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Prevalence, self-report validity, and associations to SGA and "early programming" using family and sibling design

Liv Grimstvedt Kvalvik

Avhandling for graden philosophiae doctor (ph.d.)
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UNIVERSITETET I BERGEN

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Dato for disputas: 27.04.2018

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År: 2018

Tittel: Smoking among pregnant women in Norway

Navn: Liv Grimstvedt Kvalvik

Trykk: Skipnes Kommunikasjon / Universitetet i Bergen

Scientific environment

The work presented in this PhD-thesis was initiated through the Medical Student Research Programme at the Faculty of Medicine, University of Bergen and was carried out in the research group for Reproductive epidemiology with a life course perspective, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen. The PhD scholarship was funded by the University of Bergen. I have been a member of The National Research School in Population Based Epidemiology (EPINOR).

Main supervisors have been Professor Kjell Haug and Professor Rolv Skjærven, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen.

Acknowledgements

Many physicians have used their spare time for research. I grew up watching my grandfather, a gynecologist, conducting a long time follow up of a family with malignant melanomas. Driven by curiosity, he used holidays and weekends for his research. I am utterly thankful to have had the chance to go into depth in research and I have every day been grateful to the University of Bergen for allowing me to have research as my full time job.

I have felt most privileged to work with my excellent supervisors: Professor Rolv Skjærven and Professor Kjell Haug. Ever since the first time I knocked on Kjell Haug's door he has kindly and patiently guided me into the thrilling world of perinatal epidemiology. Sharing his expertise, his supervision has been outstanding. Rolv Skjærven's extensive knowledge in perinatal epidemiology and boldness to explore the unknown is tremendously inspiring. His creative mind makes the research group an interesting and vital environment. I am very grateful for his skilled supervision.

Professor Kari Klungsøyr has generously shared her profound knowledge of the Medical Birth Registry and perinatal epidemiology. Her presence, contribution to the publications and support are encouraging and inspiring.

I also thank my other coauthors Professor Nils-Halvdan Morken, PhD Lisa DeRoo, Associate Professor Roy Miodini Nilsen, Professor Stein Emil Vollset, PhD Øivind Midttun and Professor Per Magne Ueland for their important contributions.

Professor Lorentz Irgens has played a key role in our research environment. I have highly valued his interest in my work. PhD Jannicke Igland and PhD Øystein Ariansen Haaland have most graciously made time for discussing statistics.

I'm grateful for the support and friendship offered to me by the members of the research group. My two office mates, Ph.D. Mette Tollånes and PhD-student Linn Marie Sørbye, have meant a lot to me, sharing the joys and softening the blows of

research work. I'm also grateful for the help and friendship offered to me by PhD-student Berit Skretting Solberg.

I feel privileged to have been surrounded by the skilled scientific staff at the Department of Global Public Health and Primary Care (IGS). The Epidemiology research groups offer an inspiring work environment and I thank all the professors, post.docs and PhD-students for their interest, help and encouragement. To members of EPINOR, lead so competently by Ingeborg Forthun and Carl Baravelli, I am grateful for sessions filled with interesting topics in a friendly and enjoyable atmosphere. To the administrative staff at IGS, I am grateful for all their help and kindness.

I am grateful to the families participating in the Norwegian Mother and Child Cohort Study for their efforts.

My parents, Anne and Torleiv, have supported and encouraged me to seek academic challenges. I am immensely grateful for their loving care. I am grateful to my mother-in-law, Dagny, for all her help and care. I also thank my brothers and sisters-in-law, my extended family, and friends for support and love. During my PhD-student period I have given birth to three children, Nils, Anne Engeline and Allis Tomine. I feel truly blessed to have such wonderful children. My dear, brilliant husband, Bernt, is the funniest and kindest person. I rely on his love and constant support.

During my years as a PhD-student, I have looked forward to going to work every day. The research questions, the files, the colleagues and the research group have made it a pleasant work environment. Moreover, for the investments made in me, I sincerely hope I will be able to contribute to society with using epidemiology as a tool to better health for all.

A cherished author of mine, Bjørg Vik (1935-2018), ends her trilogy about Elsi Lund in a way which also characterizes the thrills of having finished this work.

> *« På Egertorget stanser hun, kaster blikket nedover Karl Johan mot Østbanen, gaten myldrer av liv. Et vindkast feier lett mot henne, hun kjenner vinden under skjørtet, om leggene og anklene, kjenner gåsehuden, fryden som spretter ut i huden, et ørlite korallrev av fryd.*
>
> *Den travle, myldrende gaten ligger foran henne. Det er bare å gå.*
>
> *Videre.»*

Abstract

Background: Although a decline in smoking prevalence is seen in most developed countries, smoking during pregnancy remains an important public health concern, affecting both the mothers' own health as well as that of her unborn child.

Objectives: The objective was to study several aspects of smoking habits among pregnant women in Norway since 1999. Firstly, to assess changes and secular trends in smoking habits during pregnancy in the period 1999-2004. Secondly, to biochemically assess the validity of self-reported smoking habits in the Norwegian Mother and Child Cohort Study (MoBa). The third objective was to explore if women born with low birth weight more often end up as smokers as adults compared to women born with higher birth weight. The fourth aim was to assess the risk of small for gestational age (SGA) in 2nd pregnancy according to smoking habits in two successive pregnancies.

Methods: Main data sources included The Medical Birth Registry of Norway with links to other registries (*paper I*: 1999-2004, *paper III*: 1967-2014 and *paper IV*: 1999-2014) and the MoBa (*paper II*: 2002-2003). Cross sectional files as well as generational and sibling files were used to pursue the objectives.

Results: The overall daily smoking prevalence among Norwegian pregnant women decreased from 18% in 1999 to 11% in 2004 (Relative Risk (RR) 0.61, 95% Confidence Interval (CI) 0.58, 0.64)). The decline was observed in all subgroups. Maternal educational level was strongly associated with smoking at the end of pregnancy. More women quit smoking during pregnancy in the second half of the study period, compared to the first.

Among a subsample of 2 997 women in MoBa an overall mean sensitivity of 81.9% (95% CI 77.3, 86.4) and specificity of 99.4% (95% CI 99.1, 99.7) was calculated for self-reported smoking habits with plasma cotinine concentrations as the gold standard.

For the association between birth weight and later smoking habits we found that women born at term with low birth weight (<2000 grams) more often smoked at the end of their pregnancies compared with women born with higher birth weights (4 000-4 499 grams) (RR 1.8 (95% CI 1.4, 2.2)). We observed a similar trend between men's birth weight and their partners' smoking habits in pregnancy (RR 1.5 (95% CI 1.2, 2.0)).

Daily smokers throughout the first pregnancy, who abstained throughout their second pregnancy, had a 1.3 increased risk of SGA in the second pregnancy (95% CI 1.1, 1.6), compared to persistent non-smokers. About two-fold risks were found for women who smoked daily throughout their first pregnancy, but had quit by the end of the second pregnancy (RR 2.0 (95% CI 1.6, 2.4)) and for women who were non-smokers in the first pregnancy and daily smokers in their second (RR 1.8 (95% CI 1.4, 2.3)). Persistent smokers through both pregnancies had a 2.9 fold increased risk (95% CI 2.7, 3.1). Persistent smoking women who did not experience SGA in their first pregnancy, had a 2.7 fold increased risk of SGA in the 2nd pregnancy (95% CI 2.5, 3.0).

Conclusions and implications: Smoking during pregnancy declined during 1999-2004 in all subgroups, and maternal educational level was a strong indicator for smoking at the end of pregnancy. Self-reported smoking is a valid indicator of intrauterine exposure to tobacco smoke among participants in MoBa. Being born with low birth weight is associated with smoking in adulthood. This suggests a shared smoking environment through generations, and may account for some of the established association between birth weight and cardiovascular disease. Smoking information from both the beginning and the end of a pregnancy is important for adequate risk assessment of SGA in 2nd pregnancy. Persistently smoking women throughout two successive pregnancies had the highest risk of SGA in 2nd pregnancy. Women who smoked throughout both pregnancies with no previous SGA were not protected against SGA in the 2nd pregnancy.

List of publications

I. Kvalvik LG, Skjærven R, Haug K. *Smoking during pregnancy from 1999 to 2004: a study from the Medical Birth Registry of Norway.* Acta Obstetricia et Gynecologica Scandinavica 2008; 87: 280-5.

II. Kvalvik LG, Nilsen RM, Skjærven R, Vollset SE, Midttun O, Ueland PM, Haug K. *Self-reported smoking status and plasma cotinine concentrations among pregnant women in the Norwegian Mother and Child Cohort Study.* Pediatric Research 2012; 72: 101-7.

III. Kvalvik LG, Skjærven R, Klungsøyr K, Vollset SE, Haug K. *Can early programming be partly explained by smoking? Results from a prospective, population based cohort study.* Paediatric and Perinatal Epidemiology 2015; 29: 50-9.

IV. Kvalvik LG, Haug K, Klungsøyr K, Morken NH, DeRoo L, Skjærven R. Maternal Smoking Status in Successive Pregnancies and Risk of Having a Small for Gestational Age Infant. Paediatric Perinatal Epidemiology 2017; 31: 21-8.

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Terms and abbrevations

MBRN	The Medical Birth Registry of Norway
MoBa	The Norwegian Mother and Child Cohort Study
CI	Confidence Interval
HR	Hazard ratio
OR	Odds ratio
RR	Relative risk
SD	Standard deviation
SGA	Small for gestational age
NPV	Negative predictive value
LMP	Last menstrual period
BMI	Body mass index
FOAD	Fetal Origins of Adult Disease
DOHaD	Developmental Origins of Health and Disease

Contents

1. Introduction

Tobacco is a legal consumer product that might kill its users even when used as intended by manufacturers,[1] and no level of use during pregnancy is considered safe. Worldwide, more than a billion people smoke tobacco.[2] The global overall smoking prevalence (among the population older than 15 years) has dropped from 24% in 2007 to 21% in 2015, with much of the decline occurring in high-income countries. However, because of population growth, the number of people still smoking has remained stable since 2007.[2]

Tobacco products are complex combinations containing over 4 000 chemicals with several different toxic constituents, and with nicotine causing and sustaining addiction to tobacco products.[3] Nicotine in tobacco smoke is rapidly delivered through the large surface area of the alveoli and small airways to the systemic circulation and reaches the brain, stimulating nicotinic acetylcholine receptors in the central nervous system. The addictive behaviour can be seen as a neurobiological adaption to chronic nicotine exposure with several transmitter systems involved.[4] Other constituents in tobacco smoke have been identified as compounds causing cancer, as respiratory irritants and as constituents with cardiovascular effects. [5]

Even though the harm of tobacco products have been known for more than 60 years, the pace of the decline in smoking prevalence globally has been described as "remarkably slow".[6-8] Globally in 2016, smoking was the second most important risk factor for death for men and the sixth for women, attributable to 16% and 6% of deaths, respectively.[8]

In 2015, the global smoking prevalence of women was 8%.[2] Today the hazards of smoking on females' longevity are well known and include excess mortality from diseases such as chronic lung disease, lung cancer, heart disease and stroke.[9] However, novel associations are still being found between tobacco smoking and mortality from diseases that have not currently been established as caused by smoking.[10]

A healthy pregnancy is of great importance to the health of a new born. Since Winea Simpson published a possible effect of maternal smoking on fetal growth in 1957,[11] the knowledge concerning harms of tobacco in pregnancy has greatly expanded. Maternal smoking during pregnancy has since then been shown to cause pregnancy complications such as ectopic pregnancy,[4,12] spontaneous abortion[13] (though consensus has not been reached[4,13,14]) and placental abruption[15] and affect developmental endpoints such as fetal size (small for gestational age (SGA))[16,17] and growth,[18] preterm birth (before 37 gestational weeks),[15,19] stillbirths,[20,21] neonatal and perinatal death,[21] sudden infant death syndrome[22-25] and oral clefts.[4,26] Some of the adverse pregnancy outcomes associated with maternal smoking are shown in table 1. Estimates of relative risks and odds ratios associated with maternal smoking during pregnancy are ranging from lowest of around 1.1 for neonatal death to two- to fourfold for sudden infant death syndrome. Maternal smoking during pregnancy is also related to asthma and wheezing in children.[27] Studies have found effects of maternal smoking during pregnancy on brain structure and function.[28] However, environmental and genetic factors may confound the association.[4,29] Smoking is paradoxically shown to reduce the risk of preeclampsia.[30] However, among pregnant women with preeclampsia, smoking increases the risks of perinatal mortality, abruptio placenta and SGA.[30]

Table 1. Summary of published associations between smoking and adverse outcomes

Adverse pregnancy outcomes	**Relative risks or Odds ratios**
Ectopic pregnancies [4,12]	1.7 - 1.9
Placental abruption [15]	1.4 - 2.4
Small for gestational age [15-17]	1.5 - 2.9
Preterm birth [15,19]	1.2 - 1.6
Stillbirth [20,21]	1.4 - 1.8
Neonatal death [21]	1.1 - 1.3
Perinatal death [21]	1.3 - 1.4
Sudden infant death syndrome [23-25]	2.4 - 4.1

Despite a declining prevalence in most developed countries, smoking during pregnancy continues to be an important public health problem. For the strategic

period 2013-2016, the Norwegian government (The Ministry of Health and Care Services), with the strategic plan "A tobacco-free future", had a goal of reaching a smoking prevalence of less than 4 % among pregnant women by the end of the pregnancy.[31] The strategy has been extended to be valid through 2017. The vision of a tobacco-free future is described as "a future in which individuals and communities are no longer affected by tobacco's many harmful effects on health and where children and adults live healthier and longer lives".[31] A further goal in the strategy is that children born after year 2000 should not start smoking or using snus.[31]

In order to be able to address the problem and intervene, it is vital to understand the extent of maternal tobacco use. This requires nationally updated representative data. In 2016, the Medical Birth Registry of Norway (MBRN) had information on smoking habits from 92% of women giving birth and reported a daily smoking prevalence of 3.8% at the beginning of pregnancy and 2.7% at the end of pregnancy.[32] Continuous registration of the prevalence of maternal smoking during pregnancy is important for confounder control in different studies exploring associations with adverse pregnancy outcomes as well as for identifying women for whom extra efforts may be needed to increase smoking cessation rate.

Smoking during pregnancy remains a serious public health concern, affecting both the mothers' own health as well as that of her unborn child. The severity of compromising the next generation by smoking during pregnancy calls for both attention and action. Tobacco smoking is an important preventable risk factor for poor pregnancy outcomes.[33,34]

The literature search for the present thesis was finalized November 2017.

1.1 Smoking habits in the Norwegian population

Smoking prevalence has been defined as "the percentage of daily smokers in a population".[15] The tobacco epidemic has been described to follow 4 stages which

illustrate the historical evolution of tobacco consumption and tobacco related disease in the span of a century (Figure 1).[35]

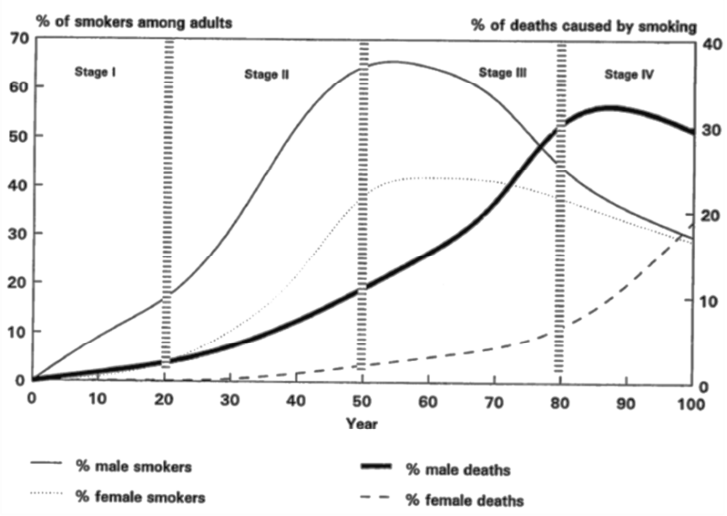

Figure 1. A model of the cigarette epidemic. Reproduced from *Tob Control* Lopez AD, Collishaw DE, Tapani P, 242-7, 1994 with permission from BMJ Publishing Group Ltd.

The first stage starts with uptake of cigarette smoking among men, either equally in all sociodemographic groups or slightly more among men with higher education. By the end of stage 3, smoking is considered socially unfavourable and the declines in smoking prevalence are greater among the higher educated population. The model characterizes the differential uptake of cigarette smoking among men and women in a population, with women characteristically lagging behind men with one to two decades. Further, it displays how the increase in prevalence of smokers exceeds the increase in smoking related mortality by three to four decades.[35] It has been suggested that the model should describe men and women separately for accurately capturing the tobacco epidemic in developing countries.[36] The universal feature of the model lies in the delayed effect of uptake of cigarette smoking on mortality, rather than the temporal gender differences.[36] The model can be used to

illustrate how the tobacco epidemic proceeded in Norway, all the way to the fourth and last phase. [37]

Mass production of cigarettes started in the early 1900s in Norway, which gradually changed the market share from chewing tobacco to smoking tobacco.[38] The smoking prevalence among Norwegian men and women has progressed differently. Statistics Norway (SSB) has collected data on smoking habits in the Norwegian population since 1973.[39] Information on smoking prevalence prior to this was collected by the Cancer Registry in Norway and a commercial pollster (Nielsen Norway).[40] From the 1930s to 1960 the smoking prevalence remained about 65% among men, while about 5% of women smoked at the beginning of the period, with an increase to 35% in 1975. The highest peak prevalence occurred for men born in 1925-1929 who reached a peak of 78% smoking prevalence when they were 20-24 years old. For women, the highest smoking prevalence was at 52% among the 1940-1944 cohort when they were 25-29 years old, and the 1945-1949 cohort when they were 20-24 years old.[40] While smoking prevalence decreased since the mid 1950's among men,[41] the prevalence among women remained around 30% and started to drop after year 2000. Since then similar trends for men and women have been seen,[42] and in 2016 the percentage daily smoking women between 16 and 74 years was 11% (Figure 2). In the recent years the lowest smoking prevalence has been observed among men and women aged 16-24 years.[39]

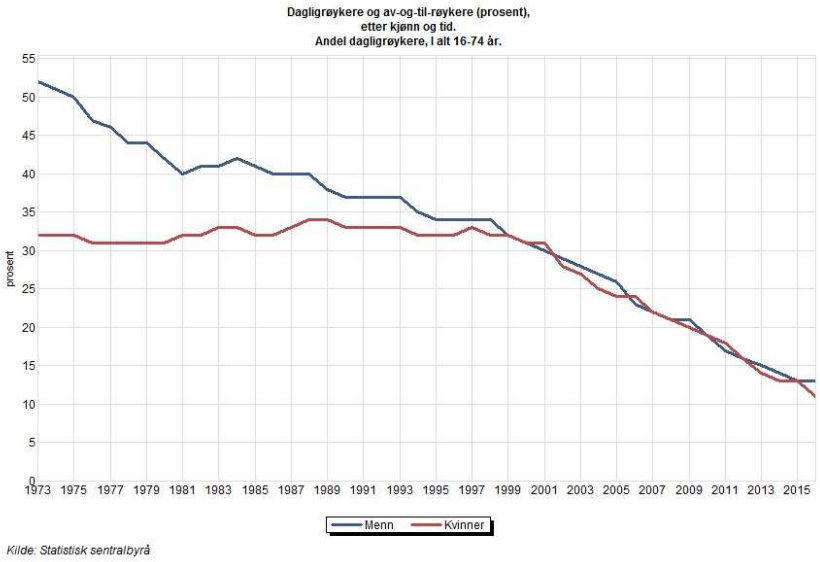

Figure 2. Percentage of daily smokers in the general population in Norway 1973-2016. Data from Statistics Norway (ssb.no).

