestational age. In *Paper I*, infants with a birth weight of less than the 10th, between the 10th and the 90th, and above the 90th percentile for a given gestational age were categorised as SGA, AGA and LGA, respectively.[132 133] When adjusting for growth, we also modelled growth as

z-scores of birth weight by gestational age, using nine levels. In *Paper II*, in order to focus on the growth component in the first generation, analyses were stratified by z-scores of birth weight by gestational age, i.e. a z-score < -0.50 (less than average growth), a z-score from -0.50 through 0.50 (average growth), and a z-score > 0.50 (average and higher growth).[133] Z-scores were calculated for each gestational week, based on the paper 'Birthweight by gestational age in Norway'.[133] In *Papers II-III*, SGA was defined as a birth weight less than the 2.5th percentile for a given gestational age.[132 133]

Congenital malformations. Congenital anomalies were registered in accordance with International Classification of Diseases, ICD-8, for the years 1967-1998, and ICD-10 thereafter. Any such diagnosis is made by paediatric examination during the initial stay at the birth clinic, and, since 1999, also during the stay at the neonatal ward for infants transferred to such units. In *Paper I*, individuals were classified as having or not having a registered major congenital anomaly, according to definitions used by Eurocat (European Surveillance of Congenital Anomalies: www.eurocat.ulster.ac.uk). In *Paper II*, individuals were classified as having or not having a registered congenital anomaly (major or minor). Ascertainment of congenital malformations has improved with time in the MBRN.[102-105]

Period of birth / time trends. Time trends were evaluated by grouping parents' year of birth into the following intervals: 1967-71, 1972-76, 1977-81 and 1982 and later. In *Paper III*, we divided the material into one early and one late time period (1981-98 and 1999-2006) according to offspring's year of birth.

Maternal education. Maternal education is the dimension of socioeconomic level that is most strongly and consistently associated with perinatal health.[134-138] Educational level referred to the highest number of completed years of education as registered in

2002, and was categorised as low (< 11 years), medium (11-14 years;) and high (> 14 years) in accordance with national recommendations.[110] Data on educational level were obtained from the National Education Database, Statistics Norway.[110] In *Paper II*, grandmothers' educational data were missing for 0.6% and 0.5% of mothers and fathers, respectively. In *Paper III*, educational data were missing for 0.6% of grandmothers and 0.3% of mothers.

Statistical analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA) version 14.0 (*Paper I*) and 15.0 (*Paper II* and *III*) and STATA (STATA intercooled release 9 (Stata Statistical Software: Release 9. College Statin, Tx: StataCorp LP)) (*Papers I* and *II*).

ORs and 95% confidence intervals (C.I.s) were calculated using contingency tables and by logistic regression. For rare outcomes, ORs with corresponding 95% C.I.s approximated relative risks (RRs). For frequent outcomes, RRs were calculated using generalised linear models as available in STATA (*Paper I*) and SPSS (*Paper II*).

Logistic regression and generalised linear models were used to estimate effects, adjust for confounding and evaluate interaction between factors.

In *Paper II*, as part of our material comprised non-independent births to the same mother, we also analysed the subset of mothers with first and second or later births using generalised linear models with clustered robust standard error (STATA), identifying the mother as the unit of analysis, accounting for dependence within a family.

In *Paper III*, the relation between mother's birth order and offspring birth weight was estimated by multiple linear regression, adjusting for possible confounders.

Pearson's correlation coefficient, r, was the measure of correlations throughout, a two-sided P-value less than 0.05 was considered statistically significant.

6. Ethical considerations

All papers were based on anonymised data and were thus exempt from institutional review board approval in Norway.

7. Review of papers

Paper I

Maternal and paternal contribution to intergenerational recurrence of breech delivery: population based cohort study. Nordtveit TI, Melve KK, Albrechtsen S, Skjaerven R. BMJ 2008; 336;872-876.

Objective. Previous studies have shown that recurrence of breech delivery in successive siblings is high, but knowledge about recurrence between generations has been lacking. We wanted to investigate intergenerational recurrence of breech delivery, with a hypothesis that both women and men who themselves were delivered in breech, contribute to an increased risk of breech delivery in their offspring.

Material and methods. The data used were from the MBRN from 1967 to 2004. Births were linked to their mother's and father's own birth records by national identification numbers, thus providing generation files with birth records on mothers and their offspring, and fathers and their offspring. Multiple pregnancies and birth weights of < 500 g in both generations were excluded. The study was restricted to first-born offspring in the second generation. The final study population thus consisted of 232,704 mother-offspring units and 154,851 father-offspring units. To specifically study effects transmitted through the fathers, we analysed 35,056 paternal half-siblings where the father had changed partner between his two first births, and both siblings were the first-born offspring of the two mothers. Birth weight by gestational age, period of birth, maternal age and maternal education, all in the first generation, were evaluated as possible confounding variables. Effect modification by birth order and

gestational age in the first generation, and mode of delivery and gestational age in the second generation were also evaluated.