While there has been a very positive trend that the youngest generations smoke less tobacco, there has been a rise in snus use (low-nitrosamine smokeless tobacco, also called moist snuff). Since 2008 (when SSB started registration) snus use has increased most among women aged 16-34 years.[43]

1.2 Social inequality in smoking habits

The socioeconomic status associated with smoking is described to be reversed from the start to the end of the tobacco epidemic.[44] The daily smoking prevalence among Norwegian doctors were more than halved from the 1950s to the 1970s (from 74% to 35% for men and from 44% to 22% for women).[45] While there was a decline in the general male population in this period, it was not of the same magnitude as for male doctors. For women in the general population there was an increase during this period. Smoking has gradually become a habit more common among those with short education.[43,44] The social gradient in smoking habits obstructs the prospects of

equality in health in the popoulation.[46] Men and women with high education have presently the lowest daily smoking prevalence with 4% and 6%, respectively. However, the greatest decline in smoking prevalence is now found among those with low education, from 34% in 2006 to 13% in 2016.[43] Among different measures of socioeconomic status, education has been shown to be tightly linked as an explanatory variable for smoking.[46,47]

While snus use is increasing among women in all educational levels, women with low education have the highest prevalence (2% in 2008 and 8 % in 2016). However, the increase is most pronounced among women with high education (from not measurable in 2008 to 5 % in 2016).[39,43]

1.3 Smoking during pregnancy among women in Norway

Smoking habits among pregnant women have been registered in The Norwegian Medical Birth Registry since 1999. Earlier available data on the smoking prevalence among Norwegian pregnant women were reported from studies of different size and settings in Norway. The daily smoking prevalence reported among pregnant women at the end of pregnancy were 26% in 1978,[48] 34% in 1978/79,[49] 43% in 1980-1982,[50] and 35% in 1987/1988.[51] The reported daily smoking prevalence at 18 weeks gestation was 34% in 1987 and 22% in 1994, this decline was the first reported significant reduction in smoking prevalence among Norwegian pregnant women.[52] Figure 3 displays the smoking prevalence among pregnant women in different regions of Norway.[48-52]

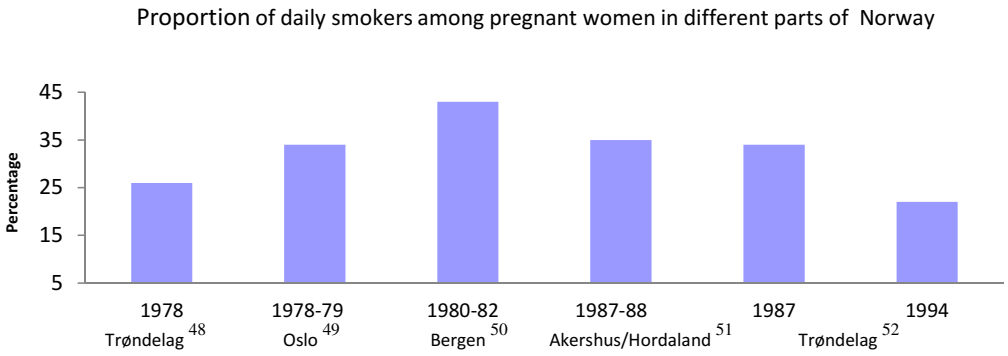

Figure 3. Proportion of reported daily smoking among pregnant women in Norway, published before national collection of data in the MBRN.[48-52]

The daily smoking prevalence at the end of pregnancy has since then fallen to 2.3% in 2016 in national data from the MBRN.[32] While the youngest women in the general population have had the lowest daily smoking prevalence in later years, teen mothers (<20 years) have had the highest smoking prevalence among pregnant women ever since smoking habits in pregnancy were first registered in the MBRN in 1999.[32] In 2014, around 10% of pregnant women younger than 25 years smoked through pregnancy, compared to a 4% smoking prevalence among women below 25 in the general population.[53] Also among pregnant women the socioeconomic differences in smoking prevalence are evident, with increasing differences in smoking prevalence across socioeconomic groups.[54,55] Snus use is not registered for pregnant women in the MBRN. Only one regional study has been published on Norwegian data,[56] and the national prevalence of snus use in pregnancy is therefore uncertain.

1.4 International comparisons of smoking prevalence among pregnant women

In the 1980's, the smoking prevalence in early pregnancy in Norway and Sweden was 39% and 30%, respectively.[57,58] At the same time period about 40% of pregnant women in Denmark also smoked during pregnancy.[59] Since then, smoking among Danish and Swedish pregnant women has decreased to 7% (2016)[60] and 4% (2014)[61], respectively. In Finland, smoking in early pregnancy remained around 15-16% from 1987 through 2015, but reached 14% in 2016.[54,62,63]

In the United States, 40% of White women and 33% of Black women smoked during pregnancy in 1967.[64] In 2014, the overall smoking prevalence during pregnancy was 7%.[65] In the United Kingdom, smoking prevalence during pregnancy were 57% in the mid-1960s,[66] 31-35% in the mid-1980s,[66,67] and 12% in 2013/2014.[68] Internationally, socioeconomic differences in smoking prevalence among pregnant women are evident.[61,65,67] A survey of 54 low- and middle-income countries found a pooled smoking prevalence among pregnant women spanning from 0.6% in the African region to 3.5% in the Western Pacific region in the years 2001 to 2012. In these low-and middle-income countries, population based estimates of smoking prevalence during pregnancy are lacking.[69] Although tobacco use is currently low, these women represent a target for the multinational tobacco companies and one may fear an increase in smoking prevalence.[69]

1.5 Validity of self-reported smoking habits in pregnancy

Smoking during pregnancy is today widely recognized as a behaviour that may harm the unborn child. On the other hand, it has been shown that women who continue to smoke during pregnancy has a higher denial of risk than non-smokers.[70] Potential negative consequences of the denormalization of tobacco use, creating a social stigma, include loss of self-esteem, feelings of guilt, defensiveness and resolving to continue smoking.[71] The validity of self-reported smoking habits has been questioned,

based on a situation where a person is under medical or social disapproval.[72,73] The self-reported smoking habits among pregnant women may therefore suffer from underreporting. More underreporting of smoking has been shown among pregnant women compared to non-pregnant women.[74] The smoking variables in registries and health studies are often used as central exposures, not only for studies concerning the harm from cigarette use, but also in other exposure-outcome studies where controlling for smoking habits is needed. The smoking prevalence among pregnant women is also used in government strategic plans to construct targets for intervention, as well as a measure of how well the population is protected against the harm of tobacco.[31,73]

Nicotine as a biomarker is specific to tobacco. However, it's half-life is short (2-3 hours) and it is therefore not recommended for use as a biomarker.[75] Cotinine, the main metabolite of nicotine, is highly specific for tobacco use, and has a longer half-life (16 hours) than nicotine. Measured in biologic fluids, it has therefore been widely used as a biomarker for tobacco exposure.[75,76] To date, the smoking information in the Norwegian Medical Birth Registry has not been validated against a biomarker. Using cotinine levels in maternal and umbilical cord serum, Swedish birth registry data on self-reported smoking is shown to be a valid measure of in utero tobacco exposure.[77]

The Norwegian Mother and Child Cohort (MoBa) study, a large, prospective pregnancy cohort, was set up aiming at capturing better exposure data than obtained in the Medical Birth Registry.[78] With its vast data on exposure and adverse endpoints, MoBa represents a valuable source for studies disentangling the aetiological factors of diseases. In this setting it is important to understand the accuracy of the self-reported smoking habits among the pregnant participants.

1.6 Second-hand smoke

Second-hand smoke exposure, sometimes called environmental tobacco smoke or passive smoking, is related to the level of smoking prevalence and to what extend

smoke-free indoor policies are implemented in a country.[79] Although the health risks of second-hand smoke are well known today,[79] evidence of the effect of second-hand smoke exposure on the fetus is more limited than for active smoking. Associations between environmental tobacco smoke and stillbirth (OR~1.2), reduced mean birth weight (by 30-60 grams) and congenital anomalies (OR~1.1) have been reported.[79,80]

1.7 Fetal growth, birth weight and small for gestational age

Birth weight is a much used variable in epidemiologic research. It is recorded precisely, often by law on birth certificates, it is free and available (for example on http://statistikkbank.fhi.no/mfr/), it is related to an infant's survival, and it has been associated with adult health and disease (the latter is reviewed in a separate paragraph; "The fetal origins of adult disease" page 31).[81]

Birth weight can be described as "the product of fetal growth rate and gestational length".[82] In large sample sizes the distribution of birth weights approaches a Gaussian distribution, characterized by an extended lower tail. Three parameters are used to describe the distribution: The first two include the mean and the standard deviation (SD), which define the predominant Gaussian distribution. The predominant distribution covers 95-98% of all births. The tail, also called the residual distribution, is the third component used to describe the birth weight distribution and it contains the births that fall outside the predominant distribution. While the predominant distribution resembles the distribution of term births (≥37 gestational weeks), the births in the residual are almost all preterm. Although the births in the residual are few, they are important as they contain the smallest infants at the highest risks, and they represent a substantial proportion of all perinatal deaths.[81,83,84]

The term "Intrauterine growth restriction" has been used to describe that expected fetal size is not reached at a given gestational age.[85] The term has been modified[83] and "Small for gestational age" (SGA) can be defined as babies with birth weight which falls within the lowest 10% of birth weights at any given gestational age, adjusted for various factors (such as infant sex , ethnicity and other factors).[85]

Also other percentiles (such as the 2.5th and 5th) have been used to define SGA, as well as two standard deviations below mean birthweight for gestational age.[86,87] Several factors may influence fetal growth, including environmental factors (smoking, medication), genetic factors, or causes linked to the mother (diseases, infections, weight, nulliparity), the placenta or the fetus (anomalies).[86,88,89]

A previous study from the MBRN covering the period 1999-2002, found that smoking could explain 12% of the SGA cases.[17] For babies exposed to maternal cigarette smoking, the birth weight distribution is shifted to the left, to lower weights, with approximately 200 grams for babies born at term,[90] compared to unexposed babies.[18,91] It is established that the main mechanism through which smoking impacts birth weight is by growth restriction, rather than shortening the gestational age.[18] In addition to shifting the curve leftwards, the residual among exposed infants is also larger than among non-exposed infants. The larger residual is a result of more very small preterm births among the exposed babies. An additional finding is that exposed infants have higher relative weight specific perinatal mortality than non-exposed babies. In comparison to smoke exposed babies, a leftward shift in the birth weight distribution has also been observed for babies born in Colorado, USA, where altitude was hypothesized to cause growth restriction. For these infants however, there was no increased residual distribution or perinatal mortality, compared to those born in the U.S. as a whole.[18] It is a generally accepted assumption that there is a direct effect of smoking on mortality, which is not mediated through birth weight.[91] The birth weight shift for the smoke exposed babies may or may not be a contributing cause of the increased mortality. Though the association between birth weight and infant mortality is one of the strongest associations seen in the field of epidemiology,[90] it is debated whether birth weight has a direct effect on mortality, or if it is due to confounding.[18,81,90,91] However, the shift in birth weight may serve as a marker for an exposure being hazardous to the fetus.[83] The mortality of babies exposed to smoking is a classic example of the “Low birth weight paradox”, which describes how low birth weight babies of high-risk populations have lower mortality compared to low birth weight babies in low-risk populations.[81]

Size at birth represents the result of a process.[92] Using SGA as a measure of intrauterine growth restriction calls to attention that not all small babies are growth restricted and some large babies are growth restricted. Factors which have an impact on fetal growth affect fetuses across the whole weight span. However, using SGA as a measure, it is possible to examine how an exposure (such as smoking) shifts the distribution of birth weights through restriction of fetal growth. As a consequence of this shift, more babies will fall below the defined tenth percentile definition of SGA. Hence, it is the general shift in distribution of birth weights rather than the specific growth restricted babies, that is detected using SGA as a measure.[83]

1.8 Implications of focusing on smoking during pregnancy

There are several reasons why it is important to focus on pregnant smoking women: Firstly, pregnancy is a golden opportunity to stop smoking.[93] Women have several encounters with health professionals during their pregnancy. This is a unique opportunity for midwifes and doctors to communicate with smoking women and emphasize the dangers of smoking and to support quit attempts. The goal is to get women to quit smoking by the time they are pregnant without relapsing postpartum. Smokers who quit at ages 25-34 years have themselves survival curves that are close to never-smokers.[94] Secondly, the fetus in utero benefits from not getting exposed to smoking. Third, children that grow up with smoking parents are at bigger risks of starting to smoke, than children whose parents didn't smoke. [95,96] Fourth, children of smoking mothers are at risk for exposure to second-hand smoke in their homes.[97] Fifth, there is already a social gradient related to the behaviour of smoking.[44] By exposing their child to smoking in utero, the inequality is further passed on to the child by limiting the child's chance of a healthy life (through the morbidity and mortality associated with exposure to smoking in utero).[15]

1.9 Theories on how tobacco smoke affect the fetus

There is an abundancy of studies linking clinical outcomes to in utero exposure to tobacco smoke. However, the physiology behind many of these associations is not completely understood. There are several plausible pathways described, such as fetal hypoxia, toxin exposure and alterations in fetal development and physiologic response. Nicotine can cross the placenta and gain access to and accumulate in fetal compartments through maternal circulation, fetal skin absorption or in utero swallowing of amniotic fluid.[98,99] Nicotine has been proposed to only have a moderate impact on fetal growth, when compared to the larger contribution of the combination of nicotine and the combustion products in cigarette smoke.[4] Users of snus have an increased risk of SGA offspring, although substantially lower than the risk observed for smokers.[16]

Some of the constituents in cigarette smoke, including carbon monoxide and oxidizing chemicals (oxides of nitrogen and several free radicals), have been called "reproductive toxins" as they may contribute to reproductive toxicity. Carbon monoxide can interfere with the transport of oxygen from maternal hemoglobin through the placenta to fetal hemoglobin by displacing oxygen and impairing the release of oxygen from hemoglobin. Oxidizing chemicals may contribute to maternal and placental vasoconstriction and premature rupture of membranes.[100]

Smoking during pregnancy has been reported to have an effect on placental anatomy and its function, through a reduction in the dimensions of the villous capillaries[101] and through thickening of the villous membrane, which might be expected to restrain gas transfer to the fetus.[102] However, others have found no significant changes in histopathological lesions in placentas comparing smokers and non-smokers, suggesting that mechanisms such as vasoconstriction might not be expressed histopathologically.[103] Fetal circulatory adaptations (like umbilical artery resistance) is also suggested as a mechanism by which maternal smoking during pregnancy influences fetal growth.[104]

It does not appear to be one single contributor in cigarette smoke that is alone responsible for the adverse outcomes seen in pregnant smokers. There are several plausible mechanisms described with several chemicals causing reproductive harm, either additively or synergistically.[100] Epigenetic mechanisms acting through several biological pathways have also been proposed as underlying mechanism through which maternal smoking may affect various outcomes. [105]

1.10 Smoking cessation efforts among pregnant women in Norway.

"Any government that is seriously committed to improving health of its population must have a strategy for controlling the use of tobacco and reducing the number of people who smoke." *Chambers et al, BMJ 1991.*[106]

Norway has been a pioneer internationally on tobacco control policies, which have now existed for more than 40 years. In Norway, the treaty called "The World Health Organization's (WHO) Framework Convention of Tobacco Control" (FCTC) entered into force in 2005. FCTC was the first global public health treaty. It provides a plan for national and global actions against the tobacco epidemic,[107] and has been called a landmark achievement in public health.[108] In a comparison to 30 European countries, Norway was in 2006 ranked as third by a Tobacco Control Scale, which sought to quantify the implementation of tobacco control policies.[109] The scores were high for price, smoking restriction in public places and advertisement ban, but low for mass media campaigns and smoking cessation efforts.[31] For the strategic period 2013-2016, the Ministry of Health and Care Services aimed at having mass media campaigns directed at pregnant women in order to motivate tobacco use cessation.[31] In 2006, a mass media campaign against snus use during pregnancy was launched.[110]

Smoking cessation during pregnancy is shown to reduce the risk of adverse harmful effects, including intrauterine growth restriction.[34,111] In 1989, a national campaign focused on motivating women to stop smoking during pregnancy.[52] In the

study years covered in the present thesis (from 1999 to 2014) information aiming specifically at pregnant women has included pamphlets delivered to mother-and-child clinics, health centres and general practitioners, training of health personnel in communication skills in motivational interviewing, and advertisement in magazines focusing on the positive aspects of staying smoke-free.[112] National smoking cessation services have been available through a quit line (Røyketelefonen) which has evolved into a website, as well as social media site and a smartphone app (slutta.no). The national guidelines for smoking cessation recommend pregnant women to stop smoking without use of nicotine replacement therapy (NRT). However, NRT should be considered when pregnant women can't stop smoking.[113]

A decrease in smoking prevalence among pregnant women was reported before the decline in smoking prevalence among women in the general population.[52] This might imply that the focus put on pregnant women in 1989 and onwards contributed to the start of the decline, while the general devaluation of being a smoker as well as tobacco control policies for the population as a whole[38,42] might have contributed to the further decline. However, in Denmark a decline in smoking among pregnant women were observed from 1989 without the presence of anti-smoking campaigns directed at pregnant women.[114] As the anti-smoking campaigns conducted by the Norwegian authorities approached women at an earlier point in the development of female smoking habits compared to the males' development, it may have contributed to the lower level of tobacco consumption among women.[40]

1.11 Tobacco transmittance across generations

It has previously been shown that women with smoking parents more often smoke as adults.[115] Whether maternal smoking during pregnancy has a causal relation to the offspring's tobacco use, distinguished from the childhood social environmental as well as genetic factors, is debated.[116,117] Studies of siblings discordant for maternal smoking during pregnancy have not shown any consistent link between maternal smoking and several measures of tobacco habits in offspring.[118-121] While one study

found no association between exposure to maternal smoking and later tobacco dependence in the offspring,[121] another study found maternal smoking to be associated with nicotine dependence in the offspring.[120] Other sibling studies suggest that previously reported higher risks of tobacco use among offspring exposed to tobacco in utero are not causal, but confounded by familial background factors (genetic or environmental).[118,119]

1.12 "The fetal origins of adult disease" hypothesis

In the 1970s, the Norwegian physician Anders Forsdahl, presented a hypothesis linking poor living conditions in childhood and adolescence with later mortality from arteriosclerotic disease.[122,123] However, a correlation with lung cancer in adulthood was also found and cigarette smoking was not excluded as a possible mediator for the correlation between infant mortality and arteriosclerotic heart disease.[123]

In 1986, David Barker and Clive Osmond proposed poor nutrition in early life to account for their discovery of geographical differences in mortality from ischaemic heart disease (in 1968-1978) and the relation to past differences in infant mortality rates (in 1921-1925) in England and Wales.[124] In 1989, David Barker and colleagues published that body weight at one year was associated with later death from ischemic heart disease among men born during 1911-1930 in Hertfordshire, England. For this population, weight in infancy and later death rates (during 1951-1987) were recorded. They found the highest mortality from ischemic heart disease among men with the lowest birth weight.[125] Associations were also found between other anthropometric measures and coronary heart disease, as well as risk factors for coronary heart disease (blood pressure, serum lipids and impaired glucose tolerance).[126-129] These associations made the foundation for "The Fetal Origins of Adult Disease" hypothesis (FOAD), proposing that the fetus in response to undernutrition goes through adaptions that persistently modify metabolism and organ structure.[128] These processes acting at critical periods of fetal and early life when the system is plastic in contrast to the later fixed capacity, define the term "programming".[130] The hypothesis has also

been called the "Barker hypothesis". Cardiovascular disease (CVD) and its risk factors were the initial outcomes studied. However, the hypothesis has gradually expanded to include a range of outcomes including chronic diseases such as asthma and obstructive lung disease, cancers, osteoporosis and mental disorders.[130] In *paper III*, we focus on alternative explanations for the birth weight – CVD relation of the "Fetal Origins of Adult Disease" hypothesis.

The concept of the "Fetal Origins of Adult Disease" hypothesis evolved into the "Developmental Origins of Health and Disease" (DOHaD) around the turn of the century, with more recognition of early life events following fetal life.[131] Focus has also shifted to include factors not only predicting disease, but also well-being and health promotion.[132] The association between birth weight and infant mortality has been suggested as non-causal, and further that caution should be made making assumptions on the causality between birth weight and adult diseases and mortality.[81,133] It has been argued, however, that Barker and others did not consider birth weight on the causal pathway to disease, but rather as a proxy for unfavourable intrauterine factors.[131]

Already in 1995, Paneth and Susser called upon findings taking maternal smoking into account.[134] The early work from Barker and colleagues covers the period (from 1920 onwards) when cigarette smoking among women began and rose rapidly.[135,136]

The controversy around the hypothesis has been expressed as the complexity of determining the relative impact of events in early life, versus that of later life such as environmental factors, on adult disease risk; namely which events have the greatest influence on health and which is potentially modifiable.[131] Criticism has been made that the associations between fetal growth restriction and later disease may be confounded by a persisting adverse environment both in intrauterine life (causing poor intrauterine growth) and through childhood/adulthood (impacting lifestyle behaviour).[135,137] These arguments have been countered by studies on birth weight and cardiovascular disease allowing for data on adult lifestyle, including smoking.[138-140]

Many claim that the associations between size at birth and risk of coronary heart disease are independent of adult life style.[128,130,131] However, residual confounding cannot be excluded.