Results. First-born men and women themselves delivered in breech had more than twice the risk of breech delivery in their own first pregnancies compared with their cephalic counterparts (OR 2.2, 95% C.I. 1.8 to 2.7 and 2.2, 95% C.I. 1.9 to 2.5, for men and women, respectively). For men and women born preterm, there was no recurrence. Adjustment for possible confounding factors did not change the results. When stratifying the analysis by offspring gestational age and offspring mode of delivery, the strongest risk of recurrence for both men and women was found for vaginally delivered offspring with a gestational age of 41-42 weeks. Men who had fathered one breech pregnancy had a 50% increased risk of fathering a breech pregnancy in another woman (OR 1.5, 95% C.I. 1.2 to 1.9).

Conclusions. Both women and men who were themselves delivered in breech at term had increased risk of breech delivery in their offspring. Since recurrence through the father was as strong as recurrence through the mother, the results indicate that genes passed on from the mother or the father to their offspring may be closely related to, and increase the risk of, breech delivery.

Paper II

Maternal and paternal birth characteristics and perinatal mortality in their offspring: a population based cohort study. Nordtveit TI, Melve KK, Skjaerven R.

Objective. Our aim was to examine the associations between parents' gestational age and birth weight and perinatal mortality in their offspring, with particular focus on the paternal relations. By comparing maternal and paternal associations, we aimed to acquire more knowledge about how risk factors for perinatal mortality may be transmitted through generations.

Material and methods. We used population-based generational data from the MBRN from 1967 to 2006. Singletons in both generations were included, forming 520,794 mother-offspring and 376,924 father-offspring units for birth weight analyses. To exclude obviously misclassified parental gestational ages, births with birth weight z-scores ≥ 4 were excluded. The study population left for analyses regarding gestational age thus comprised 487,013 mother-offspring and 353,460 father-offspring units. Grandmothers' age, grandmothers' education and parents' year of birth were evaluated as possible confounding variables. Growth (birth weight z-scores for gestational age, three categories) was evaluated as a possible effect modifier for the relation between parental gestational age and offspring mortality. For rare outcomes, ORs were estimated using logistic regression and approximated RR. For frequent outcomes, RRs were calculated using RR modelling (log link) as available in SPSS's generalised linear models.

Results. Perinatal mortality in offspring was not significantly associated with paternal gestational age or birth weight. In contrast, there was a strong inverse association between maternal gestational age and perinatal mortality in offspring. A threefold increased risk in perinatal mortality was found among the offspring of mothers born at 28-30 weeks of gestation compared with the offspring of mothers born at term (37-43 weeks) (RR 2.9, 95% C.I. 1.9 to 4.6). Among preterm mothers, a larger proportion of offspring deaths were preterm births compared with mothers born at term. There was also a clear reduction in perinatal mortality risk as maternal birth weight increased. The highest perinatal mortality risk was found for offspring whose mother's birth weight was < 2000 g (crude RR 1.5, 95% C.I. 1.1 to 1.9) compared with mothers whose birth weight was 3500-3999 g. However, confined to mothers born at ≥ 34 weeks of gestation, the birth weight association was not significant, indicating that maternal immaturity rather than birth weight itself may be the important factor. Weight-specific perinatal mortality in offspring was dependent on the birth weight of the mother and the father, i.e. offspring who were small relative to their mother's or father's birth weight had increased perinatal mortality.

Conclusions. A mother's gestational age, and not her birth weight, was significantly associated with perinatal mortality in her offspring, while there was no such association for the father. The contrast between the maternal and paternal associations indicates that preterm delivery in females, but not in males, is linked to increased perinatal mortality risk in the next generation. A possible explanation for the association between maternal gestational age and offspring perinatal mortality could thus be genetic factors, predominantly through maternal genes, related to preterm delivery. Fetal genes seem less important since there was no association between paternal gestational age and offspring mortality. Increased perinatal mortality through the maternal line may also reflect environmental factors correlated across generations.

Paper III

Intergenerational birth weight associations by mother's birth order - The mechanisms behind the paradox: A population-based cohort study. Nordtveit TI, Melve KK, Skjaerven R. Early Human Development 85 (2009) 577–581.

Objective. Two previous studies have shown that a mother's birth order is inversely associated with offspring birth weight despite being positively associated with the mother's own birth weight. As maternal and offspring birth weight are positively correlated, it is interesting that there is no monotone relation between mother's birth weight and offspring birth weight. In the present study, intergenerational birth weight associations by mother's birth order were further explored, with the emphasis on possible mechanisms behind this paradox.