It has been suggested that individual published studies of the association between birth size and later cardiovascular disease lack statistical power to be reliable, and that confounding control has varied, underlining the need for systematic reviews to carefully examine the evidence.[141] Systematic reviews have found birth weight to be inversely associated with cardiovascular disease. Huxley et al, found a 10-20% lower risk of ischemic heart disease per 1 kg higher birth weight.[141] In a systematic review and meta-analysis of 22 studies, Risnes et al found a 12% lower risk for cardiovascular mortality per kg increase in birthweight (HR 0.88 (98% CI 0.85, 0.91)).[142] However, the authors acknowledge that controlling for confounding factors (such as smoking, socioeconomic status and gestational age) were limited in some studies.[141,142] Though a consistent finding, Huxley et al question its impact for public health.[141] A review by Skogen et al highlights how associations within the "Fetal Origin of Adult Disease" framework have unclear independent public health impact. The framework should rather complement an approach focused on genetic factors and adult lifestyle as causes of adult disease.[143] The most recent review on birth weight and later cardiovascular disease describes evidence as highly suggestive, but not convincing, and finds weak evidence for birth weight to be an effective marker for public health interventions.[144]

2. Objectives

The overall objective was to study several aspects of smoking habits among pregnant women in Norway. Specific research aims were:

1. To study changes and secular trends in smoking habits among Norwegian pregnant women in the period 1999-2004 and explore if there was a general decline in smoking in this group, or whether there were specific subgroups with differing trends.

2. Underreporting of smoking among participants in epidemiologic studies may lead to validity problems, causing biased association measures. In order to study if self-reported tobacco use is a valid marker for tobacco exposure in the Norwegian Mother and Child Cohort Study (MoBa), we validated self-reported tobacco use in the mothers in a subsample of the MoBa against nicotine exposure assessed by maternal plasma cotinine.

3. There are numerous publications describing the associations between being born with low birth weight and later disease, referred to as the "Fetal Origins of Adult Disease" hypothesis. The aim of the third study was to explore if women born with low birth weight more often end up as smokers in adulthood compared to women born with higher birth weight, and indirectly, if the "Fetal Origins of Adult Disease" hypothesis may partly be explained by residual smoking confounding.

4. To estimate the risk of small for gestational age (SGA) in second pregnancy among women who stopped or started smoking from one pregnancy to the next, as well as among those who continued smoking through both pregnancies, compared to persistent non-smokers. Further, we wanted to explore if women who smoked in the first pregnancy without having an SGA infant and who continued to smoke in the second pregnancy were "protected" against growth restriction in the second pregnancy.

3. Material and Methods

3.1 Datasources

3.1.1 The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) is a large, population based database, which has received compulsory notification of all births from at least 16 gestational weeks since 1967 (from 12 gestational weeks since 2002, but with underreporting of the smallest fetuses).[145-147] During pregnancy, a standard antenatal form is completed at visits to either a general practitioner or a midwife. The mother brings the form to the hospital when admitted for childbirth, and a midwife transfers information to the MBRN notification form. Additional information is included during the stay at the maternity department. The notification form contains information on demographic variables, the mothers' health before and during pregnancy, complications and interventions during pregnancy and delivery, and pregnancy outcomes, as well as mothers' national identification number and birth date of the child. The MBRN notification form was revised and extended in December 1998 and introduced checkboxes as the main way to notify data (Appendix A). Checkboxes have been shown to transfer more valid information to registries than written text.[148] New information included maternal smoking habits at the beginning and at the end of pregnancy, folate- and multivitamin intake and medicines used in pregnancy, as well as ultrasound-based estimation of gestational age. Separate notification from the neonatal intensive care units for all infants transferred to such a unit after birth has also been mandatory since December 1998. From 2014 information on maternal country of birth is available from the MBRN.

Information on smoking habits is obtained through interview during antenatal care and noted on the women's antenatal charts. This information, registered by checkboxes, is transferred to the MBRN notification form by a midwife at the time of delivery. In contrast to other information notified to the MBRN, women can refrain

from giving information on smoking habits. This may be one reason for the relatively large proportion of missing information for smoking habits. On the MBRN notification form there are checkboxes for non-smoking, occasional smoking and daily smoking as well as information about number of cigarettes smoked daily. A separate checkbox notifies that women refrain from giving smoking information. However, the use of this checkbox has not been optimal.[146] In *papers I, III* and *IV,* the proportion of women missing information on smoking habits included both women refraining from giving information as well as those without any information on smoking habits.

Most births (≥99%) in Norway take place in a hospital.[32] The proportion of births that is captured by the MBRN is close to 100%.[145] Valid information is essential for registry-based research and several variables have been validated in the MBRN.[149-158] Birth weight and gestational age, variables which are related to the papers in the present thesis have been validated with satisfactory results.[149] MBRN data was used for *papers I-IV*.

3.1.2 The Norwegian Mother and Child Cohort Study

The Norwegian Mother and Child Cohort Study (MoBa) is a population-based pregnancy observational study conducted by the Norwegian Institute of Public Health. [78,159,160] During 1999-2008 pregnant women were recruited by postal invitation together with the appointment for the ultrasound examination in gestational week 17-20. The participation rate was 41%.[78] Institutions with >100 births per year were targeted. The recruitment started in Hordaland County in 1999 with a gradual expansion and became nationwide with 50 out of 52 hospitals with maternity units participating in 2005. At present, the cohort includes 114 000 children, 95 000 mothers and 75 000 fathers.[78] Biological material from mothers, fathers and children has been collected and stored in a bio bank. EDTA (Ethylene Diamine-Tetra-acetic Acid) whole blood was collected from both parents during pregnancy, as well as post-partum from the mothers and from the child's umbilical cord immediately after birth. Regular questionnaires collect information on general health, diet and environmental

exposures. Linkage to the child's standard MBRN notification form is part of the MoBa database. Bias due to self-selection is shown to affect prevalence estimates for exposures and outcomes, but not exposure-outcome associations.[161] For the purpose of *paper II,* we used the blood sample obtained from the mother at gestational week 19 and the baseline questionnaire sent to the mother when she was about 15 gestational weeks pregnant.

3.1.3 Statistics Norway

Statistics Norway has the general responsibility for official statistics in Norway. Statistics Norway provided information on mother's country of birth, which was used in *paper I.* The National education database is also located at Statistics Norway. This register contains attained education for the Norwegian population on an individual level, and is updated annually with information on all residents 16 years or more. In this thesis, highest achieved education defined the educational level and was used in *papers I*, *III and IV*. Education was categorized as ≤10 years, 11-14 years and ≥ 15 years in *papers I* and *III* and dichotomized as ≤10 years and ≥ 11 years in *paper IV*.

3.1.4 The Cause of Death Registry

Death certificates completed by a doctor are collected by the Cause of Death Registry and coded by the International Classification of Diseases (ICD) coding system. Since 1925, Statistics Norway had the responsibility for the statistics on causes of death. From 2014, the Norwegian Institute of Public Health has had the full responsibility for the registry. The registry contains digitized records on causes of death from 1951.[162] Mothers' in the first generation (G1, see Figure 5) causes of death were used in *paper III*.

3.1.5 The National Registry

The Directorate of Taxes is responsible for the National Registry. Live births are reported to this registry, where a national identification number is generated for each new born.[147] The number consists of 11 digits, where the six first digits contain the

person's date of birth. The three next digits represent an individual number where the third digit is gender specific, even numbers for women and odd numbers for men. The two last digits represent control digits. The national identification numbers of the child and the father as well as dates of death of mother, father or child are reported to the MBRN. For quality assurance, records in the MBRN are routinely matched against the National Registry.

3.2 Study populations and design

Paper I is a historical population based cohort study, with data collected prospectively by the MBRN. Data were obtained from the MBRN and Statistics Norway, including the National education database. The study population consisted of 259 573 Norwegian born women who gave birth from 1999 through April 2004 (see Figure 4 for a flowchart with inclusions and exclusions for the study population). Exposures/explanatory variables were period (calendar years), maternal age, parity, marital status and education level. Outcome was smoking habits at the end of pregnancy. The proportion who quit smoking during pregnancy was a secondary outcome.

Paper II is a validation study of a subsample from MoBa, a national prospective cohort study. A subsample of 3000 mothers was randomly selected from MoBa participants who had donated blood samples at the ultrasound examination, and who had births registered in the MBRN. Additionally, they had completed a baseline questionnaire as well as a food frequency questionnaire during the second trimester. Further details on the sampling process are described elsewhere.[163] The participating women had given birth during the period July 2002 to December 2003. Three women were excluded because of missing plasma cotinine data, resulting in a study population of 2 997 women. In this validation study, measured plasma cotinine were considered the gold standard against which self-reported smoking habits were examined.

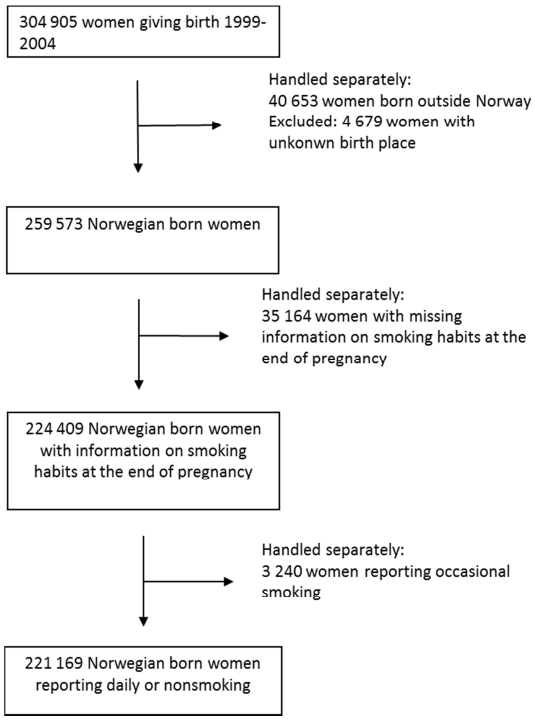

Figure 4. Overview of the study population in *Paper I*.

Paper III is a historical population based cohort study, with data collected prospectively by the MBRN. We used data from the MBRN, the National education database and the Cause of Death Registry, and included 293 237 singleton women born 1967-1995. The birth records of these women (second generation; G2) were linked to their own first registered childbirth with available smoking habits between 1999 and 2009 in a generational structure (Figure 5). Women registered in the MBRN with more than one birth in this period were thus only counted once. Information on smoking habits was missing for 29 168 (9.9%) women and these were excluded from the study population, as well as 3 837 (1.3%) occasional smokers and women whose birth weights were missing (n=306) or whose birth weights were less than 500 grams or more than 6000 grams (n = 6). A total of 11 918 (4.1%) women with missing gestational age were also excluded from the analyses. For absolute birth weight analyses, the focus was on women born at term (≥37 weeks) and for gestational week specific birth weight z-score analyses, 298 (<1%) women with absolute z-score

values equal to or above five were excluded. The women's birth weight was the exposure and her smoking habits when she was pregnant 13-42 years later were the outcomes. The final study populations were 247 704 singleton women for birth weight z-score analyses and 238 488 term born singleton women for absolute birth weight analyses.

In addition, we linked a total of 194 652 singleton men (G2, Figure 5) born 1967-1994 to their own first registered infant delivered in 1999-2009. Inclusion criteria were available information on men's birth weight and gestational age as well as partners' smoking habits in their first pregnancy with registered smoking habits from 1999. The men's birth weights were the exposures and his partner's smoking habits in pregnancy were the outcomes.

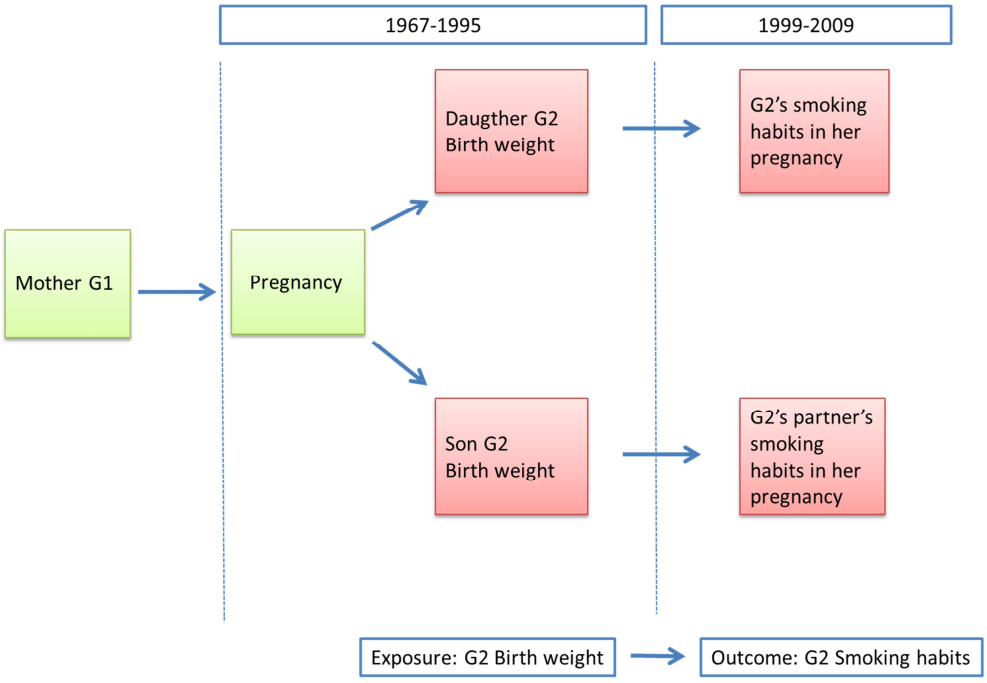

Figure 5. Overview of the study design in *paper III*. The figure depicts the first generation of mothers (G1), giving birth to sons and daughters in the second generation (G2), and the variables in focus in the main analyses in *paper III*.

Finally, for 222 808 women whose smoking habits at the end of the pregnancy were registered, we explored their mothers' (G1) causes of death relative their daughters (G2) smoking habits. Data on causes of death were retrieved from the national Cause of Death Registry, 1969- 2009.

Paper IV is a historical population based cohort study, with data collected prospectively by the MBRN. We used data from the MBRN and the National education database, and linked births to their mothers by means of the mothers' unique national identification numbers to construct sibling structures, with the mother as the observation unit. A total of 118 355 Nordic born women giving birth to their first and second singleton infants during 1999 - 2014 were included in the study (see Figure 6 for a flowchart with inclusions and exclusions for the study population).

To avoid misclassification of growth restriction due to constitution, women born outside the Nordic countries (Norway, Sweden, Denmark, Finland and Iceland) as well as women with unknown country of birth were excluded from the study population. In our material, women born outside the Nordic countries gave birth to babies whose birth weight were on average 119 grams less than babies born to Nordic women (t-test $p<0.005$). Further exclusions included 1803 (1.0%) women with missing information on birth weight, gestational age and sex of the second child, 5 (<1%) women with negative inter-pregnancies intervals, and 204 (<1%) women who had late spontaneous abortions (<22 gestational weeks and birth weight <500 grams). Higher proportion of missing information for various variables in stillbirths and late spontaneous abortions is reported.[152] 122 479 women reported non-smoking or daily smoking at the end of the first two pregnancies. Women with missing information on smoking habits at the end in one of the pregnancies (n=50 089 women, 27%) or in both pregnancies (n=9 820, 5.3%), were excluded as well as women who reported occasional smoking at the end of pregnancies (n= 2 510, 1.4%).

To look further into the smoking habits both early and late in the two successive pregnancies we divided non-smoking and daily smoking into nine smoking trajectories through the two pregnancies, excluding women whose smoking information was either missing at all registration points (n= 60 431, 33%), who were

occasional smokers at any registration points (n=5 805, 3.1%) or women who had unusual smoking trajectories (n=307, <1%). For these analyses we therefore had a study population of 118 355 women.

Previous SGA due to any cause is a strong risk factor for recurrent SGA. In order to avoid mixing the effect of smoking with the effect associated with recurrent SGA due to other causes, additional analyses limited to women without SGA in the first pregnancy (n= 116 468 women) were done. Women who gave birth to an SGA baby in the first pregnancy (n=11 087) were analysed separately. Information on maternal education was only available for women giving birth in the period 1999-2010 and this population consisted of 76 161 women (missing information: n=504, <1%). In this subset, we analysed the association between smoking trajectories as exposures and SGA in the second pregnancy as outcome while adjusting for or stratifying on maternal educational level.

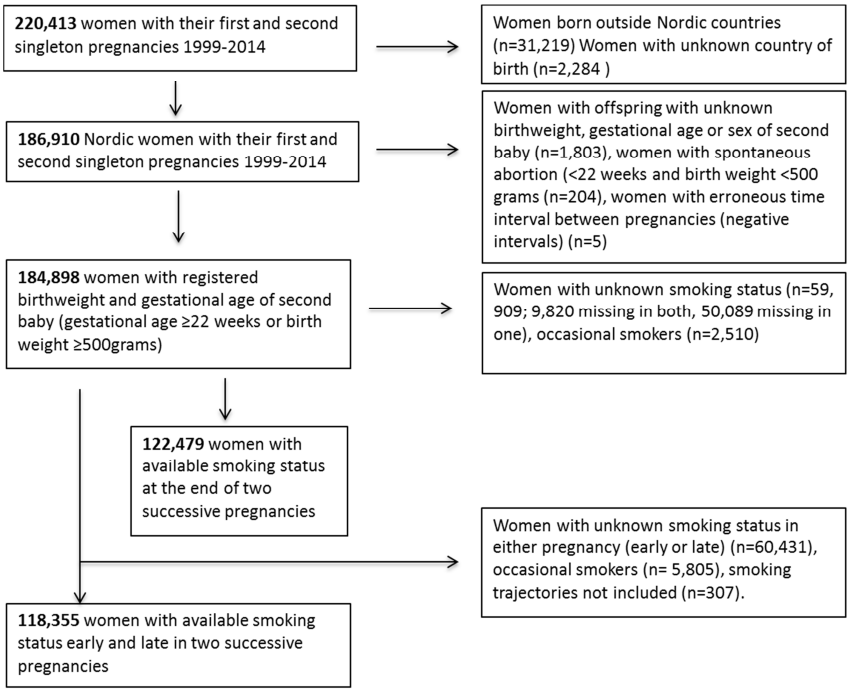

Figure 6. Flowchart over the population in *paper IV*.

3.3 Exposure variables, confounding variables/covariates

In *paper 1,* all the covariates were obtained from the MBRN except maternal education and country of birth. These included parity (i.e. the number of previous births, para 0, para 1, para 2, para ≥3), maternal age in years (<20, 20-24, 25-29, 30-34, ≥35), and marital status (married, cohabitant, single or other). Data for parity and maternal age was complete. The "other" category in marital status is a composite category including divorced/separated/widowed/other, as well as 1 057 (<1%) women with missing information. Maternal educational level was obtained from the National education database and contains the highest achieved education by year 2002. Data on educational level was missing for 581 (<1%) women. The study period from 1999 to the first 4 months of 2004 were categorized into two groups; 1999-2001 and 2002-2004. In *paper I,* women born in Norway were included in the main analyses while women born outside Norway (n = 40 653) were analysed separately. The women born outside Norway were expected to differ in smoking prevalence compared to Norwegian-born women. Differences in smoking prevalence between the different counties of Norway were evaluated both with regards to smoking prevalence as well as the proportion with missing information on smoking habits.

In *paper II,* the covariates obtained from the MBRN included parity (grouped as above), maternal age at delivery (<25, 25-34, ≥35) and marital status (as above). Data on parity, maternal age and marital status was missing for 10, 10 and 36 participants, respectively. Information on prepregnancy body mass index (BMI) (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0) and highest level of completed maternal education (≤12, 13-16, ≥17 years) were obtained from the MoBa baseline questionnaire and was missing for 116 (3.9%) and 77 (2.6%) participants, respectively. Self-reported nicotine exposure was obtained from the baseline questionnaire. Women could tick checkboxes if they smoked before or during the second trimester, if they were exposed to passive smoke at home or at work or both, and if they used chewing tobacco/snus, nicotine chewing gum, nicotine adhesive patch or nicotine inhaler. Snus use has not been registered for pregnant women in the

MBRN and has therefore not been available to study in the other 3 papers of this thesis. In *paper II,* a small number of women used snus according to MoBa.

In *paper III,* all covariates except women's (G2) and their mothers' (G1) education was obtained from the MBRN. The main exposure was women's (G2) own absolute birth weight and birth weight by gestational week z-score.[164] Birth weight (in grams) is measured by the attending midwife immediately after birth. Ultrasound-based estimation of gestational age was not available in the MBRN before 1999. In *paper III*, gestational age for the women (G2) was therefore based on the first day of the last menstrual period (LMP).

Smoking primarily affects fetal growth in the third trimester in pregnancy.[165] We focused on women born at term (gestational week ≥37) when examining absolute birth weight, in order to avoid mixing reduced birth weight caused by preterm delivery with reduced birth weight caused by intrauterine growth restriction.

Birthweight can be transferred to a z-score, which is defined as units of standard deviations from the mean.[18] The z-score scale is based on the assumption that birth weights in groups being compared have an underlying Gaussian distribution. With this approach it is possible to compare groups with the same relative birth weights (relative to the Gaussian distribution of weight for the specific groups) rather than absolute birth weights.[166] Z-scores for birth weight by gestational age were calculated by applying Norwegian birth weight by sex and gestational age standards,[164] and were then categorized into 9 group from -4.99 to +4.99. The z-score category 0.50 to 1.49 was chosen as the reference group in all analyses.

The women's birth order was considered a potential confounding variable (first born, second born, third or later born) and was missing for 547 (<1%) women. The women's year of birth was also considered as a potential confounding variable (1967-1976, 1977-1986 and 1987-1995). Other covariates used to describe the study population, were the women's year of childbirth (categorized into 1999-2003 and 2004-2009), and the women's parity (grouped as before).

Highest achieved educational level for the women (G2) and their mothers (G1) was obtained from the National education database in 2009, and was grouped in three: low (<11 years), medium (11-14 years) and high (college or university level: >14 years). For 348 (<1%) women (G2) and 907 (<1%) of their mothers (G1), information on education were missing. The mothers' (G1) education was considered a potential confounding variable.

Men's (G2) birth weight was an additional exposure. Men with missing birth weight (n = 284, <1%), those with birth weight more than 6000 grams (n = 4), and those missing gestational age (n= 8 736, 4%) were excluded, leaving a study population of 194 652 men.

In a sub analysis, the causes of death for women's mothers (G1) were analysed in relation to the women's (G2) smoking habits. Smoking habits will be further described under outcome variables.

In *paper IV,* all variables except education were obtained from the MBRN. Smoking habits in two successive pregnancies was the main exposure variable. The covariates obtained from the MBRN included maternal age at delivery and marital status (both grouped as in *paper I*). Due to time trends in smoking habits and birth weight, year of first birth (1999-2007, 2008-2014) was considered a potential confounder for the association between smoking and SGA. Information on maternal education was available from the National education database for the period 1999-2010. Adjustment/stratification for different levels of education (≤10 and ≥11years) when analysing the effect of smoking on SGA, was done in this subset.

Gestational age was based on LMP. If the difference between LMP and ultrasound was >10 days or LMP was missing, gestational age was based on second trimester ultrasound measurements.

3.4 Outcome variables

In paper I, the main outcome was smoking habits at the end of pregnancy, which was notified to the MBRN by three checkbox alternatives on the MBRN form: non-smoking, occasional smoking and daily smoking. Smoking habits in the beginning of pregnancy were also used to evaluate the proportion of women quitting smoking during pregnancy. In a sub analysis we compared birth weight among non-smokers, daily smokers and non-responders.

In *paper II,* the outcome was cotinine measured in plasma. Non-fasting blood samples in EDTA–tubes were collected from the women at the time of routine ultrasound appointment (median gestational week 18), centrifuged within 30 minutes, and placed in refrigerators. The samples were shipped by mail to the MoBa Biobank, where they were distributed onto polypropylene microtiter plates, at the day of reception (usually 1-2 days after sample donation), sealed with heat-sealing foil sheets and stored at – 80 degrees Celsius. Bevital AS analysed the samples. For plasma cotinine concentrations, a liquid chromatography tandem mass spectrometry method was used.[167] Limit of detection for plasma cotinine was 1nmol/l (1.18ng/ml) and 111 women had concentrations below the limit. For these women values were imputed by giving each of them a random plasma cotinine value in the range 0-1 nmol/l. For the sensitivity and specificity calculations, the main analyses included women reporting either daily smoking or non-smoking. In supplemental analyses women reporting occasional smokers were included.

The metabolic clearance of nicotine and cotinine is shown to be markedly accelerated during pregnancy, with almost 50 % shorter half-life of cotinine than in non-pregnant state, resulting in a half -life of about 9 hours.[168] A density plot of log plasma cotinine concentrations showed two distinct distributions. The lowest point between the two distributions were estimated using kernel density estimation and a bootstrap method (described under Statistical analyses), yielding a geometric mean of 29.8nmol/l (95% CI 20.0, 56.0) which was used as a cut-off value to validate self-reported daily smoking.

In *paper III,* the primary outcome was the association between own birth weight and adult smoking habits at the end of pregnancy. In addition, we studied the relation between a man's birth weight and his female partner's smoking habits at the end of her pregnancy. In further analysis, we looked at total mortality, death caused by cardiovascular disease and by lung cancer as outcomes for the mothers (G1). Cardiovascular disease was defined as deaths due to coronary heart disease and stroke, classified by The International Classification of Diseases (ICD): Version 8 and 9: 410-414, 430-438, Version 10: G45, I20-I25, I60-65, I67, I69. Lung cancer was defined by ICD-8 and ICD-9: 162 and ICD-10: C33-C34. We also included one category called "Death from all other causes combined" which included all deaths except those from cardiovascular disease and lung cancer.

In paper IV, the outcome was having an SGA infant in the second pregnancy. SGA was defined as birth weight by gestational age below the 10th percentile based on Norwegian birth weight by sex and gestational age standards.[164] Additional analyses were done with SGA defined as birthweight below the 2.5th percentile.

3.5 Statistical analysis

Paper I: Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 12.0. Smoking habits were dichotomized into daily smoking and non-smoking. Occasional smokers were analysed separately. Crude odds ratios (OR) and relative risks (RR) with corresponding 95% confidence intervals (CI) were calculated from contingency tables, and represented changes in smoking prevalence during the study period. To estimate the effect of period, parity, maternal age, marital status and maternal education on women's smoking habits, we used multiple logistic regression analysis with OR as the reported effect measure. To describe the variability of birth weight, we reported means and standard deviations (SD). For rare outcomes, ORs correspond well with RR estimates.[169] Since logistic regression was used in *paper I,* and thereby adjusted ORs were the measures of association, the results could only be interpreted as RR estimates for the rare outcomes (for example smoking among highly educated women).

Paper II: Statistical analyses were performed using SPSS version 15, SAS (Statistical Analyses System) version 9.2 (SAS Institute, Cary, NC) and R version 2.8.1 software (The R Foundation for Statistical Computing) for graphics. To get less skewed distribution of data, plasma cotinine concentrations were log-transformed and reported as geometric means, which is the antilog of means of the logarithmic values.[170] The association between plasma cotinine and numbers of cigarettes smoked were estimated with Spearman's correlation coefficient with 95% CIs. We used a nonparametric bootstrap method (the SURVEYSELECT procedure in SAS) to estimate the lowest point between two distinct distributions of log plasma cotinine in order to distinguish active smokers from passive smokers and non-smokers (dichotomized). By random resampling 10 000 times from the total population we made 10 000 alternative data sets. Kernel density estimation was used to find the lowest log plasma cotinine point between the two peaks in each set. The geometric mean was estimated from the 10 000 point estimates and defined the plasma cotinine cut-off separating active smokers and passive/non-smokers. By extracting the 2.5^{th} percentile and 97.5^{th} percentile from the 10 000 estimates, a corresponding 95 % CI was calculated. The bootstrap procedure was also used to calculate the overall sensitivity and specificity for self-reported daily smoking.

Sensitivity and specificity describe the ability of a test to distinguish between individuals with and without disease. Sensitivity measures how well a test correctly identifies individuals with the disease, whereas specificity measures how well a test correctly identifies individuals without the disease. [171]

In *paper II*, the measured plasma cotinine cut-off was the "gold standard" and self-reported smoking habits was the "test". Sensitivity was thus the proportion of women with plasma cotinine concentrations above the cut-off that were correctly identified by self-report as daily smokers. Specificity was the proportion of women with plasma cotinine concentrations below cut-off that were correctly identified by self-report as non-smokers (Table 2). 95% CIs for sensitivity and specificity were calculated using Wilson procedure without correction for continuity. [172]

Table 2. Representation of self-reported smoking habits as the test and plasma cotinine concentration as the gold standard.

		Plasma cotinine measurement (gold standard)		
		≥30 nmol/l	<30 nmol/l	Total
Self–reported smoking (test)	Daily smoking	a	*b*	*a+b*
	Nonsmoking	c	*d*	*c+d*
	Total	*a+c*	*b+d*	*n*

Sensitivity = $a/(a+c)$ Specificity = $d/(b+d)$

Paper III: Statistical analyses were done using STATA, version 12.1 and IBM SPSS version 20. RR with 95% CI and p-values were calculated using generalised linear models for the binomial family in STATA with absolute birth weight and z-scores for birth weight by gestational age as independent variables and dichotomized smoking status as the outcome. In this design, true confounders were factors that affected women's birth weight (exposure) and the outcome (here women's smoking habits when pregnant). We have therefore avoided adjusting for variables on the causal path between women's own birth weight and her adult smoking habits, such as attained educational level. Variables that might be a common cause for both the women's birth weight as well as the women's own smoking habits were adjusted for and included educational level of women's mothers'(G1), women's (G2) year of birth and birth order. Birth order was included as a potential confounder as it is associated with both birth weight and adult smoking habits (first born siblings smoke less than

later born siblings).[173] Cox proportional hazards models were used to analyse the hazard ratios for women's mothers' (G1) death by the women's (G2) smoking habits at the end of pregnancy. We used a log-log survival plot to assess the proportionality assumption. Mothers' (G1) age was the underlying time variable in the analysis, and mothers entered the follow-up at the year of their daughters' (G2) birth. The analyses were adjusted for mothers' (G1) education.

Paper IV: Statistical analyses were performed using STATA, version 14.0 Intercooled for Windows (StataCorp LP, College Station, Texas). We used generalized linear models for the binominal family to calculate relative risks (RR) with 95% CIs for the association between smoking status in two pregnancies and risk of SGA in second pregnancy. Dichotomized smoking habits in the two pregnancies were categorized into 4 trajectories by smoking status at the end of two successive pregnancies: persistent non-smokers (No-No), quitters from first to second pregnancy (Daily-No), starters from first to second pregnancy (No-Daily) and persistent smokers (Daily-Daily). Smoking habits early and late in the two successive pregnancies were then used to construct nine trajectories of smoking habits. Non-smokers throughout both pregnancies were considered the reference group. Confounders for the association between maternal smoking trajectories and a SGA baby in second pregnancy were considered after drawing causal diagrams (Figure 7)[174], and included maternal age at first birth, marital status at first birth, year of first birth and maternal education. Directed Acyclic Graphs (DAGs) represent a type of causal diagrams, and are drawn by linking variables by arrows that represent causal effects.[91] Maternal age, marital status, year of birth and maternal education may have effects on both smoking habits and SGA. Unknown factors represent unknown, common causes for SGA in both first and second pregnancy. Due to the addictive nature of tobacco, an arrow was drawn from smoking in first pregnancy to smoking in second pregnancy. No arrows were drawn from SGA in first pregnancy to smoking in second pregnancy as the data did not support that experiencing SGA was associated with a change in smoking habits in the second pregnancy.

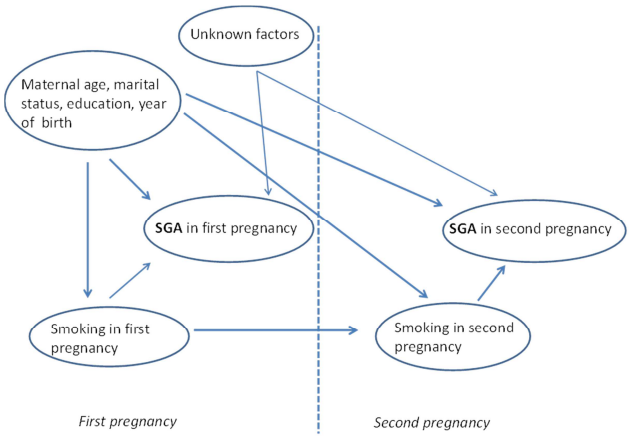

Figure 7. Proposed Directed Acyclic Graph (DAG) for the causal pathway between smoking and SGA in 2nd pregnancy.

We used the 10th percentile of birth weight by gestational age to define SGA, however, we also included analyses based on the 2.5th percentile. Due to small numbers, this was not included in further analyses. To evaluate if smoking habits in two successive pregnancies were more closely associated with SGA babies in term pregnancies, separate analyses were done restricted to term born babies. This also excluded a possible selection bias linked to an increasing proportion of missing smoking habits at the end of pregnancy by decreasing gestational age: For term infants the proportion of missing smoking information at the end of pregnancy was 18%, for infants born at 30 weeks this proportion was 25% and for infants born at 23 weeks it was 41%.

We explored if smoking trajectories had the same associations with SGA in second birth in different levels of maternal education in the subset of women giving birth in 1999-2010. We used two samples t-tests comparing group means (number of cigarettes smoked daily) to study the smoking dose in the different smoking categories. For these analyses we also split the study period in two as daily smoking has declined during the study period both among pregnant women (from 18 to 11% in 1999-2004)[175] and among women in the general female population (aged 25-34 years; from 32% to 13% from 1999 to 2014).[39]

Women who had missing information on smoking habits at any of the four time points of their two first pregnancies were grouped into different categories and their risk of SGA in the second pregnancy was examined using non-smoking women in both pregnancies as reference.

3.6 Ethical considerations

Necessary approvals were obtained from the Regional Committees for Medical and Health Research Ethics. Informed consent was obtained from each subject before inclusion in the Norwegian Mother and Child Cohort Study.

4. Summary of main results

4.1 Paper I

In *paper I,* we had information on smoking habits at the end of pregnancy from 224 409 (86%) of 259 573 Norwegian born women giving birth in the period 1999-2004. We found a decrease in overall daily smoking prevalence among Norwegian pregnant women during the study period from 18% in 1999 to 11% in 2004 (RR 0.61 (95% CI 0.58, 0.64)). When analysing characteristics related to changes in smoking habits, the study period was divided in two: 1999-2001 and 2002-2004. Both in crude and adjusted analyses a decline in smoking prevalence was observed from the first to the second study period in all women. Women with the highest parity and age as well as single women and women with low education had the smallest change in smoking prevalence between the two study periods. In a fully adjusted model, the odds ratio for being a daily smoker at the end of pregnancy increased with parity and with being unmarried. Maternal age did not seem to have an effect after adjustment, while maternal educational level was established as the most influential variable in the analysis. Factors pointing at which women quit and which continue smoking are important as they can be useful in intervention programs.

We observed a higher prevalence of women quitting smoking during pregnancy in the second study period (32%) than in the first (23%) (RR 1.36 (95% CI 1.32, 1.40)). The increase was observed for in all strata of studied sociodemographic variables.

Cigarette consumption among daily smokers remained constant during the study period with 7.4 cigarettes per day.

Nationally, there were large differences between counties in smoking prevalence at the end of pregnancy. The highest proportion of daily smokers was found in Finnmark (24%) and the lowest in Oslo (9.0%).

Occasional smoking during pregnancy decreased from the 1.9% to 1.4% from the first to the second study period. Both daily and occasional smoking was more frequent among women with low education.

Smoking habits were available for 82% of women born outside Norway. These women had approximately half the smoking prevalence of women born in Norway. We observed a significant decline in daily smoking also among these women during the study period.

The proportion of women with missing smoking habits at both the beginning and at the end of pregnancy increased during the study period from 11% to 13%. The highest proportions of women with missing smoking habits were found in Oslo (28%) and in Finnmark (19%).

The mean birth weight of infants delivered to daily smoking women were 229 grams lower than what was found for non-smokers, while it was 114 grams lower for women with missing information on smoking habits. Given that the reduction in the group with missing smoking information was due to maternal smoking, approximately half of these women could be daily smokers. Adding this proportion of estimated smokers gave a smoking prevalence of 20.2% in the first study period and 17.9% in the second period.

4.2 Paper II

Among the 2 997 women in the MoBa subsample, daily smoking during pregnancy was reported by 263 (8.8%) women, and occasional smoking by 126 (4.2%) women. Ever smoking was reported by 1 491 (50%) women and 698 (23%) reported smoking daily the last 3 months prior to pregnancy. 472 (16%) women reported being exposed to passive smoking, either at work (n=216), at home (n=194) or both (n=62). Only 27 women reported using smokeless nicotine products during pregnancy, 15 reported chewing tobacco or snus, 9 reported using nicotine chewing gum, 2 reported using nicotine inhaler and 1 used nicotine adhesive patches.

We found that plasma cotinine concentrations increased with increasing number of reported cigarettes smoked daily by daily smokers and weekly by occasional smokers. Passive smoking exposed non-smokers had low cotinine plasma concentrations (geometric mean less than 2 nmol/l), while women using smokeless nicotine products had plasma cotinine concentrations approximately at 100 nmol/l.

In the validation analyses, occasional smokers, users of smokeless nicotine products as well as women with missing self-reported smoking habits were excluded. With plasma cotinine concentrations as the gold standard, a cut-off at 29.8 nmol/l (95% CI 20.0, 56.0), estimated from the study population, was used to calculate sensitivity and specificity of self-reported smoking habits. The overall mean sensitivity was 81.9% (95% CI 77.3, 86.4) and specificity was 99.4% (95% CI 99.1, 99.7). We evaluated the uncertainty in sensitivity and specificity by using different cut-offs than the geometric mean (from 2.5^{th} - 97.5^{th} percentile), and this showed larger differences in percentile values for sensitivity (77.3-86.4%) than for specificity (99.1-99.7%).

296 women in the study had cotinine values equal to or over the cut-off value (≥29.8nmol/l). Among these, 242 (82%) had reported daily smoking, while 54 (18%) had reported non-smoking. The 54 women who reported non-smoking, but were biochemically assessed as smokers, most often reported being ever smokers (n=45). More than half (n=30) reported daily smoking during the last 3 months prior to pregnancy and 13 reported being exposed to passive smoking.

For the 121 women reporting occasional smoking (excluding those using smokeless nicotine products), 66% had cotinine levels above or equal to the cut-off value. For the 27 women reporting use of smokeless nicotine products during pregnancy, 11 reported daily or occasional smoking and 16 reported non-smoking, and a total of 21 women had plasma cotinine concentrations above or equal to the cut-off level.

Self-reported smoking habits were missing for 22 women (<1%). Plasma cotinine concentrations were <1nmol/l for the majority of the women (n=13), <5nmol/l for 6 women and above the cut-off value for the last 3 women.

4.3 Paper III

In *paper III,* the association between birth weight and adult smoking was examined. There was an inverse trend between women's own birth weight z-scores and prevalence of smoking in adulthood. Adjusting for women's mothers' (G1) education, women's birth order and year of birth slightly weakened the results. Women with the lowest birth weight z-scores (-4.99, -3.51), had 80% increased risk of being a daily smoker in adult life, compared to women with birth weight z-score 0.50-1.49 (RR 1.81 (95% CI 1.42, 2.31)).

A similar trend between men's (G2) birth weight z-scores and their partners' adult smoking habits was found. For men in the two lowest birth weight z-score categories (-4.99, -3.51) and (-3.50, 2.51), the risk of having a smoking partner was about 40% increased compared to men with z-score 0.50-1.49. (RR 1.38 (95% CI 0.94, 2.05)) and (RR 1.36 (95% CI 1.18, 1.57)). The lowest z-score category of men included only 21 partners.