Material and methods. We used population-based generational data from the MBRN from 1967 to 2006. In the main analyses, multiple pregnancies in both generations were excluded and we restricted the study to first-born offspring, which left us with a study population of 272,674 mother-offspring units. In most analyses, mothers with birth orders of fourth and higher were merged. Grandmother's attained education was

used as a proxy variable for social class, categorised as low, medium and high based on the highest number of completed years of education as registered in 2002. Other demographic variables available for the mothers and associated with offspring birth weight included educational level, age at delivery, marital status and smoking habits. The relation between mother's birth order and various demographic variables was calculated using contingency tables. The relation between mother's birth order and offspring birth weight was estimated by multiple linear regression, adjusting for possible confounders.

Results. Maternal birth weight increased steadily with increasing birth order, while, in contrast, there was a negative association between mother's birth order and offspring birth weight (9.1 g decrease for each increase in birth order, 95% C.I. 6.8 to 11.4). First-born mothers tended to be older, to have higher education, to more often be married or cohabiting, and to smoke less at the time of their pregnancy than later-born mothers, i.e. first-born mothers in general have more favourable adult behaviour. Similar to the overall relations, we found a negative association between mother's birth order and offspring birth weight in the lowest social class (crude; 7.1 g decrease per birth order, 95% C.I. 4.5 to 9.7). The association was less evident, and non-significant, for mothers in the highest social class (crude; 2.3 g decrease per birth order, 95% C.I. -4.5 to 9.0, P = 0.51).

Conclusions. The general reduced birth weight among first-born mothers is not transferred to the next generation; on the contrary, first-born mothers have offspring with an even higher mean birth weight than later-born mothers. We suggest that the causes of this inverse relation are more of social than of biological origin.

8. Discussion of methods

Internal validity

Internal validity refers to the degree of systematic error in a study. It refers to validity of inference for the study subjects. The main types of systematic errors can be classified into three categories: selection bias, information bias and confounding.

Selection bias / selection of individuals

There is selection bias when the association between exposure and outcome differs for those who are included in the study population and those who are not.[139]

In this thesis, all registered births in Norway make up the source population, with very close to 100% coverage of all births in the country in the MBRN. Since the whole population is the basis for inclusion, selection bias is an unlikely explanation for the results. There is selection to the study by design, however, since it is a generational study: stillbirths, individuals who die before reproductive age and individuals who for some social or biological reason do not reproduce are excluded from the first generation (Figure 3, adapted from [63] and Figure 4, adapted from [53]).

Figure 3

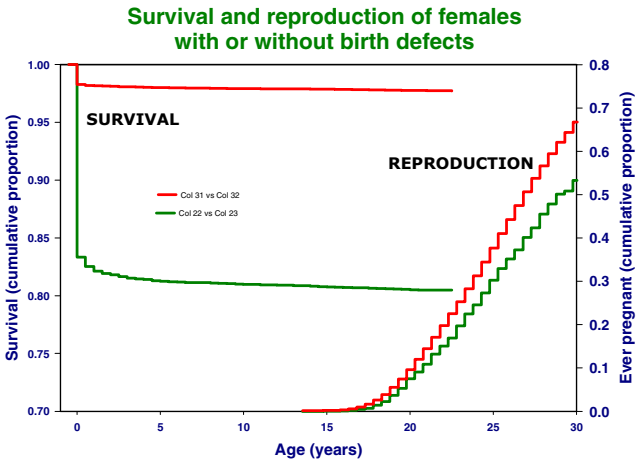
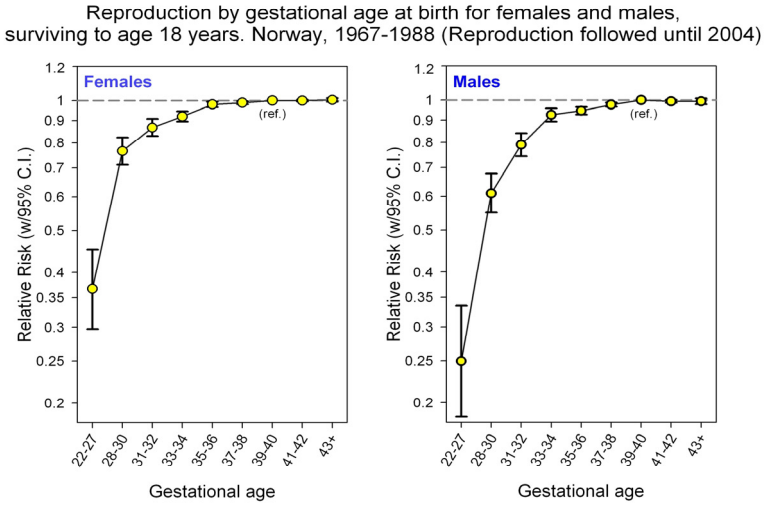


Figure 4



However, this does not represent an ordinary selection bias, but is the result of natural selection in the source population. The individuals who are 'selected' to the studies are therefore all individuals born after 1967 in Norway who themselves reproduce in Norway. The reason for the considerably higher number of mothers than fathers is described on page 32 (see also Figure 2 on page 33). The offspring generation is complete, i.e. stillbirths and infant deaths are included.

One possible 'ordinary' selection bias that may be present in many intergenerational studies is that associated with inadequate follow-up time. Previous work on intergenerational data from Norway and other countries have used very early data sets where truncation of parents' age is a significant problem, i.e. the vast majority of parents are young when they reproduce.[62 63 81] The present studies underline the need for intergenerational studies to allow sufficiently long follow-up time. The MBRN now have data covering 40 years, and this provides a basis for more complete generational data sets, as the first birth cohorts have now almost completed their reproduction. However, the problem is still present for the younger cohorts of the first generation.

Information bias

Information bias arises because of errors in the information collected about the subjects or errors in the classification of subjects.[139] If the variable is measured on a categorical scale, such information bias is often referred to as misclassification. Misclassification of subjects can be either non-differential, if the misclassification of exposure or outcome is not dependent on the other, or differential, if the misclassification of exposure or outcome depends on the value of the other. In non-differential misclassification, the effect, if present, will always be biased towards the null value, whereas, in differential misclassification, the effect can either be exaggerated or underestimated.[139]

In *Papers I* and *II,* both mothers and fathers were analysed. As described on page 32, information about fathers is missing for around 2% of births in the MBRN. Estimates have not been made of the proportion of infants with wrong paternity, in which infants have a different biological father than recorded in the MBRN, but recent population-based genetic studies suggest that paternity information is incorrect for less than 5% of Norwegian infants (Min Shi, as referred in [15]). The low level of error in the paternity information would only have an insignificant influence on paternal estimates, but, if anything, this would leads to underestimation of the genetic component of the covariance between fathers and offspring. Estimates of wrong paternity in other countries have been reported to be up to 20%.[140-142]

Paper I - Breech delivery in parents and offspring. As described on page 36, an improved notification form with a checkbox for breech delivery was introduced in the MBRN in 1999, and breech delivery data may have been missing, inconsistently recorded or misclassified in both parents and offspring prior to that date. It is unlikely, however, that any misclassification in the second generation would be related to presentation in the first, since questions about the parents' presentation at birth are not part of routine antenatal health care for pregnant women in Norway. Any misclassification would therefore be non-differential, and the true intergenerational

association would be underestimated. The extent of this problem is considered to be marginal, however. Furthermore, we found similar estimates for the recurrence of breech delivery in the two time periods 1967-98 and 1999-2004, despite changes in the registration practice, and, if anything, the effects were stronger in the first time period.

Paper II - Gestational age and stillbirth, early neonatal and perinatal mortality. Gestational age is known to be biased by a certain misclassification, especially before 1999 when it was based solely on reported menstrual dates.[10 121 122] Perinatal mortality is probably less hampered by misclassification, and neonatal death is a valid outcome that is recorded in the Central Population Registry. As gestational age and early neonatal mortality are registered in two different registries, any misclassification would be non-differential, and the effect, if present, would be biased towards the null-value. Moreover, it is unlikely that a midwife reporting any perinatal deaths to the MBRN would be aware of the parents' gestational ages at their birth.

Paper III - Social class. Grandmother's attained education was used as a proxy variable for social class.[136 138] The proportion of grandmothers with low, medium and high education was 74%, 12% and 14%, respectively. The proportion of grandmothers with low education (< 11 years) is high, and probably reflects the fact that it was more common for women in the 1960s and 1970s to stay at home. Grandmother's education may thus not be a good proxy for social class, and some mothers may be misclassified as belonging to the lowest social class. Since grandmother's education and birth weight are registered in two different registries, any misclassification would be non-differential, and the effect would be biased towards the null value.

Confounding

A simple definition of confounding would be confusion or mixing of effects. This definition implies that the effect of the exposure is mixed together with the effect of another variable, leading to a bias.[139] More precisely, there is confounding when the association between exposure and outcome includes a non-causal component attributable to their having an uncontrolled common cause.[143] In the present work, we evaluated possible confounders on the basis of a hypothesis about common causes. Maternal age,[128-131] maternal education[134-138] and year of birth,[125 144 145] all in the first generation, were considered as potential confounders in all three papers. Given their temporal order, we adjusted for first generation variables, and not second generation variables. However, adjustment did not change the estimates to a large extent. We think this is due to the fact that the relations between the confounding variables and the outcome are much weaker than the intergenerational effect.

Effect modification

Effect modification, also called interaction, means that the magnitude of a measure of effect of an exposure variable on an outcome varies according to the level of a third variable.[146]. Effect modification was evaluated by stratification and by the inclusion of an interaction term in multivariate analyses. We only tested for effect modification when there was a clear a priori reason for doing so.