Results with absolute birth weight among women and men born at term showed similar results. Significantly increased risks of adult smoking were found for all birth weight categories lower than the reference group (4 000-4 499 grams), and with a dose-response relationship.

Compared to mothers (G1) of non-smoking women (G2), the hazard ratios of cardiovascular death or death from lung cancer among mothers (G1) of smoking women (G2) were twofold: HR 2.1 (95 % CI 1.9, 2.3) and HR 2.3 (95% CI 2.1, 2.7), respectively. Death from other causes combined and death from any cause had a hazard ratio of 1.5 (95% CI 1.5, 1.6) and 1.7 (1.6, 1.7), respectively. Adjustment for the mothers' (G1) education slightly attenuated the results; HR 1.8 (95 % CI 1.6, 2.0)

for cardiovascular death, HR 2.0 (95% CI 1.7, 2.2) for death from lung cancer, HR 1.4 (95% CI 1.3, 1.5) for death for other cause and HR 1.5 (95% CI 1.4, 1.6) from death from any cause.

4.4 Paper IV

In *paper IV*, we studied the association between smoking trajectories across two successive pregnancies in the MBRN during 1999-2014 and the risk of SGA in the second pregnancy. First, smoking habits at the end of two successive pregnancies and the risk of SGA in second pregnancy were explored among 122 479 women. Compared to non-smokers at the end of both pregnancies, women registered as daily smokers in both pregnancies (persistent smokers) had a 2.9 fold increased risk (95% CI 2.7, 3.1) of SGA in second pregnancy, while women registered as daily smokers at the end of first pregnancy and non-smoker at the end of second pregnancy (quitters) had a 1.5 fold increased risk (95% CI 1.3, 1.7). Defining SGA below the 2.5th percentile resulted in similar RR estimates for quitters and higher RR estimates for persistent smokers.

118 355 women had available smoking habits both at the beginning and at the end of two successive pregnancies. Women who smoked throughout the first pregnancy, but were non-smokers throughout their second pregnancy, had 30% increased risk of SGA in the second pregnancy (RR 1.3 (95% CI 1.1-1.6)). Women who smoked daily at the beginning of each pregnancy and quit smoking by the end of each pregnancy did not have increased risk of SGA in the second pregnancy. Women who smoked daily throughout their first pregnancy and at the beginning of the second, but had quit by the end of the second pregnancy, had a twofold risk of SGA in the second pregnancy (RR 2.0 (95% CI 1.6, 2.4)). Women who were non-smokers in the first pregnancy and smoked daily throughout their second pregnancy, had a 80% increased risk of SGA in the second pregnancy (RR 1.8 (95% CI 1.4, 2.3)), although lower than for persistent smokers (RR 2.9 (95% CI 2.7, 3.1)). Restricting analyses to only term births in the second pregnancy resulted in similar relative risks

of SGA. Among women who did not experience SGA in their first pregnancy, persistent daily smokers had close to threefold increased risk of SGA in the second pregnancy (RR 2.7 (95% CI 2.5, 3.0)). When restricting analyses to women with recurrent SGA, the risk of SGA in second pregnancy was increased among persistent smokers (RR 1.8 (95% CI 1.6, 2.0)) but was lower than among women who did not experience SGA in first birth. However, women who experienced SGA in the first pregnancy had more than five times higher risk of a recurrent SGA in the second pregnancy, compared to women without SGA in the first pregnancy (RR 5.5 (95% CI 5.2, 5.8)). The additional risk related to persistent smoking might therefore play a smaller role for SGA recurrence among these women than for women without SGA in the first pregnancy.

Three of the smoking trajectories included daily smoking at the end of second pregnancy. The mean number of reported cigarettes smoked daily at the end of the second pregnancy was higher in the persistent smokers group (7.8 (95% CI 7.6, 7.9) in the *Daily-Daily-Daily-Daily* group*)* than in each of the two other groups (6.3 (95% CI 6.1, 6.6) in the *Daily-No-Daily-Daily* group and 5.8 (95% CI 5.5, 6.1) in the *No-No-Daily-Daily* group) (Two sample t-tests, $P < 0.05$). The number of cigarettes was also higher in the *Daily-No-Daily-Daily* group than in the *No-No-Daily-Daily* group ($P=0.01$). This agrees well with the observed higher risk of SGA in the second pregnancy among persistent smokers.

The strong association between persistent smoking and SGA in the second pregnancy was observed both among women with low and high education.

The population of women with two successive singleton births in 1999-2014 included a total of 184 898 women. Of these, 9 820 (5.3%) women had missing smoking information at the end of both pregnancies, and 50 089 (27%) women had missing smoking information at the end in one of the pregnancies. Women who were daily smokers in the first pregnancy and had missing smoking status in the second, had a doubled risk of SGA in the second pregnancy (RR 2.2 (95% CI 1.9, 2.6)) compared to persistent non-smokers.

5. Discussion

5.1 Discussion of methods

5.1.1 Study design

Papers I, III and *IV* are all historical cohort studies, based on registries where information about the women, the births and the infants were registered prospectively. *Paper II* was a validation study based on a national, prospective cohort study. The women giving birth were the study unit in cross sectional files in *papers I* and *II*. In *Paper I,* women could contribute with several births (51 751 (20%) women contributed with more than 1 birth), implying dependencies in data with slight reduction in standard errors. Dependencies can be accounted for by use of a cluster procedure in STATA (vce), estimating robust standard errors.[176] We found only minimal changes to the confidence intervals. In *Paper II,* all the women were unique mothers, contributing with only one pregnancy to the study population.

For *paper III,* the principal design spanned over two pregnancies and three generations, and was based on a generation-linked data file. Women in the first generation (G1) contributed with their first registered singleton pregnancy in the MBRN during 1967-1995. We studied the birth weight variation of daughters (G2) and sons (G2) and its relation to smoking habits of the daughters (G2 women) when they became pregnant, or the smoking habits of the son's partner when she was pregnant (G2 partner). The offspring from these pregnancies (the third generation) was born during the years 1999-2009.

Paper IV had a sibling design where our focus was the mother with her two first successive births. Since smoking has been registered since 1999, the study population was restricted to women with at least two singleton births born in the period 1999-2014.

A major strength of the *papers I, III* and *IV* is the use of population based, compulsory registries. The MBRN has compulsory registration of all births (≥16 gestational weeks) in Norway. Through the national identification numbers, given to all individuals living in Norway, the registry is routinely linked with the National Registry. In the MBRN, several manual and computer based quality controls take place to solve inconsistencies and deal with registration errors.

Paper II is based on the Norwegian Mother and Child Cohort Study (MoBa). With its prospective design, information on smoking habits is obtained before birth in gestational week 19. Since the participation rate is slightly above 40%, the study is not representative of the Norwegian population and not suited for prevalence studies.

5.1.2 Precision

Precision is high in the absence of random errors. Random error can be described as "…variability in the data that cannot be readily explained".[177] Options to reduce random error include increasing study size or modifying study designs in order to obtain information in the most efficient manner.[178] The confidence intervals describe both the strength and the direction of the association studied. It also offers information on precision or the random variability of the point estimate.[177,178] In *papers I*, *III* and *IV,* the study sizes were large, and in the main analyses the association measures were generally precise with narrow confidence intervals. For *paper II,* the study size was smaller and for subgroup analyses the confidence interval were wider, however the precision of the estimates from the total material was not problematic.

5.1.3 Validity

Internal Validity

Internal validity refers to whether conclusions about causal relations in a study population are valid for the source population, or whether they may be affected by systemic errors. Three main categories of systemic errors can violate the internal validity: information bias, selection bias and confounding.[178]

Information bias (misclassification)

Information bias or misclassification may cause error to the estimates if there are measurement errors in the information about the study participants, the exposures or the outcomes. In large registries, although quality controls are implemented, errors in registration of both exposures and outcomes may remain. Recall bias/differential misclassification is not likely in the papers in this thesis, since all information on exposures was gathered prospectively, before the outcome. Nondifferential misclassification of the exposure occurs if exposure is misclassified independently of the outcome. Nondifferential misclassification of the outcome occurs if outcome is misclassified independently of the exposures of interest, or proxies for these. Nondifferential misclassification of a binary exposure or outcome may bias the effect estimates towards the null.[178]

Women may change their smoking habits during pregnancy. 85% of the women in *paper II* had returned the questionnaire with self-reported smoking habits within 4 weeks of the timing of when the blood sample was taken. A recent Swedish study had a longer span between self-report and cotinine sampling. [77] A greater time span from self-reporting to cotinine sampling has the potential to misclassify women who quit smoking during pregnancy as smokers based on self-report. Participants in MoBa, as well as attending nurses, were informed that blood samples could be used for research, but not specifically tested for nicotine exposure. It is therefore not likely that information on intended purpose of the blood sample influenced the accuracy of self-reported smoking habits or led to changes in smoking status.

Completeness of smoking information in the Medical Birth Registry of Norway

Missing information on smoking habits in the MBRN is a challenge for the researchers and health authorities using the registry data. Information may be missing at random, or because smoking women feel stigmatized and do not want to inform about their smoking habits, or missing because situations around the birth made it less likely for the midwife to be able to register all the information requested. If the latter happens, that is of great concern when using these variables. In the MBRN data, the

proportion of women with missing information on smoking habits at the end of pregnancy decreased with advancing gestational age (Figure 8).

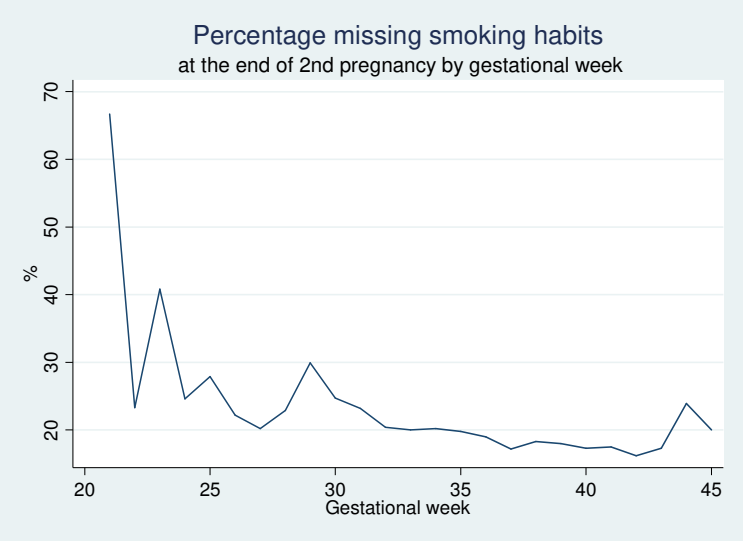

Figure 8. Percentage of women with non-reported smoking habits at the end of 2nd pregnancy by gestational week, data from MBRN 1999-2014.

However, not only adverse events at delivery matter for the registration of smoking habits. The maternity units play an important part. Ullevål hospital (Norway's largest delivery unit) in Oslo has delivered around 12% of the birth notifications nationally.[146] For several of the years from 1999 to 2014, approximately 60% of women delivering at Ullevål hospital refrained from informing about smoking habits in pregnancy. When Ullevål hospital (merged into Oslo University Hospital from 2009 together with Rikshospitalet) changed their notification procedures from paper forms to an electronic system (Partus) in 2014, the proportion refraining from giving information on smoking habits decreased considerably (from 67% to 16%).[146] This also occurred after the MBRN had informed Ullevål about their high proportion of missing smoking information (Kari Klungsøyr, senior medical officer at the MBRN, personal communication December 28th 2017). The proportion

of births delivered at Ullevål hospital with registered smoking habits subsequently increased from 34% in 2013 to 86% in 2015.[32] However, at Rikshospitalet, the transition from an old (Obstetrix) to a new (Partus) electronic system, led to an increase in proportion of women refraining from giving information on smoking habits (from 0 to 14%).[146] As these differences in reporting seem to be on a system level rather than an individual level, they may affect smokers and non-smokers in a similar way and thus not lead to differential misclassification.

Among women born outside Norway, the proportion of women refraining from giving information on smoking habits is higher than among Norwegian born women. This suggests that also communication difficulties may play a role in registration of smoking habits.[146]

In the following paragraphs, sensitivity analyses are presented for *papers I, III and IV* to examine the potential bias introduced by missing smoking information. Few women had missing smoking information in *paper II* and that paper is therefore less focused in this regard.

In *paper I,* 53 082 (20%) women had missing information on smoking habits at the end of pregnancy. Among these, 17 918 women had missing information about smoking at the end of pregnancy, but reported non-smoking at the beginning of pregnancy. These women were counted as non-smokers at the end. For the remaining 35 164 women missing smoking information at the end of pregnancy, a total of 31 199 had missing information on smoking habits both at the beginning and at the end of pregnancy, 663 reported occasional smoking and 3 302 reported daily smoking at the beginning of the pregnancy.

As mentioned above, Ullevål hospital in Oslo has had higher proportions of women with missing smoking information than other institutions. In *paper I,* women giving birth at Ullevål represented 6.5% of the study population (n=259 573 Norwegian born women). Of these women, as much as 42% (n=7 119) had missing information on smoking habits. The women giving birth at Ullevål represented 23% of all the women with missing smoking information. The other hospitals in that area

such as Rikshospitalet and Aker had a prevalence of women with missing smoking habits of 15% and 6.8%, respectively. This is important to the interpretation of the smoking prevalence among pregnant women in Oslo, as well as the interpretation of the prevalence of women with missing smoking information. This difference in reporting of smoking habits between the hospitals suggests that the proportion of women with missing smoking information is not only influenced by the proportion of women who want to hide their actual smoking habits. The proportion of women with missing information on smoking is also influenced by which institution they give birth at, suggesting a more non-differential misclassification of smoking habits/missing smoking habits.

In *paper II*, information on smoking habits were missing for only 22 women (<1%) and among these, 3 women had cotinine value above the cut-off, suggestive of daily smoking. The small number of women with missing information on smoking information suggests less possibility for bias.

In *paper III,* 9.9% of the single born women had missing smoking information. The percentage of women with missing smoking information was lower in *paper III* than in *paper I* due to the different design. In *paper III,* women contributed with the first birth *after* 1999 when smoking habits were registered. If most of the women with missing smoking information were born to smoking mothers, one would expect a strong relation to low birth weight. We observed a weak association between the occurrence of low birth weight and missing smoking information in adulthood (RR 1.1 (95% CI 1.0, 1.2)). In a sensitivity analysis, all women with missing smoking information were assigned as daily smokers and were added to the main analyses. The reclassification attenuated the results, but did not change the dose-response pattern between birth weight and adult smoking habits.

In *paper IV*, for women with two successive pregnancies, 5.3% (n=9 820) had missing information on smoking habits at the end of both pregnancies and 27% (n=50 089) had missing information in one of the pregnancies. Information on smoking habits at the beginning and at the end of the two pregnancies (4 time points)

was missing for 33% of the study population. Figure 9 displays the relative risk of SGA in second pregnancy by missing smoking information. In this figure the presented trajectories include most of the women; 90% of the women with missing smoking information are presented (n= 54 728). The remaining women have trajectories which only a few women share (n=307), and 1 604 women have a mix of statuses of missing and occasional smoking. Of the 54 728 women in figure 9, 50 584 women belong to the trajectories involving non-smoking and missing, while 4 144 women belong to the trajectories involving daily smoking, non-smoking and missing. Women who were daily smokers in first pregnancy and had missing information in the in second pregnancy had twofold increased risk of SGA in second pregnancy compared to persistent non-smokers. Women who had missing smoking information on all 4 times points had only a weak association to SGA in second pregnancy: (RR 1.2 (95% CI 1.1, 1.3)). For several of the categories, the estimate as well as the confidence interval is above 1. This indicates that our results for women with registered smoking habits are not much overestimated by missing information.

For women who did not experience SGA in second pregnancy, 18% had missing smoking habits at the end of pregnancy. In comparison, the proportion was 19% for those experiencing SGA in second pregnancy (RR 1.1 (95% CI 1.02, 1.1)). We conclude that it is not likely that the results are biased by this.

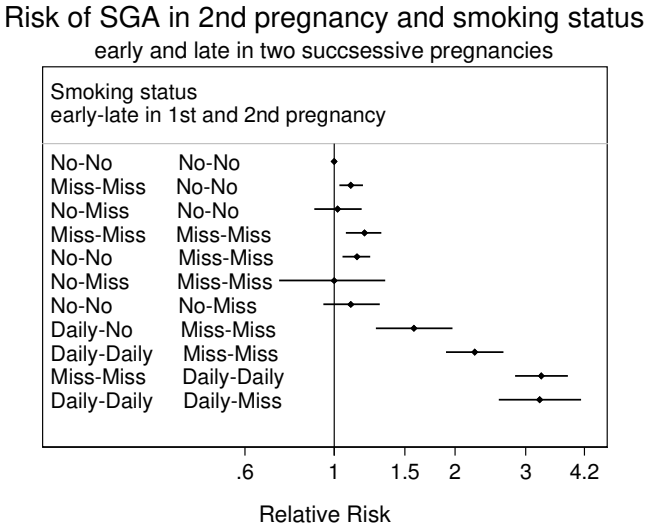

Figure 9. Trajectories including missing information on smoking habits and the adjusted relative risk of SGA (10th percentile) in 2nd pregnancy among Nordic born women with two successive singleton pregnancies 1999-2014. Persistent non-smokers serve as reference category. Analysis was adjusted for maternal age, marital status and year of first birth. Reprint from *paper IV* (supplemental material).

Maternal Education

We used attained education as a proxy for measuring socioeconomic status. In recent years, smoking and education are closely related. Obtaining information on education from Statistics Norway through record linkage should ensure minimal potential for differential misclassification in *papers I, III,* and *IV*, as smoking habits and education were collected from different sources. After defining the study populations, less than 1% of women in *paper I, III* and *IV* had missing information on education (or their mothers' education in *paper III*). In *paper II,* education was obtained from the MoBA questionnaire and was missing for 2.6%. Since only few women had missing information on education, the likelyhood of bias is minimal.

In *paper I,* maternal education was the strongest predictor of smoking during pregnancy. In *paper II*, sensitivity of self-reported smoking was lowest in women with high education; however this group included few women. In *paper III*, adjusting for women's mothers (G1) education slightly attenuated the results. In *paper IV*, stratifying on women with high and low education revealed a strong association between persistent smoking and SGA in second pregnancy in both groups. Therefore, the results changed little when education was used as an adjustment variable.

Cotinine

Cotinine was measured in a subsample of women in MoBa. In the study it was possible to exclude snus users, which is another source of nicotine reflected in cotinine measurements. Differences in nicotine metabolism may lead to misclassification of smoking women as non-smokers, based on their cotinine serum levels and the chosen cut-off value in *paper II*. Genetic polymorphisms of the CYP2A6 gene are associated with the variability in the nicotine clearance to cotinine and may give rise to inter-individual differences in nicotine metabolism.[179] We evaluated the uncertainty of the chosen cut-off and found that the percentile values in sensitivity varied somewhat more (77.3-86.4%) than the values of specificity (99.1-99.7) for different cut-offs.

Parity

In *paper IV* in the sibling analyses, we included women's second birth that was registered in the MBRN. The sibling file is sorted by women's successive pregnancies registered in the MBRN, and this succession was the basis for the analyses. This may in some instances not reflect a woman's actual second pregnancy since early miscarriages are not registered in the MBRN, and are also quite frequent.[180]

Gestational age

Gestational age together with birth weight is the basis for z-score for birth weight by gestational week calculations and SGA. Only LMP based gestational age was

recorded in the MBRN until 1998, after which ultrasound based estimations were included in the registry. In both *papers III* and *IV*, gestational age was based LMP. In *paper IV*, if LMP was missing or there was a difference of more than 10 days between LMP and ultrasound based gestational ages, ultrasound based gestational age was used. Information on gestational age was missing for 4% in *paper III* and for <1% of second births in *paper IV*. Gestational age in the MBRN was missing for ~4% for the first ten registry years (1967-1978), and then gradually increased to ~10% in the 1990s. After 1999 less than 0.1% of births had missing gestational age. Gestational age could potentially be misclassified through uncertain last menstrual date, bleeding in early pregnancy mistaken for a period, or errors in registration.[181] Z-scores for birth weight by gestational week and SGA (birth weight below the 10th percentile) were computed by applying Norwegian birth weight standards based on data from the MBRN.[164] Using this standard we could identify and exclude erroneous gestational ages given the birth weight, as birth weight is registered less erroneous than dates.[164,181] In *paper III*, absolute z-score values of 5 or more were excluded. In *paper IV*, this exclusion was not done. However the number of women with second births with absolute z-score values of five or more were very few (n= 14) in the study population and the results did not change when these were excluded.

Birth weight and small for gestational age

Birth weight is a precise and more reliable measure than gestational age estimates.[164,181] In *papers III* and *IV,* birth weight was missing for less than 0.5% of the study populations. *In paper III,* z-scores for birthweight by gestational week equal to or above an absolute value of five were excluded (n=298, <1%,) in order to eliminate those with likely misclassified gestational age. Analyses on associations between adult smoking habits and a person's own absolute birth weight at term or z-score for birth weight by gestational week resulted in similar patterns. In *paper IV,* SGA was defined as birth weight below the 10th percentile for gestational age and sex. To examine if a more strict definition of SGA would change the results, the analyses were repeated applying a definition of SGA below the 2.5th percentile. This

resulted in higher relative risks for persistent smokers and starters and similar risks for quitters.

Cause of death

The Cause of Death Registry has near complete coverage for medical information on all deaths. Quality control is done by linkage with the National Registry, and reminders are sent out to Chief Municipal Medical Officers for missing certificates.[162] The death certificate is completed by a doctor who may or may not know the dead person, depending on time and place of death. The most important issue in data quality is the frequent use of unspecific codes for underlying cause of death, reflecting terminal stage or complication rather than information on disease.[162]

Confounding

A structural definition of confounding is bias that occurs when there are common causes of the exposure and the outcome of interest (so-called open backdoor paths).[182] Providing first the definition of confounding; Hernan et al have defined a confounder as "any variable that can be used to help eliminate confounding."[182]

Confounders, and also surrogates of proper confounders, may be stratified on or adjusted for to block confounding paths, though with caution as to how closely the surrogate is associated with the actual confounder.[178] In the studies included in the present thesis, confounders were identified a priori.

In *paper I,* the change in smoking habits from first part of the study period (1999-2001) to the second part (2002-2004) was evaluated in strata of parity, maternal age, marital status and maternal education level. Within each stratum, we first only adjusted for period as the independent variable within each category, and then with period and all the other factors as independent variables. Full adjustments led to slight changes. To study which factors (of parity, maternal age, marital status, maternal education level and time period) was the most important for smoking at the end of pregnancy, fully adjusted analyses showed that low education resulted in the highest odds ratio for smoking at the end of pregnancy.

In *paper II,* the sensitivity and specificity for self-reported daily smoking was stratified on background variables; maternal age, parity, marital status, pre-pregnancy BMI, and maternal education. Women with high education had the lowest sensitivity (68%) of self-reported smoking habits. However, the number of self-reported smokers in this group was small and the 95% confidence interval was wide; 46%-85%.

In *paper III,* analyses were based on records of births in two successive generations. The main exposure was the offspring's birth weight in the first birth record, including the first generation as mothers (GI) and the second generation as offspring (G2). These offspring served as mothers and fathers in the next set of birth records, and our focus was the maternal smoking status (G2, Figure 5). The association between the woman's birth weight and later adult smoking habits were adjusted for her mothers' (G1) educational level, the women's (G2) birth order and year or birth. The adjustment did attenuate the results slightly, but the pattern remained similar to the unadjusted analyses. The analyses of the association between birth weight of men and their partners' smoking habits were not adjusted since we did not identify any obvious common causes for men's birth weight and the partners' smoking habits in pregnancy. As the main aim was to study the association between men's birth weight and partner's smoking habits, we did not find adjustment for partner's education appropriate (no confounder).

For the association between women's smoking habits and mother's cause of death, the analyses using Cox proportional Hazards model, were adjusted for women's mothers' education. This somewhat weakened the results, but they remained significant.

In *paper IV,* the following variables were considered as potential confounders for the association between maternal smoking trajectories and SGA in second pregnancy; maternal age at first birth, marital status at first birth, year of first birth and maternal education. Adjusting for maternal age, marital status, and year of first birth did not change the results. Education was only available for a subset of the study

population (births in 1999-2010), but for this subgroup, the results remained similar when adjusting for education as well. In order to examine if persistently smoking women who did not experience SGA in first pregnancy were "protected" against experiencing SGA in second pregnancy, analyses were restricted to women who did not experience SGA in first pregnancy. By conditioning on SGA in first pregnancy, a "backdoor path" may be opened through unmeasured factors (see DAG in Figure 6). These unmeasured factors may represent genetic factors causally related to SGA in first and second pregnancy, and opening this path might introduce bias.[183] As the results did not change much, the amount of bias could not have been substantial.

There will be unmeasured confounders for all our studied associations. In *paper IV*, a woman's pre-pregnancy BMI might have been a relevant variable when studying the association between smoking in two pregnancies and the risk of SGA in the second pregnancy. However, as smoking can affect BMI, and BMI can affect risk of SGA, BMI would be an intermediate in this analysis. As the main interest was to study the total effect of smoking on SGA, adjusting for BMI may not be warranted. Being a smoker might be associated with other unhealthy behaviours that we were not able to measure. Other possible confounders include caffeine and alcohol intake during pregnancy.

Effect-measure modification

Effect-measure modification can be defined as the situation where the measured effect of one variable on another is different across strata of a third variable.[178] In *paper III,* the association between birth weight and later adult smoking was assessed across different levels of women's mothers (G1) education. For women (G2) whose mothers (G1) had high education, those with birth weight z-scores ≤-2 had a RR of 1.4 (95% CI 0.96, 2.05) of later being a smoker, compared to women with z- score ≥0. Among women whose mothers had low education, the corresponding RR was 1.5 (95% CI 1.3, 1.6). The relative risks estimates were not significantly different with overlapping confidence intervals, and we concluded that there was little effect medication by the mothers' (G1) educational level.

Likewise, in order to examine if there were differences in hazard ratios for death of mothers by daughters smoking habits within the study period, the period was split into two; 1999-2003 and 2004-2009. The hazard ratios for the four causes of death categories were higher in second period than the first, but again, with overlapping confidence intervals.

In *paper IV*, the association between persistent smoking and SGA in second pregnancy was examined in strata of maternal education. For women with low and high education, we observed similar estimates (RR 3.1 (95% CI 2.8, 3.6)) and (RR 2.7 (95% CI 2.4, 3.1)), respectively. Little evidence of modification of education was observed as RR estimates were similar and confidence intervals overlapped. In this analysis we used non-smoking women with high education as the common reference.

Selection bias

Selection bias is bias that may distort results due to procedures related to selection of study subjects and from influencing factors relating to study participation. [178]

Paper I, III and *IV* are based on the MBRN which has national coverage of births and diminishes the possibility for selection bias. However, the design of *paper III* implies a cohort of women who have reproduced. To be included in the study, women must have been born in Norway after 1967 and have had at least one pregnancy from 1999 onwards. Women born outside Norway as well as women who did not reproduce are not included in the cohort. Being exposed to smoking in utero is associated with reduced fertility in the offspring.[184] It might be that the babies most exposed to smoking and with the lowest birth weights did not contribute to the analyses. If these women had given birth, our estimates would most likely have been strengthened.

Paper II, using MoBa data, is by design more vulnerable to selection bias than the studies from the MBRN. Women who agree to participate in a study may have different risk profiles than the total population, leaving the study participants with

different prevalence of risk factors than the total population. Self-selection bias may cause systematic errors in studies if an underlying factor both influences participation and some given outcome. The participation rate was slightly about 40% in the MoBa cohort.[78] The questionnaires were in Norwegian, which by itself excluded women who were unable to read Norwegian. Young women, women living alone as well as mothers with more than two previous births were underrepresented, and the smoking prevalence was considerable lower in MoBa than in the MBRN.[161] Also numbers of cigarettes smoked per day were lower in MoBa than in the MBRN and there were fewer women with unknown smoking habits. Also for pregnancy outcomes, there were differences between MoBa participants and the total population. Despite differences in prevalence estimates of exposures and outcomes between participants in MoBa and women giving birth registered in the MBRN, the exposure-outcome measures were not biased in MoBa[161]. In *paper II,* 3 000 women were drawn randomly from the MoBa participants who had donated blood samples around week 18 as well as having completed the baseline questionnaire and the food frequency questionnaire and who were registered in the MBRN. The population in the subsample has been described as being similar to the full MoBa cohort at the time the subsample was drawn.[163]

External validity

External validity refers to how well the results and conclusions drawn from a study may be generalized to the population outside the study.[178] Internal validity is a prerequisite. The MBRN cover all births in Norway and in that sense the results in *papers I, II* and *IV* are applicable to women giving birth in Norway. Norway is in the fourth stage of the Tobacco Epidemic.[35] Results may be less applicable to developed countries in different stages of the Tobacco Epidemic. The results in the descriptive cross-sectional aspect in paper I, the validity study in paper II, the generational aspect in paper III and the successive births aspect in paper IV are all tied to this model of the Tobacco Epidemic.

The women participating in MoBa may differ on some exposure and outcome variables from women giving birth in the general population.[161] However, the well-known study of British male doctors' smoking habits and health, serves a prime example of a cohort study that was not representative of the general population, but contributed to new evidence on the hazards of tobacco smoking due to the selected cohort being homogeneous for confounders and behaviours.[6]

The specific cotinine cut-off values used in one study should be used with caution in other populations. The sensitivity and specificity for a given cotinine cut-off may vary with regions, with population characteristics and over time. With effective tobacco control efforts, the tobacco exposure for non-smokers should lessen and the distribution curve for serum cotinine should shift to the left towards non-detectable levels. This has implications for the cut-off value which might be reduced compared to its level in times and regions with less tobacco control measures.[185]

Although the results in *paper II* should be informative for the validation of self-reported smoking habits in MoBa, this information is not necessarily applicable to the entire Norwegian pregnant population, as the proportion of smokers among women who agreed to participate in MoBa is lower than in the entire pregnant population.[161] However, recent results from the Swedish Medical Birth Registry,[77] based on women who did not participate in any study, show high agreement between self-reported smoking habits and cotinine levels. These results lend support to the view that pregnant women in Norway and Sweden report their smoking habits fairly accurately.

5.2 Discussion of main results

5.2.1 Paper I

In *paper I,* a decline in smoking prevalence at the end of pregnancy from 1999 to 2004 was identified. The decline was evident in all subgroups studied, but of different magnitude. Decline in smoking prevalence among pregnant women in Norway has previously been described from the late 1980s to early 1990s,[52,186] but this is the first

study that describes smoking data from the MBRN, with national coverage of all births in Norway. Maternal educational level was the most important explanatory variable for daily smoking at the end of pregnancy in adjusted logistic regression analyses. Occasional smoking at the end of pregnancy was more prevalent among women with low than high education. This was in contrast to what has been reported for women in the general population: In 2006, occasional smoking was most common among higher educated women. After 2009, this pattern among occasional smokers has changed, and women with high education have now the lowest occasional smoking prevalence.[43]

In *paper I,* an independent samples t-test between smokers in the first and second study period showed no difference in mean cigarette consumption between the time periods. Mean number of cigarettes smoked daily in the first period was 7.43 (SD 4.53), and 7.39 (SD 4.48) in the second period. This is consistent with a previous Danish study that found little change in mean number of cigarettes smoked daily during the years 1989-1996. [114] However, a previous study from a Norwegian county found a reduction in number of cigarettes smoked daily among pregnant women from 1987-1994.[52]

Women who continue to smoke in pregnancy more frequently have low income, low education and mental health problems.[187-189] In *paper I,* we identified one third of teen mothers as daily smokers at the end of pregnancy. Young pregnant women may adjust less to tobacco policy measures than older pregnant women. This polarization in smoking habits by age among pregnant women was still evident ten years later.[53] However, when adjusting for period, parity, marital status and maternal education level, it was evident that maternal age barely affected the odds of smoking. Maternal education was the most important factor for smoking habits in the adjusted analyses. In *paper I*, education was last updated in 2002. This means that some women might have attained higher education that was not available in our data. As a teen mother cannot have reached high education when she gives birth, her potential for later education might not have been captured in this study. It might be that the potential for more education in these women drove the analyses so that maternal age

became the least important variable in the adjusted variables. Additional analyses done on the same material, but with education updated in 2009, showed that among women who gave their first birth as teenagers, the smoking prevalence was 39 % among those not achieving higher education later (at 2009), compared to 14% among those achieving higher education. To further explore how much "support" these teen mothers had, a generational approach was used: Among mothers (G1) with low education, their daughters (G2) who became teen mothers had a 30% daily smoking prevalence at the end of pregnancy, compared to an 18% smoking prevalence of pregnant teen mothers whose own mothers had high education. These analyses show that although there is high smoking prevalence among teen mothers, there is also socioeconomic heterogeneity within this group, associated with smoking prevalence.

Smoking habits among pregnant women is a sensitive subject and women may underreport such behaviour. In the study population, 20% had missing smoking habits at the end of pregnancy and 12% had missing smoking habits both at the beginning and at the end of pregnancy. Among those with missing smoking habits at the end, about 1/3 were registered as non-smokers at the beginning of pregnancy and they were in our analyses counted as non-smokers throughout. In comparison, the Swedish Medical Birth Register have registered smoking habits in week 30-32 since 1991, but due to the high proportion of missing data (67-89%) this variable has only been used for statistics since year 2000. However, smoking in the beginning of pregnancy has been registered since 1983. In 2005 and 2006 the proportion of pregnant women with missing smoking habits in week 30-32 were 15% and 9%, respectively. [190,191]

5.2.2 Paper II

The Norwegian Mother and Child Cohort Study (MoBa) is a large population-based cohort study aiming at identifying causes of diseases.[78] The validity of self-reported smoking habits in MoBa had not previously been described. Some studies have found the validity of self-reported smoking habits among pregnant women to be in good agreement with biomarkers,[77,192-194] others have not,[195-197] while others again just state

the amount of misclassified self-reported non-smokers.[198] A smaller Swedish study found similar sensitivity and specificity for self-reported active smoking as we found in our study. However, they lacked information on occasional smoking. The misclassification on smoking habits was higher among women who reported recent smoking cessation.[192] Similarly, in our study among the 54 self-reported non-smokers with plasma cotinine levels above cut off, 30 women reported daily smoking the last 3 months before pregnancy. Consistent with others, we found a bimodal distribution of log plasma cotinine concentrations,[76,199,200] suggestive of a distinction between active smokers and non-smokers/ passive smokers. We suggested a cut-off at 29.8 nmol/L (5.3ng/ml) plasma cotinine after identifying this as the lowest point between the two distributions. Studies on non-pregnant populations have used higher serum cotinine cut off levels to identify active smokers: 80-85 nmol/L.[199,201,202] Studies of pregnant women have used cut off levels in the range of 17 to 99 nmol/L (3-18 ng/ml).[73,74,193,194,198,203,204] For cord serum, similar cut-off values have been used (17-85 nmol/L, 3-15 ng/ml).[77,205] The lower range cut-off levels (17 nmol/l, 3 ng/ml), were used in the more recent studies.[77,204] A cut-off level at 17 nmol/l (3 ng/ml) has been proposed as an overall cut-off for the U.S population, and 27 nmol/l (4.7 ng/ml) for non-Hispanic white women.[76] However, a general cut-off value for pregnant women has not been established.

The strengths of the study include the detailed available information on active smoking, occasional smoking, smokeless nicotine exposure and different sources of exposure to passive smoking (at home and at work), which is more detailed than other studies that miss either one or more of these exposures.[77,192,198] There were few women with missing self-reported smoking habits (<1%) in the MoBa study sample.

Negative predictive value (NPV) is described as “the proportions of patients with negative test results who are correctly diagnosed”,[169] and might also be of interest in a validation study. Sensitivity and specificity is not affected by the prevalence of the disease of interest, however NPV depends on this prevalence. Additional analyses not included in *paper II* showed that negative predictive value (NPV) (in table 2: *d/(c+d)* was 2516/(2516+54) = 97.9%). A NPV of 98% means that

among women who were self-reported non-smokers, 2% had cotinine values suggesting daily smoking.

Women who participate in a study where they agree to fill in several detailed questionnaires will likely differ from women in the general population, captured by the MBRN, with regards to a more accurate reporting of their smoking habits. There are several reasons as to why validity of self-reported smoking habits may differ across studies, for example differences in cut-off values, the setting in which self-reported smoking habits was obtained (population based or a specific study) and the degree of stigma surrounding pregnant smokers. This highlights the importance of explicit examining the validity of self-reported smoking habits in MoBa.

While the cotinine concentration in biological fluids such as plasma, salvia and urine is considered a good biomarker for current ongoing exposure to smoking, either as active smoking or second-hand smoke exposure, one of its limitations is that it does not measure long-term exposure. For studying long-term exposure, measurement of nicotine in hair or nails is an option.[75]

5.2.3 Paper III

The hypothesis of paper III was that women born with low birth weight more often end up being adult smokers than women born with higher birth weights, and this places them at increased risk of later cardiovascular disease. This hypothesis was based on an assumption of smoking habits being passed on from one generation to the next: thus daily smoking in the first generation could cause both low birth weight in the second generation and also daily smoking when these low birth weight babies grow up. Their daily smoking as adults will increase their risk of cardiovascular disease.

The MBRN includes information on birth weight since 1967 and maternal smoking habits since 1999. The association between birth weight of women and smoking habits at the end of their own pregnancy 13-42 years later was studied.

In order to further examine this non-biological association, we also tried to evaluate whether men born with low birth weight more often grew up in a smoking environment. This was done by studying the association between birth weight of men and their partners' smoking habits when pregnant. Since partners frequently share smoking habits,[206] their partners' smoking habits would serve as a proxy for the men's own smoking habits. The association between men's low birth weight and their partners' daily smoking may indicate that parts of the well-known association between low birth weight and later cardiovascular disease could be confounded by cross-generational smoking habits.

The ideal situation to test the hypothesis would be to have information on smoking habits in two generations. As smoking habits during pregnancy were not registered in the MBRN before 1999, it was not possible to study smoking habits in two generations directly. However, to explore whether women's smoking habits were related to their mothers' smoking habits, we studied the relation between women's (G2) smoking in pregnancy and their mothers' (G1) smoking-related deaths. We observed a twofold risk of dying from lung cancer and from cardiovascular disease among mothers (G1) of smoking women (G2) compared to mothers of non-smoking women.

The difficulties in associating early life factors with adult disease has been problematized also by others who found accumulation of risk factors being strongly associated with social class at birth.[207] In *paper I*, we discussed that there seems to be an increasing social polarisation among smoking pregnant women concerning education. In *paper III,* we show that women born with low birth weight more often smoke as adults, and interpret this as a result of women whose mothers smoke, more often "inherit" the habit of smoking. Others have also shown that smoking is a behaviour repeated by the next generation.[184,207,208] While we found a strikingly similar pattern for women's risk of smoking by her own birth weight and men's risk of having a smoking partner by his own birth weight, others have found weaker associations between maternal smoking during pregnancy and sons' later smoking habits than daughters'.[209] The latter study was small, which may partly explain the

differing results. However, parental smoking behaviour is likely not the only determinant of adult smoking habits, and experiences of hardships during childhood are also shown to be a determinant of smoking status.[210,211]

Smoking during pregnancy was in a review from 1987 acknowledged as the most important single factor for low birth weight in developed countries.[86] In *paper III,* we showed a significant trend between decreasing birth weight and increasing smoking rates. Several studies have found no such association between birth weight and adult smoking habits.[140,212,213] Two of these studies are from the UK and one has 1 394 female study participants aged 60-79 years in 1999-2001,[212] while the other has 1 258 male participants aged 45-59 in 1973-1983. [213] The third study is from the U.S. and has 70 297 female participants aged 46-71 in 1992.[140] The three studies together cover both sexes and cohorts born in the 1920s to 1940s. All the three studies are based on self-reported birth weights, which could potentially lead to misclassification of birth weights. While some have reported sufficient accuracy in self-reported birth weights,[214] others have found lower sensitivity for self-reported birth weights among individuals whose birth weights were lower than among those with higher birth weights.[208] In *paper III,* the women were born between 1967 and 1995. Although smoking was on the rise in both the UK[136] and the U.S.[215] in the 1920s and the 1940s, our study population consists of offspring of women whose birth cohorts reached the historically highest peak smoking prevalence around 1970. The cohorts of women born in 1940 - 1944 and 1945-1949 had a peak smoking prevalence at 52%, aged 25-29 and 20-24 years respectively.[40] Although these are not prevalences of smoking during pregnancy, it does indicate that women in *paper III* were born in a time when smoking among women in general was common. The Nurses' Health study was the largest of the mentioned studies.[140] This study population consisted merely of nurses which makes the study less generalizable than the study in *paper III*, which is population based.