Paper I. Analyses were stratified by gestational age and birth order in the first generation. The highest recurrence risk of breech delivery was observed for first-born men and women delivered at term, whereas for preterm-born men and women we essentially observed no recurrence between generations. An obvious interaction was found between presentation and gestational age for both men and women ($P = 0.008$ and $P = 0.036$, respectively, Wald test). Also, when stratifying the analysis by mode of delivery and gestational age in the second generation, the strongest recurrence risks were found for vaginally delivered offspring with a gestational age of 41-42 weeks.

Paper II. In *Paper II*, most importantly, when including only mothers born at ≥ 34 weeks of gestation in the birth weight analyses, mothers with a birth weight < 2000 grams were no longer at increased risk of experiencing a perinatal death, indicating interaction with gestational age. In order to study whether maternal growth influenced the relation between maternal gestational age and perinatal mortality in offspring, z-scores for birth weight by gestational age – three categories – were included in the model. There was no statistically significant interaction between growth and gestational age (P = 0.91, Wald test). Moreover, there was no statistically significant interaction between maternal age (< 25 and ≥ 25 years) and maternal gestational age or maternal birth weight.

Paper III. Analyses were stratified according to social class. The inverse association between mother's birth order and offspring birth weight was still evident for mothers born into the lowest social class, but it was less and non-significant for mothers who were born into the highest social class (P for interaction between birth order and social class = 0.11, Wald test).

External validity

External validity or generalisability implies validity of the inferences as they pertain to people outside the source population.[146] Internal validity is a prerequisite for external validity.

The conclusion in *Paper III,* that social factors account for the inverse relation between mother's birth order and offspring birth weight, may be driven by cultural factors linked to the Nordic countries, and may be different elsewhere. The results in *Papers I* and *II* may to a larger extent be explained biologically, and they may therefore be more generalisable to other populations. Moreover, in *Paper II*, similar findings were reported in other populations.[25 90]

Precision

Random errors reduce precision in reported associations. Precision can be improved by either increasing the study size or by modifying the study design. The former is the principal way of increasing precision in epidemiological studies.[146]

In this thesis, the large study size and standardized collection of data provide high precision in the effect estimates, i.e. with narrow confidence intervals. However, some analyses, e.g. analyses concerning early neonatal mortality in *Paper II*, were hampered by few cases.

9. Discussion of the results

Paper I

As most research has been on the consequences of breech delivery and on delivery methods with a view to reducing the risk for both the fetus and the mother, less focus has been placed on the causes of breech delivery. Risk factors for breech delivery include maternal characteristics (both high and low parity, high maternal age, uterine abnormalities and pelvic tumours), characteristics of the pregnancy (multiple fetuses, hydramnios, oligohydramnios and placenta implantation site, e.g. placenta previa) and fetal factors (preterm birth, LBW, growth restriction, neuromuscular dysfunction and congenital anomalies, e.g. hydrocephaly and anencephaly).[112 114 116 147-150] However, such risk factors were only identified in 7-15% of breech delivery cases.[149-151] Unexpectedly, no strong association was found between breech delivery and a contracted pelvis.[149 150]

Our main conclusion was that an increased risk of breech delivery in offspring was associated with both a maternal and a paternal history of breech delivery at term, with the paternal effect being as strong as the maternal effect.

Recurrence between generations may be explained by genetic factors or persisting environmental factors. The possibility of genetic factors being important was strengthened by the strong paternal effects. We could not think of any persisting environmental factors that could explain these relations, and we therefore suggest a genetic component in the aetiology of breech delivery. Contrary to what we might expect, the effect of maternal genes seems to be low, since recurrence from mother to offspring, being a sum of the effect of fetal genes passed on from the mother plus maternal genes, is similar to the effect of fetal genes passed on from the father.[13]

The recurrence of breech delivery across generations could perhaps be explained by increased use of planned CS at a lower gestational age among individuals themselves delivered in breech. However, questions about the mother's and especially the father's presentation at birth have not been part of routine antenatal health care for pregnant women, since knowledge of recurrence of breech delivery between generations has been lacking. When stratifying the analysis by mode of delivery in the second generation, we found the highest recurrence of breech delivery among those delivered vaginally, and, among those delivered by elective CS, the recurrence was actually lowest for both mothers and fathers. Furthermore, when stratifying the analysis by gestational age in the second generation, there was a tendency towards higher recurrence with higher gestational age.

To investigate the paternal effects further, paternal half-siblings, i.e. siblings with the same father and different mothers, were also examined. Increased recurrence of breech delivery among paternal half-siblings supports the hypothesis of a fetal genetic component of breech delivery from the father. Half-siblings are second-degree relatives, and the empirical recurrence risk for the second infant is lower than if the infants had both parents in common. However, men who fathered one breech pregnancy had an approximately 50% increased risk of fathering a breech pregnancy in a different woman, indicating a shared risk among paternal half-siblings.

Genital anomalies, inherited from mothers by their daughters, could have an impact on the recurrence of breech delivery. However, only 22 reproducing women in the study population were registered with a genital anomaly. These included congenital anomalies in the uterus and cervix uteri (e.g. uterus bicornis and uterus unicornis). We assumed that 22 cases was too small a number to have an impact on the recurrence risk of breech delivery.

Some mothers and fathers are represented with more than one child. Since the recurrence of breech delivery in successive siblings is high,[149-152] not all mother-offspring units would be independent if we had included all birth orders in the second generation. Therefore, only first-born offspring were included. However, similar results were found for second or later-born offspring in the second generation.

Three per cent of breech deliveries in the second generation were attributable to breech delivery in the father, and 3% were attributable to breech delivery in the mother. Thus, 6% of the breech deliveries in the second generation were accounted for by parental influence.[139] Thus, use of the parental association is unlikely to dramatically increase the detection rate of breech presentation. Still, our findings on recurrence of breech delivery are novel. Janet Hardy at the University of Massachusetts, USA, wrote in the British Medical Journal (BMJ) that 'multiple biological mechanisms probably contribute to the risk of breech delivery, some genetic, maternal or paternal, or both, some related to the uterine environment, and some a combination of both'.[153] She further suggested that future research should look at the offspring's environment and specific characteristics, e.g. specific major malformations, in the context of parental factors, as this may provide some insight into the maternal and paternal effects. Strength of evidence will come from additional epidemiological studies and from lab-based studies with consistent conclusions.

Breech delivery is associated with significantly increased perinatal mortality and morbidity.[154-156] The number of undiagnosed breech presentations before delivery has been shown to be high, ranging from 20-30%.[157-159] Clinicians should therefore gather information about the mother's and father's own presentation at birth, since such

information can serve to alert the clinicians to the possibility of breech delivery and contribute to better birth planning.

Paper II

In recent years, studies focusing on the mother's and father's own conditions at birth as determinants of their reproductive capabilities have attracted interest. We investigated the associations between parents' gestational age and birth weight and perinatal mortality in their offspring, with particular focus on paternal relations. Our conclusion was that a mother's gestational age, and not her birth weight, was significantly associated with perinatal mortality in her offspring, while there was no association for the father. Similar patterns of maternal associations were also found for stillbirth and early neonatal mortality, although the analysis concerning early neonatal mortality was hampered by few cases.

Perinatal mortality is a commonly used outcome. However, it may be important to carry out analyses of the two components of perinatal mortality separately for several reasons, since the meaning of perinatal mortality has changed during recent decades.[126] Firstly, the relative contribution of stillbirths to perinatal mortality has increased.[160] Secondly, the causes of stillbirth and early neonatal mortality have diverged. For instance, as a consequence of more effective prenatal care, stillbirth has decreased significantly for women affected by preeclampsia.[161] On the other hand, major risk factors for stillbirth are high maternal age and overweight, and the prevalence of both of them is rising rapidly in developed countries. [162] In addition, as a result of more effective prenatal and neonatal care, early neonatal mortality has decreased significantly for preterm deliveries and LBW infants, while the stillbirth rate has decreased less.[125 126] However, the distinction between stillbirth and early neonatal mortality may be difficult to draw in some cases, especially for the smallest infants.[126 127] In our material, most of the early neonatal deaths occurred during the first 24 hours after birth.

If the described intergenerational associations indicate causal effects, it is important to try to separate the birth weight effect from the gestational age effect, as these two parameters reflect different underlying mechanisms. In our cohort, the group of parents with a birth weight < 2000 g was a largely heterogeneous group with respect to maturity, with gestational ages ranging from 23 to 40 weeks. Thus, part of the birth weight effect could be explained by a gestational age effect. When analysing the birth weight relations among women born at ≥34 weeks of gestation (34 weeks of gestation was used instead of term because a birth weight < 2000 g hardly exists at term), there was no longer an increased mortality risk for offspring of mothers < 2000 g, indicating that maternal immaturity rather than birth weight itself may be the important factor. A few studies have shown that a mother's birth weight is associated with perinatal mortality of her offspring.[25 81 90] Our study suggests that the birth weight relations most likely represent gestational age relations.