Several studies that have examined size at birth (or weight at one year[216]) and later cardiovascular disease state that the association remain after adjustment for smoking.[128,140,212,213,216-218] However, the relationship has not been accounted for in

detail, and there may be residual confounding. While some studies have obtained information on birth weight from self-report,[140,212,213,217] other studies have no data on gestational age.[128,212,217] With *paper III,* the aim was to elaborate on adult lifestyle as an important factor for the association between birth weight and later cardiovascular risk. In this study, it was possible to examine the relation between birth weight by gestational age z-scores and adult smoking habits in a large material.

Publications on size in early life and later health outcomes have been criticized for failing to explore whether the measured effect is partly or wholly related to postnatal or prenatal factors, due to both misinterpretation of results as well as lack of using appropriate statistical models.[219] Criticism has also been directed at studies supporting the "Fetal Origins of Adult Disease" (FOAD) hypothesis examining the relation between birth weight and adult blood pressure. Tu and colleagues have addressed how caution should be made when adjusting for variables that lie on the causal pathway between birth weight and adult blood pressure, such as adult body weight. Further, they have argued how failures to justify choice of confounders across studies make results difficult to compare.[220,221]

A possible explanation for the observed associations between size at birth and adult cardiovascular disease is common genetic and/ or environmental factors that predispose to both low size at birth and adult cardiovascular disease. The *fetal insulin hypothesis* suggests common genetic factors related to insulin resistance could lead to impaired fetal growth as well as insulin resistance and vascular disease in adulthood[222]. Support of this hypothesis has been shown with offspring's size at birth being inversely related to both mothers' and fathers' cardiovascular mortality.[223]

The work of David Barker and colleagues on FOAD, and subsequently DOHaD, has been characterized as a catalyst for life course thinking in epidemiology.[224] Life course epidemiology has been defined by Kuh and Ben-Shlomo as "the study of long-term biological, behaviour and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life or across generations". This

definition was recently judged to have passed the test of time.[224] The similarities between the approaches are the common interest in understanding how developmental factors are related to later health and disease. However, there are important differences. The DOHaD model sees chronic disease as result of an adaption to a fetal/early childhood life that turns into a maladaptation in adult life. Within life course epidemiology, survival into later life is considered a trait favoured in human societies, hence the "programming" appear too deterministic. Life course epidemiology has been interested in function; its maintenance or decline and the impact of factors acting across the lifespan. While life course epidemiology has aimed at examining timing of interventions, also in later life, in order to modify disease risk or change disease progression, DOHaD has been less interested in its potential beyond early life.[224] Although differences between approaches, there is now a wish to "cross-fertilize"[224] for future research.[132]

5.2.4 Paper IV

Smoking is an important risk factor not only for SGA,[15,225] but also for morbidity of SGA infants.[226] Reduced risk of SGA among women who quit smoking has previously been studied.[16,34] However, while others have only looked at smoking habits at the beginning of each pregnancy,[227] or just within one pregnancy,[16,34] we had the opportunity to look at smoking habits both early and late in two successive pregnancies. A Swedish study using smoking information obtained during the first antenatal visit in two successive pregnancies, found an increase in birthweight in the second pregnancy among offspring of women who smoked in the first pregnancy, but not in the second.[227] We found different risk patterns depending on the smoking trajectories throughout two successive pregnancies, and that smoking habits only at the beginning or only at the end of pregnancies did not sufficiently convey the risk for SGA in second pregnancy. Women who quit smoking before the end of second pregnancy had a lower risk increase than women who continued to smoke throughout her second pregnancy. Women who smoked daily throughout two pregnancies had an almost threefold risk of SGA in the second pregnancy, and this is in accordance with the previous study looking at SGA risk and smoking within one pregnancy.[16] We

further found that women who smoked in both pregnancies, but did not experience SGA in the first pregnancy, were not "protected" against SGA in the second pregnancy.

Comparing women with and without recurrent SGA in the first pregnancy, we concluded that the association between persistent smoking and SGA in second pregnancy was lower among women with recurrent SGA (RR 1.8 (95% CI 1.6, 2.0)) than among those whose first birth was not SGA (RR 2.7 (95% CI 2.5, 3.0)). However, women with recurrent SGA have a higher baseline risk for SGA (RR 5.5 (95% CI 5.2, 5.8)), also among non-smokers. Using non-smoking women without SGA in the first pregnancy as the common reference group, we analysed the risk of SGA in second pregnancy by smoking trajectories: Non-smoking women with recurrent SGA had more than fivefold risk increase (RR 5.6 (95% CI 5.3, 6.0)), and persistent daily smokers with recurrent SGA more than nine fold risk increase (RR 9.4 (95% CI 8.5, 10.5)). Although the RRs were higher among women with recurrent SGA, the increase in RR from non-smokers to persistent smokers did not exceed the increase from non-smoking to persistent smoking women among women without recurrent SGA.

Some of the analyses on women with available smoking habits at the end of the two pregnancies were repeated after defining SGA by the 2.5th percentile. This led to higher RR estimates among persistent smokers (*Daily-Daily*) and starters (*No-Daily*).

Although we lacked information on maternal height and pre-pregnancy weight, it was possible to adjust for several other potential confounders; however these did not lead to great changes in the estimates, and indicates that unmeasured confounding is probably not a large threat to our conclusions.

We found that quitting smoking reduced the risk of SGA. However, among women who smoked throughout the first pregnancy, but were non-smokers in the second pregnancy; we did observe a modest, but statistically significant 20% increased risk of SGA in second pregnancy. This observation calls into question

whether smoking in a previous pregnancy truly affects the growth conditions for the fetus in the next pregnancy. Although we cannot rule out changes in maternal cardiovascular status which in turn could affect fetal growth conditions, the women who have reported smoking through one pregnancy might be different from persistent non-smokers concerning the accuracy of reporting smoking habits, health consciousness or other health related behaviours. In *paper II,* we found that among the 54 women who reported non-smoking, but had cotinine levels above cut off, 45 women were ever-smokers and 30 women reported being daily smokers the last 3 months prior to pregnancy.

6. Conclusions

We observed a considerable decline in smoking during pregnancy among Norwegian women in the period 1999-2004. The decline was evident in all subgroups, but the magnitude differed, especially in strata of maternal educational level.

Using a subsample of nearly 3,000 women in The Norwegian Mother and Child Cohort Study with maternal plasma cotinine measurements, we found that self-reported tobacco status in pregnancy had a sensitivity of 82% and specificity of 99%. The findings suggest that self-reported smoking status is a valid marker for tobacco exposure in the MoBa cohort.

The birth weight of women born in 1967-1995 was associated with the women's own smoking habits at the end of their first registered pregnancy in 1999-2009, with more daily smokers among women with lower birth weights. The birth weight of men was associated with their partners' smoking habits at the end of their first registered pregnancy in 1999-2009 in the same way. We further found that mothers of smoking women had higher risks of dying from lung cancer and from cardiovascular disease compared to mothers of non-smoking women. The indications of shared smoking environment through generations could have implications for the established association between birth weight and later cardiovascular disease. The findings may add to the discussion of what impact early life factors have for later disease.

Quitting smoking reduced the risk of SGA in second pregnancy. Compared to persistent smokers, the risk of SGA in the second pregnancy was reduced even among women who smoked in two pregnancies, but quit smoking before the end of the second pregnancy. Persistent daily smokers throughout two pregnancies had a higher risk of SGA in second pregnancy than women who smoked daily only in the second pregnancy. Women who smoked throughout both pregnancies and had not experienced SGA in the first pregnancy were not "protected" against SGA in the second pregnancy.

7. Future impliactions

Although a decline in smoking during pregnancy has been documented, some fetuses are still exposed to tobacco smoke. This emphasizes the continued importance of striving for a tobacco-free future, as aimed at by the Norwegian government.[31] Addressing health inequalities should start at the beginning of life.[228]

The first paper, the prevalence study of maternal smoking during pregnancy should warrant greater efforts to make pregnant women stop smoking and to encourage a greater focus on smoking cessation among fertile women. Tobacco control policies have not lead to the same reduction in smoking during pregnancy among all demographic groups. In 2013/2014, ten years after the last period in *paper 1* (2004), 21 % of women with low education smoked daily at the beginning of the pregnancy compared to 2% among women with high education.[55] The tobacco-free future[31] is not yet for all new-borns and efforts on tobacco control should continue.

The second paper infers that the smoking variable can be used in the Norwegian Mother and Child Cohort Study for confounder control for smoking in future studies based on women in the cohort.

The third paper warrants a more cautious attitude in proposing causal associations between birth weight and later disease in adulthood.

The benefits of quitting smoking during pregnancy should be highlighted for every pregnant woman. Although stigma on a societal level could certainly contribute to lower smoking prevalence in the general population, there is a potential for negative consequences for some, making smoking cessation more difficult through loss of self-esteem, guilt and defensiveness.[71] In patient meetings, consideration of lifestyle choices should be discussed with respect and empathy. The addictive nature of nicotine should not be a resting pillow, but should motivate and emphasize for health personnel the importance to support quit attempts among smoking pregnant women.

Norway is a rich country and its citizens as a whole do not face challenges of unclean water, scarcity of food or lack of shelter. However, the social gradient acting throughout the life of a human being, from early childhood, through adolescent health and school performances, through employment and adult health gives rise to inequality in health. The social gradient in health should inspire to a quest for the causes of inequalities as well as policies to enhance healthy lifestyle choices.[228]

With the knowledge gained during the tobacco epidemic in developed countries, the opportunity to avoid the epidemic in low- and middle income countries should be seized. WHO have stated that if countries continue the tobacco control activities at current strength, the decline in smoking prevalence in low- and middle-income countries by 2030 will be slower than in high-income countries. The male smoking prevalence in high-income countries will decline to around 20%, while middle-income countries will have a constant high male smoking prevalence of above 30%. For women the smoking prevalence is predicted to fall below 15% in high–income countries, and remain under 5% in low- and middle-income countries.[2] The end of the tobacco epidemic has not yet been reached. There has been progress in implementing smoke-free legislation worldwide, and by now almost two thirds of the world's population are covered by at least one best-practice-level tobacco control measure. However, in 2016 only 20% of the world's population were covered by laws to protect people from tobacco smoke.[2]

What is the way forward? The need for "tailored approaches" to combat the epidemic in locations with different patterns of tobacco use and understanding what works in different contexts and subgroups have been called upon.[8] With 7 million deaths annually worldwide due to tobacco–related diseases (most due to smoking tobacco[8]), WHO suggest implementing its Framework Convention on Tobacco Control (WHO FCTC) to its completest range as "the world's best chance of reducing this toll".[2]

8. Errata

Paper I; table II, the 95% CI for OR_1 for “Maternal age 25-29” should be (1.02,1.08)

9. Source of data/ References

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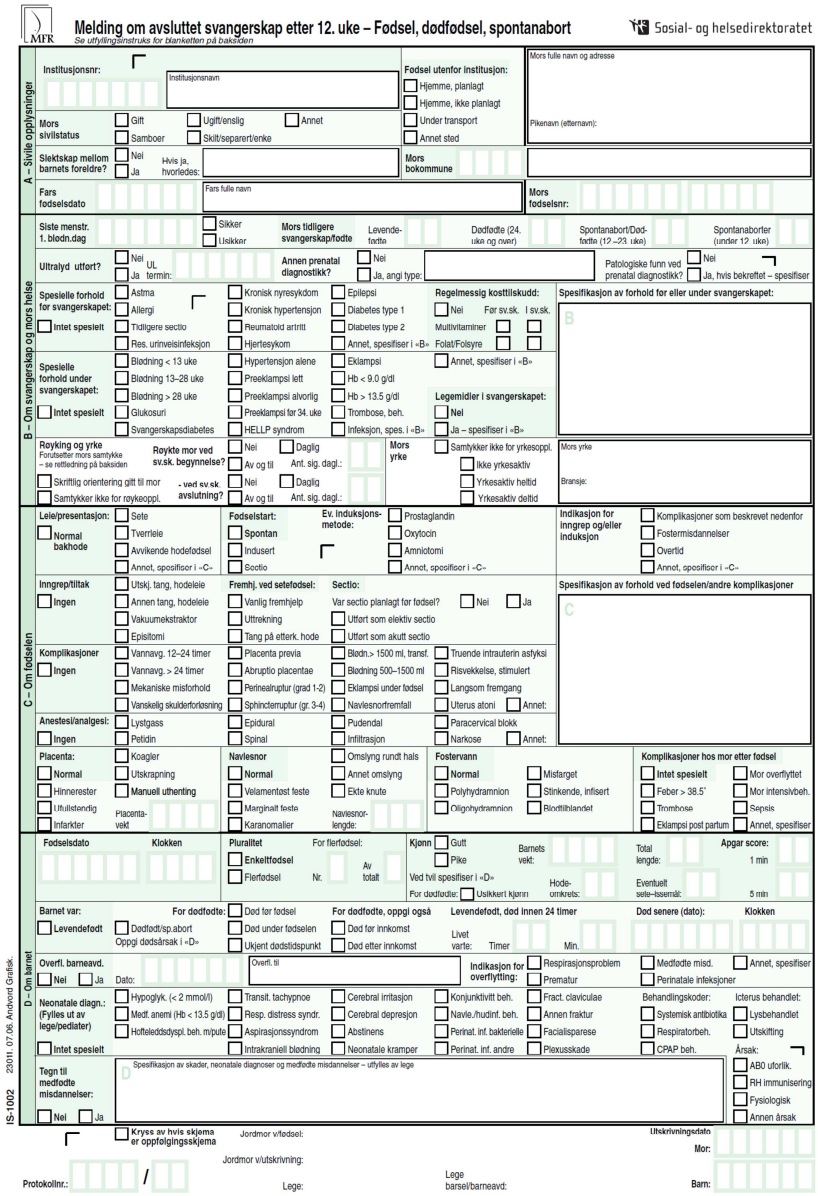
10. Appendix

10.1 Appendix A: *The MBRN notification form*



MFR

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn | Fødsel utenfor institusjon: Hjemme, planlagt / Hjemme, ikke planlagt / Under transport / Annet sted | Mors fulle navn og adresse | Pikenavn (etternavn):

Mors sivilstatus: Gift / Ugift/enslig / Annet / Samboer / Skilt/separert/enke

Slektskap mellom barnets foreldre? Nei / Ja. Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn | Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blodn.dag | Sikker / Usikker | Mors tidligere svangerskap/fødte: Levende-fødte | Dødfødte (24. uke og over) | Spontanabort/Død-fødte (17–23 uke) | Spontanaborter (under 17 uke)

Ultralyd utført? Nei / Ja. UL termin: | Annen prenatal diagnostikk? Nei / Ja, angi type: | Patologiske funn ved prenatal diagnostikk? Nei / Ja, hvis bekreftet – spesifiser

Spesielle forhold for svangerskapet: Intet spesielt | Astma, Allergi, Tidligere sectio, Res. urinveisinfeksjon | Kronisk nyresykdom, Kronisk hypertensjon, Reumatoid artritt, Hjertesykom | Epilepsi, Diabetes type 1, Diabetes type 2, Annet, spesifiser i «B»

Regelmessig kosttilskudd: Nei / Før sv.sk. / I sv.sk. — Multivitaminer, Folat/Folsyre

Spesifikasjon av forhold for eller under svangerskapet: B

Spesielle forhold under svangerskapet: Intet spesielt | Blødning < 13 uke, Blødning 13–28 uke, Blødning > 28 uke, Glukosuri, Svangerskapsdiabetes | Hypertensjon alene, Preeklampsi lett, Preeklampsi alvorlig, Preeklampsi før 34. uke, HELLP syndrom | Eklampsi, Hb < 9.0 g/dl, Hb > 13.5 g/dl, Trombose, beh., Infeksjon, spes. i «B» | Annet, spesifiser i «B»

Legemidler i svangerskapet: Nei / Ja – spesifiser i «B»

Røyking og yrke — Forutsetter mors samtykke – se rettledning på baksiden: Røykte mor ved sv.sk. begynnelse? Nei / Daglig / Av og til, Ant. sig. dagl.: — Skriftlig orientering gitt til mor / Samtykker ikke for røykeoppl. — ved sv.sk. avslutning? Nei / Daglig / Av og til, Ant. sig. dagl.:

Mors yrke: Samtykker ikke for yrkesoppl. / Ikke yrkesaktiv / Yrkesaktiv heltid / Yrkesaktiv deltid

Mors yrke | Bransje:

C – Om fødselen

Leie/presentasjon: Sete, Tverrleie, Avvikende hodefødsel, Annet, spesifiser i «C»

Fødselstart: Spontan / Indusert / Sectio

Ev. induksjons-metode: Prostaglandin, Oxytocin, Amniotomi, Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon: Komplikasjoner som beskrevet nedenfor, Fostermisdannelser, Overtid, Annet, spesifiser i «C»

Inngrep/tiltak: Ingen | Utskj. tang, hodeleie, Annen tang, hodeleie, Vakuumekstraktor, Episiotomi | Fremhj. ved setefødsel: Vanlig fremhjelp, Utrekning, Tang på etterk. hode | Sectio: Var sectio planlagt før fødsel? Nei / Ja. Utført som elektiv sectio, Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner: C

Komplikasjoner: Ingen | Vannavg. 12–24 timer, Vannavg. > 24 timer, Mekaniske misforhold, Vanskelig skulderforløsning | Placenta previa, Abruptio placentae, Perinealruptur (grad 1-2), Sphincterruptur (gr. 3-4) | Blødn.> 1500 ml, transf., Blødning 500–1500 ml, Eklampsi under fødsel, Navlesnorfremfall | Truende intrauterin asfyksi, Risvekkelse, stimulert, Langsom fremgang, Uterus atoni, Annet:

Anestesi/analgesi: Ingen | Lystgass, Petidin | Epidural, Spinal | Pudendal, Paracervical blokk, Narkose, Annet:

Placenta: Normal, Hinnerester, Ufullstendig, Infarkter | Koagler, Utskrapning, Manuell uthenting, Placenta-vekt

Navlesnor: Normal, Velamentøst feste, Marginalt feste, Karanomalier | Omslyng rundt hals, Annet omslyng, Ekte knute, Navlesnor-lengde:

Fostervann: Normal, Polyhydramnion, Oligohydramnion | Misfarget, Stinkende, infisert, Blodtilblandet

Komplikasjoner hos mor etter fødsel: Intet spesielt, Feber > 38.5°, Trombose, Eklampsi post partum | Mor overflyttet, Mor intensivbeh., Sepsis, Annet, spesifiser

D – Om barnet

Fødselsdato | Klokken | Pluralitet: Enkeltfødsel / Flerfødsel. For flerfødsel: Nr. Av totalt | Kjønn: Gutt / Pike / Ved tvil spesifiser i «D». For dødfødte: Usikkert kjønn | Barnets vekt: | Hode-omkrets: | Total lengde: | Eventuelt sete–issemål: | Apgar score: 1 min, 5 min

Barnet var: Levendefødt / Dødfødt/sp.abort. Oppgi dødsårsak i «D» | For dødfødte: Død før fødsel, Død under fødselen, Ukjent dødstidspunkt | For dødfødte, oppgi også: Død før innkomst, Død etter innkomst | Levendefødt, død innen 24 timer: Livet varte: Timer Min. | Død senere (dato): | Klokken

Overfl. barneavd. Nei / Ja. Dato: | Overf. til | Indikasjon for overflytting: Respirasjonsproblem, Prematur, Medfødte misd., Perinatale infeksjoner, Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater) Intet spesielt | Hypoglyk. (< 2 mmol/l), Medf. anemi (Hb < 13.5 g/dl), Hofteleddsdyspl. beh. m/pute | Transit. tachypnoe, Resp. distress syndr., Aspirasjonssyndrom, Intrakraniell blødning | Cerebral irritasjon, Cerebral depresjon, Abstinens, Neonatale kramper | Konjunktivitt beh., Navle./hudinf. beh., Perinat. inf. bakterielle, Perinat. inf. andre | Fract. claviculae, Annen fraktur, Facialisparese, Plexusskade | Medfødte misd., Perinatale infeksjoner | Behandlingskoder: Systemisk antibiotika, Respiratorbeh., CPAP beh. | Icterus behandlet: Lysbehandlet, Utskifting | Årsak: AB0 uforlik., RH immunisering, Fysiologisk, Annen årsak

Tegn til medfødte misdannelser: Nei / Ja

D: Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

IS-1002 2301. 07.06. Andvord Grafisk.