The underlying reasons for the association between preterm delivery in females and perinatal mortality in their offspring remain to be determined. However, among preterm mothers, a larger proportion of offspring deaths were preterm births compared with mothers born at term. A possible explanation for the association between maternal gestational age and offspring perinatal mortality could thus be genetic factors, possibly through maternal genes, related to preterm delivery. Fetal genes seem to be less important since there was no association between paternal gestational age and offspring mortality. This finding supports another study from the MBRN, which found no indication of fetal genes in preterm birth risk.[15] Increased perinatal mortality through the maternal line may also reflect environmental factors correlated across generations.[73 135 163]

Offspring's mean birth weight decreased and the proportion of LBW offspring increased as maternal and paternal gestational age decreased. We questioned whether this reduced birth weight in offspring could be a cause of mortality by itself. Basso et al. postulated that a baby's birth weight was not itself on the causal path to mortality; the relation between a baby's birth weight and mortality could instead be explained by the presence of confounding factors that decrease birth weight and increase mortality,

e.g. congenital malformations and placental dysfunction.[164] Wilcox suggested that reduced birth weight is not sufficient by itself to increase mortality, and that moderately reduced *in utero* growth does not necessarily increase an individual baby's mortality risk.[165 166] Our finding may support this hypothesis, since perinatal mortality in offspring was not influenced by paternal gestational age despite an increase in the proportion of LBW offspring, from 3.7% in the highest to 6.8% in the lowest gestational age group.

The present study is a necessary and important follow-up study of the previously published work by Skjaerven et al. in which generational data from the MBRN from 1967 to 1994 were used.[81] The previous study only analysed maternal relations, and little was known about the mortality risk in the offspring of fathers with low birth weight. Furthermore, the previous study only focused on birth weight, and it was unclear whether the results reflected an increased risk due to the mothers being preterm or growth restricted, or a combination of the two. Finally, the study was a very early intergenerational study from the MBRN, with the oldest mothers in the first generation being 28 years old. This maternal age truncation introduced a selection bias, with the large majority of mothers in the study being young when they reproduced.

In the previous study by Skjaerven et al, mothers with a birth weight < 2000 g were twice as likely to lose their baby in the perinatal period as mothers with a higher birth weight.[81] Thus, the stronger association found in the previous study compared with our results could be due to truncation of maternal age, whereby the youngest mothers drive the findings.[81] However, when we stratified the birth weight analyses by maternal age (< 25 and ≥ 25 years), the estimates were the same, indicating that an overrepresentation of young mothers probably does not represent a bias in the previous study. Time trends in perinatal mortality are probably the explanation for the difference in perinatal mortality found between the studies. For mothers born at 28-30 weeks of gestation, the risk of perinatal mortality was equally strong for young and old mothers, again indicating that the relation between maternal gestational age and offspring mortality is not explained by the mothers being younger.

The ‘developmental origins of adult disease’ hypothesis, often called the ‘Barker hypothesis’ states that adverse influences early in development and particularly during intrauterine life, e.g. reduced fetal growth and low birth weight, are strongly associated with a number of chronic conditions later in life, including cardiovascular heart disease, hypertension, diabetes and strokes.[7 167] The theory of ‘intrauterine programming’ in humans remains controversial.[168 169] We suggest that the ‘Barker hypothesis’ concerning fetal origin of adult disease may be valid for mothers with low gestational age. This is another example of how perinatal outcome may have long-term consequences in adulthood.

‘The birth weight paradox’. We also found that offspring who were small relative to both their mother’s or father’s birth weight were at increased risk of dying in the perinatal period. The acknowledged correlation between parents’ and offspring birth weight, partly explained by genetic and environmental factors,[28] has implications for offspring birth weight distribution, and also for weight-specific perinatal mortality risk.[165 170] A given birth weight value has different locations on the different offspring birth weight distributions, and thus on the corresponding weight-specific mortality curves. Among mothers with the highest birth weights, LBW in their offspring more likely reflects serious pathology, e.g. congenital anomalies or preterm birth. Among mothers with lower birth weights, LBW in their offspring is more likely to be constitutional or linked to environmental influences such as smoking and nutrition that are less associated with perinatal mortality.[170] The ‘low birth weight paradox’ may be explained by selection bias arising when stratifying on a variable (offspring birth weight) that is affected by the exposure (parental birth weight) and shares common causes with the outcome (perinatal mortality).[170] The finding that a baby has elevated mortality when it is smaller than expected has previously been reported in sibling studies, for instance.[171-173]

In this paper, we did not link mother, father and offspring records, i.e. we did not organise the data in trios. The reason for this is, firstly, that there is a very low correlation between mothers’ and fathers’ birth weights (in our population, Pearson

Correlation = 0.02) and gestational ages. Secondly, organising in trios would decrease the study population substantially.

Some parents are represented with more than one child (around half of the mothers had more than one birth), which means that part of the material will comprise non-independent births to the same parents (interdependency of outcomes within the family structure).[174] We analysed the subset of mothers with first and second or later births using RR modelling with clustered robust standard error as available through STATA, identifying the mother as the unit of analysis. Modelling this non-independence did not notably influence the risk estimates or confidence intervals. If anything, when stratifying the analysis by offspring birth order, maternal gestational age and birth weight were more closely associated with perinatal mortality among second or later-born than among first-born infants.

Smoking is related to a number of adverse pregnancy outcomes, [163 165 175-177] but it was not included in the MBRN until 1999, which is a weakness of the study. However, smoking is related to other risk factors, including age and socioeconomic status,[138] although the correlation between smoking and socioeconomic level primarily applies to recent years.

The contrast between the maternal and paternal associations adds new knowledge about how preterm delivery is linked to intergenerational risk of perinatal death through the maternal side only. The absolute risk of experiencing perinatal death was low. For mothers born at 28-30 weeks of gestation, the absolute risk of experiencing perinatal death in their offspring was 2.9% compared with 1.0% for mothers born at term. The main importance of the present study may thus not be its clinical implications. However, individuals who have been delivered very preterm and survive to reproductive age are now becoming an increasingly large population. This should warrant extra attention being devoted to pregnant women who were themselves delivered preterm.

Paper III

The present study confirmed intergenerational birth weight associations by mother's birth order.[39 49] Despite mother's birth weight increasing as mother's birth order increases and a positive mother-offspring correlation in birth weight,[39] mother's birth order was inversely associated with offspring birth weight. Previous studies did not focus on the causes behind the relations. Therefore, our emphasis was on possible mechanisms behind the findings.

We suggest the causes of the inverse relation to be more of social than of biological origin. First-born mothers probably have the same biological potential for achieving similar sized offspring as later-born mothers, but, due to less adverse socio-demographic characteristics, their offspring have a higher birth weight on average than the offspring of later-born mothers. We defined mothers as belonging to the lowest and highest social class when their own mothers had a low and high educational level, respectively. As for the overall relations, there was a negative association between mother's birth order and offspring birth weight in the lowest social class. This association was less evident, and non-significant, when the mothers belonged to the highest social class. We suggest that mothers born into a high social class keep their social position independent of birth order.

Birth order has been shown to affect many aspects of a person's life, e.g. a person's personality, self-esteem and cognitive achievement.[178-180] First-born children are in general seen as being more responsible and tend to have higher educational motivation and academic achievement than later-born children,[181 182] perhaps as a result of higher expectations and greater attention from the parents.[183]

Another possible explanation for the inverse relation between mother's birth order and offspring birth weight could be a confounding effect of social class. That is, if family size, i.e. grandmother's number of children, is a function of social class, and families with high social class tend to have smaller families than families with low social class, then mothers with high birth order may come from a low social class, which in turn may explain the lower birth weight in their offspring. However, contrary to what one

might expect, families with only one child were more common among grandmothers with low education than those with high education, whereas the opposite was the case for families with two to four children. As expected, the proportion of grandmothers with five or six children was higher among grandmothers with low education than among those with high education, but five and six children are rare even among grandmothers with low education.

In both generations, the risk of LBW, preterm delivery and SGA was higher for fourth- and later-born mothers when compared with second-born mothers, reflecting the phenomenon of 'selective fertility'. This means that deaths are likely to lead to replacement pregnancies of higher parities, complicating the interpretation of the results.[184]

We concluded that the reduced birth weight experienced by first-born mothers is not a risk factor for reduced birth weight in their offspring. The positive association of a healthy life style with offspring birth weight tends to counterbalance the expected effect of first-born mothers' reduced birth weight on their offspring's birth weight.

10. Conclusions

Associations of birth outcomes across two generations were described. Generational data consisting of birth records for mothers and their offspring and fathers and their offspring were derived from the MBRN for the period 1967-2006. Intergenerational recurrence of birth outcomes and intergenerational associations between the mother's and father's own birth characteristics and different outcomes in their offspring were studied. Hypotheses were proposed about how genetic and environmental, behavioural and socioeconomic factors may act on reproduction and birth outcomes through generations.

We showed that the experiences of one generation influence the health of the next generation. We found similarities, but also apparent dissimilarities, between the parents' relative contribution to predictors of adverse birth outcomes in their offspring. The comparison between maternal and paternal intergenerational relations provided important new insight that may prove useful when focusing on possible causal mechanisms. The recurrence risk of breech delivery in offspring was equally high when transmitted through fathers as through mothers, suggesting that fetal genes from either the mother or the father are related to breech delivery in the next generation. In contrast, there was a strong inverse association between maternal gestational age and perinatal mortality in offspring, while there was no such association for the father, suggesting that maternal genes influencing a woman's reproductive capability may be related to offspring survival. However, offspring survival may also reflect environmental factors correlated across generations, with a greater tendency for mothers and daughters to share environmental risk factors important to the outcome of their pregnancy. Finally, mother's birth order was inversely associated with offspring birth weight despite being positively associated with the mother's own birth weight, suggesting that the causes of the inverse relation are more of social than of biological origin, as first-born mothers in general had more favourable adult behaviour.

Although our results may be relevant to public health and clinical practice, we believe that the main importance of intergenerational associations is the hypotheses they give

rise to concerning possible causes of birth outcomes. Intergenerational reproductive associations may reflect the presence of shared genetic causes and be good candidates for future genetic studies.

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