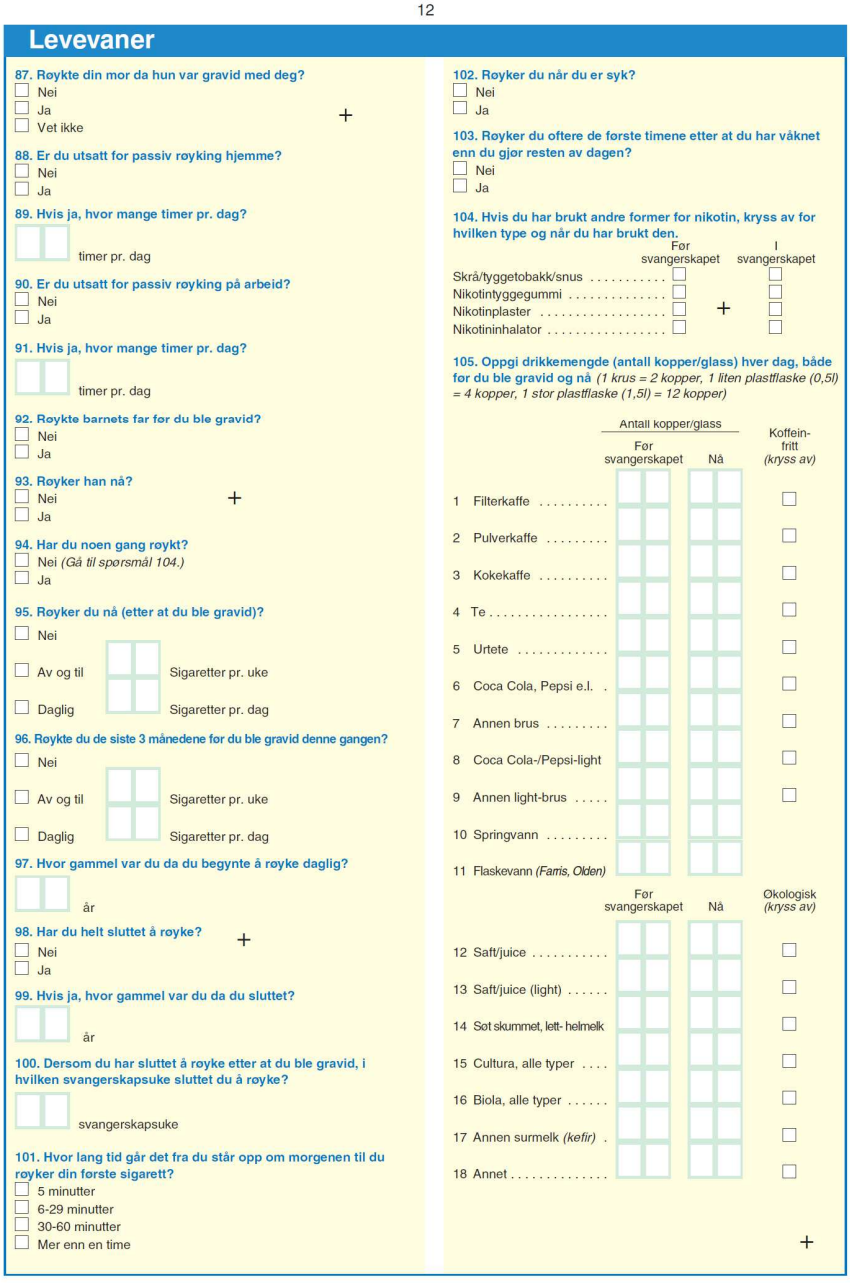
Kryss av hvis skjema er oppfølgingsskjema

Jordmor v/fødsel: | Jordmor v/utskrivning: | Lege: | Lege barsel/barneavd: | Utskrivningsdato Mor: Barn:

Protokollnr.:

10.2 Appendix B: *Questionnaire 1, page 12 from MoBa.*

In Norwegian:



12

Levevaner

87. Røykte din mor da hun var gravid med deg?
☐ Nei
☐ Ja
☐ Vet ikke

88. Er du utsatt for passiv røyking hjemme?
☐ Nei
☐ Ja

89. Hvis ja, hvor mange timer pr. dag?
☐☐ timer pr. dag

90. Er du utsatt for passiv røyking på arbeid?
☐ Nei
☐ Ja

91. Hvis ja, hvor mange timer pr. dag?
☐☐ timer pr. dag

92. Røykte barnets far før du ble gravid?
☐ Nei
☐ Ja

93. Røyker han nå?
☐ Nei
☐ Ja

94. Har du noen gang røykt?
☐ Nei *(Gå til spørsmål 104.)*
☐ Ja

95. Røyker du nå (etter at du ble gravid)?
☐ Nei
☐ Av og til ☐☐ Sigaretter pr. uke
☐ Daglig ☐☐ Sigaretter pr. dag

96. Røykte du de siste 3 månedene før du ble gravid denne gangen?
☐ Nei
☐ Av og til ☐☐ Sigaretter pr. uke
☐ Daglig ☐☐ Sigaretter pr. dag

97. Hvor gammel var du da du begynte å røyke daglig?
☐☐ år

98. Har du helt sluttet å røyke?
☐ Nei
☐ Ja

99. Hvis ja, hvor gammel var du da du sluttet?
☐☐ år

100. Dersom du har sluttet å røyke etter at du ble gravid, i hvilken svangerskapsuke sluttet du å røyke?
☐☐ svangerskapsuke

101. Hvor lang tid går det fra du står opp om morgenen til du røyker din første sigarett?
☐ 5 minutter
☐ 6-29 minutter
☐ 30-60 minutter
☐ Mer enn en time

102. Røyker du når du er syk?
☐ Nei
☐ Ja

103. Røyker du oftere de første timene etter at du har våknet enn du gjør resten av dagen?
☐ Nei
☐ Ja

104. Hvis du har brukt andre former for nikotin, kryss av for hvilken type og når du har brukt den.

	Før svangerskapet	I svangerskapet
Skrå/tyggetobakk/snus	☐	☐
Nikotintyggegummi	☐	☐
Nikotinplaster	☐	☐
Nikotininhalator	☐	☐

105. Oppgi drikkemengde (antall kopper/glass) hver dag, både før du ble gravid og nå *(1 krus = 2 kopper, 1 liten plastflaske (0,5l) = 4 kopper, 1 stor plastflaske (1,5l) = 12 kopper)*

	Antall kopper/glass: Før svangerskapet	Antall kopper/glass: Nå	Koffeinfritt *(kryss av)*
1 Filterkaffe	☐☐	☐☐	☐
2 Pulverkaffe	☐☐	☐☐	☐
3 Kokekaffe	☐☐	☐☐	☐
4 Te	☐☐	☐☐	☐
5 Urtete	☐☐	☐☐	☐
6 Coca Cola, Pepsi e.l.	☐☐	☐☐	☐
7 Annen brus	☐☐	☐☐	☐
8 Coca Cola-/Pepsi-light	☐☐	☐☐	☐
9 Annen light-brus	☐☐	☐☐	☐
10 Springvann	☐☐	☐☐	
11 Flaskevann *(Farris, Olden)*	☐☐	☐☐	

	Før svangerskapet	Nå	Økologisk *(kryss av)*
12 Saft/juice	☐☐	☐☐	☐
13 Saft/juice (light)	☐☐	☐☐	☐
14 Søt skummet, lett- helmelk	☐☐	☐☐	☐
15 Cultura, alle typer	☐☐	☐☐	☐
16 Biola, alle typer	☐☐	☐☐	☐
17 Annen surmelk *(kefir)*	☐☐	☐☐	☐
18 Annet	☐☐	☐☐	☐

English translation:

12

Living habits

87. Did your mother smoke when she was pregnant with you?
☐ No
☐ Yes
☐ Don't Know

88. Are you exposed to passive smoking at home?
☐ No
☐ Yes

89. If yes, how many hours a day are you exposed to passive smoking?
☐☐ hours per day

90. Are you exposed to passive smoking at work?
☐ No
☐ Yes

91. If yes, how many hours a day are you exposed to passive smoking?
☐☐ hours per day

92. Did the baby's father smoke before you became pregnant?
☐ No
☐ Yes

93. Does he smoke now?
☐ No
☐ Yes

94. Have you ever smoked?
☐ No (proceed to question 104)
☐ Yes

95. Do you smoke now (after you became pregnant)?
☐ No
☐ Sometimes ☐☐ cigarettes per week
☐ Daily ☐☐ cigarettes per day

96. Did you smoke during the last 3 months before you became pregnant this time?
☐ No
☐ Sometimes ☐☐ cigarettes per week
☐ Daily ☐☐ cigarettes per day

97. How old were you when you started to smoke on a daily basis?
☐☐ Years

98. Have you stopped smoking completely?
☐ No
☐ Yes

99. If yes, how old were you when you stopped smoking?
☐☐ Years

100. If you stopped smoking after you became pregnant, in which week of pregnancy did you stop?
☐☐ week of pregnancy

101. How long after you get up in the morning until you light your first cigarette?
☐ 5 minutes
☐ 6-29 minutes
☐ 30-60 minutes
☐ More than one hour

102. Do you smoke when you are ill?
☐ No
☐ Yes

103. Do you smoke more often during the first few hours after you wake up than you do during the rest of the day?
☐ No
☐ Yes

104. If you have used other kinds of nicotine indicate which and when you used them.

	Before pregnancy	During pregnancy
Chewing tobacco/snuff	☐	☐
Nicotine chewing gum	☐	☐
Nicotine adhesive patch	☐	☐
Nicotine inhaler	☐	☐

105. What was your fluid consumption (number of cups/glasses) per day before and during pregnancy? (1 mug = 2 cups, 1 small plastic bottle (0.5 litre) = 4 cups, 1 large plastic bottle (1.5 litres) = 12 cups)

	Number of cups/glasses: Before pregnancy	Number of cups/glasses: Now	Decaffeinated (Enter a cross)
1 Filter coffee	☐☐	☐☐	☐
2 Instant coffee	☐☐	☐☐	☐
3 Boiled coffee	☐☐	☐☐	☐
4 Tea	☐☐	☐☐	☐
5 Herbal tea	☐☐	☐☐	☐
6 Coca Cola/Pepsi etc.	☐☐	☐☐	☐
7 Other fizzy drinks	☐☐	☐☐	☐
8 Diet Coca Cola/Pepsi	☐☐	☐☐	☐
9 Other diet fizzy drinks	☐☐	☐☐	☐
10 Tap water	☐☐	☐☐	☐
11 Bottled water	☐☐	☐☐	☐

	Before pregnancy	Now	Ecological (Enter a cross)
12 Juice/squash	☐☐	☐☐	☐
13 Diet juice/squash	☐☐	☐☐	☐
14 Milk (skim, low fat, whole)	☐☐	☐☐	☐
15 Yogurt, all types	☐☐	☐☐	☐
16 Yogurt/active Lactobacillus	☐☐	☐☐	☐
17 Other type of cultured milk - Kefir	☐☐	☐☐	☐
18 Other	☐☐	☐☐	☐

11. Papers I-IV

I

Acta Obstetricia et Gynecologica. 2008; 87: 280–285

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ORIGINAL ARTICLE

Smoking during pregnancy from 1999 to 2004: a study from the Medical Birth Registry of Norway

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Abstract

Background. The aims of the study were to describe changes in smoking habits and evaluate secular trends among all Norwegian pregnant women during the period 1999–2004. We wanted to investigate whether there was a general decline in smoking habits among pregnant women. We also wanted to identify population subgroups with diverging trends. *Methods.* The Medical Birth Registry of Norway (MBR) has national coverage of all births of 16 or more gestational weeks. Since 1999, women have been asked about tobacco smoking at the beginning and at the end of pregnancy. We included records from 304,905 women giving birth in the period January 1999 through April 2004. Women born outside Norway were handled separately. The selection left a dataset containing 259,573 Norwegian-born women. *Results.* We obtained information on smoking habits from 86% at the end of pregnancy. Among those, the daily smoking prevalence was reduced from 17.3% in 1999–2001 to 13.2% in 2002–2004. Higher smoking prevalence was found among multiparous (3+), teenage mothers, single women, and women with low educational level. *Conclusions.* From 1999 to 2004, a substantial decline in smoking prevalence among Norwegian pregnant women was identified in all subgroups. However, an increasing social polarisation with regard to education and smoking habits was observed in the study period. In order to reduce the smoking-related risks for unsuccessful pregnancy outcome, special attention should be paid to smoking habits among multiparous, teenage women, single women and women with low education.

Key words: *Smoking, pregnancy, secular trends, sociodemographic variables*

Abbreviations: *RR: relative risk, CI: confidence intervals, SD: standard deviation*

During the last 10 years, the prevalence of smoking among women has decreased in most developed countries (1). In Norway, a substantial fall in everyday smoking has been documented. In 2006, equal proportions of daily smokers were found among men and women. The smoking prevalence among women aged 16–24, 25–34 and 35–44 was 22, 20 and 28%, respectively (2).

Smoking habits among pregnant women in the Nordic countries have also changed markedly over the last 20 years. In 1987, 34% of Norwegian pregnant women were everyday smokers compared to 22% in 1994 (3). In Sweden, smoking in early pregnancy has declined by 1% annually over the last 20 years, and in 2002 the smoking prevalence was 11% (4). In Denmark, the proportion of smokers at 16 weeks' gestation decreased from 34% in 1989 to 21% in 1996 (5).

The aims of this study were to describe changes in smoking habits and evaluate secular trends among all Norwegian pregnant women during the period 1999–2004. We wanted to investigate whether there was a general decline in smoking habits among pregnant women. We also wanted to identify population subgroups with diverging trends.

Material and methods

We used data from the Medical Birth Registry of Norway (MBR), which has national coverage of all

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(Received 6 June 2007; accepted 30 November 2007)

ISSN 0001-6349 print/ISSN 1600-0412 online © 2008 Taylor & Francis
DOI: 10.1080/00016340701837801

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births after 16 or more gestational weeks. Midwives or physicians complete standardised forms for the MBR, a mandatory procedure that has existed since 1967. The notification form is completed by interviewing the women and using their hospital medical charts. Data from the MBR provide information on the woman's obstetric history, age and marital status.

Since 1999, registration of smoking habits during pregnancy has been included in the standardised notification form and reported to the MBR. Women are asked if they smoked at the beginning and/or at the end of the pregnancy, to which they can answer 'no', 'occasionally' or 'daily', and report the 'number of cigarettes daily' or they can decline to answer. Smoking status was coded as a dichotomous variable with the classification non-smoker or daily smoker. Women who reported smoking occasionally were handled in separate analyses. Information on smoking habits at the beginning and at the end of the pregnancy was available from 226,877 (87%) and 206,491 (80%) women, respectively. Among women who were non-smokers at the beginning of pregnancy, data on smoking habits at the end of pregnancy were missing for 17,918. They were classified as non-smokers also at the end of the pregnancy. Therefore, we recognised information on smoking habits at the end of pregnancy from 224,409 women (86%). By comparing the birth weight of babies of non-smokers, daily smokers and non-responders, we estimated the number of daily smokers in the non-responder group.

We included records from all births in Norway during the years 1999–2003, and for the first 4 months of 2004 ($n = 304{,}905$). We dichotomised the study period into period 1 (1999–2001) and period 2 (2002–2004).

Women born outside Norway were not included in the main analysis and were handled separately. Birthplace outside of Norway was recorded in 40,653 women, and was unknown for 4,679. The selection left a dataset containing 259,573 Norwegian-born women.

Smoking habits in the general population and educational level was retrieved from Statistics Norway. Educational level was categorised into elementary school ($\leq$10 years), high school (11–14 years) and university ($\geq$15 years), according to the highest completed education.

Statistical analyses were carried out with Statistical Package for the Social Sciences (SPSS) 12.0. Multiple logistic regression analysis was performed to estimate the effect of the following variables on smoking habits: period, parity, maternal age, marital status and maternal education level. In order to perform covariate adjustments, odds ratio (OR) were used. The results are presented as relative risks (RR), OR and adjusted OR with 95% confidence intervals (CI). The RR represents changes in smoking prevalence during the study period.

Results

A general trend of decreased smoking prevalence during the study period was observed. Pregnant women were about half as likely as women in the general population to be daily smokers. Daily smoking among the general population decreased from 33% in 1999 to 23% in 2004 (RR = 0.70 (95% CI: 0.67–0.72)), while among pregnant women, a greater decline in smoking prevalence was observed, from 18% in 1999 to 11% in 2004 (RR = 0.61 (95% CI: 0.58–0.64)) (Figure 1).

Based on reported smoking habits, daily smoking at the end of pregnancy was 17.3% in the first period and 13.2% in the second period (Table I). The adjusted OR for parity showed small differences. Maternal age did not seem to affect the adjusted OR, except for the oldest women. Single women had a smaller decline in smoking prevalence during the study period than other categories of marital status. The greatest differences were found among women with different education levels. Women with elementary school only had a 19% reduction in smoking prevalence from the first

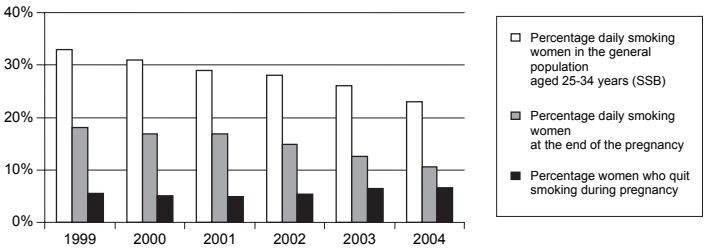

Figure 1. Smoking habits among women in the general population and pregnant women in Norway (1999–2004).

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Table I. Smoking habits during pregnancy from 1999 to 2004 in relation to sociodemographic variables.

	1999–2001		2002–2004							
	n_{total}†	$\%_{smokers}$	n_{total}†	$\%_{smokers}$	RR††	95% CI	OR_1⋆	95% CI	OR_2⋆⋆	95% CI
Parity										
0	52,088	15.3	36,257	11.9	0.78	0.75–0.89	0.75	0.72–0.78	0.74	0.71–0.77
1	46,509	17.0	34,052	12.6	0.74	0.72–0.77	0.71	0.68–0.74	0.75	0.72–0.79
2	22,621	19.8	15,471	14.7	0.74	0.71–0.78	0.70	0.66–0.74	0.73	0.68–0.77
3+	8,520	25.2	5,651	20.9	0.83	0.78–0.88	0.79	0.72–0.85	0.80	0.73–0.87
Maternal age										
<20	3,260	33.0	2,092	29.9	0.90	0.83–0.98	0.87	0.77–0.97	0.74	0.65–0.83
20–24	19,533	24.1	12,804	20.2	0.84	0.80–0.87	0.80	0.75–0.84	0.76	0.72–0.81
25–29	46,917	15.7	30,874	11.4	0.73	0.70–0.76	0.70	0.67–0.73	0.73	0.70–0.76
30–34	41,935	15.2	31,452	10.8	0.71	0.69–0.74	0.68	0.65–0.71	0.72	0.68–0.75
35+	18,093	16.5	14,209	13.6	0.82	0.78–0.87	0.79	0.75–0.84	0.84	0.78–0.89
Marital status										
Married	61,715	10.7	41,485	7.6	0.70	0.68–0.73	0.68	0.65–0.71	0.75	0.72–0.79
Cohabitant	58,166	20.8	44,017	15.5	0.75	0.73–0.77	0.70	0.68–0.72	0.73	0.70–0.75
Single	8,807	38.4	5,146	36.6	0.96	0.91–1.00	0.93	0.87–1.00	0.86	0.79–0.92
Other	1,050	35.1	783	27.3	0.78	0.68–0.90	0.69	0.57–0.85	0.74	0.60–0.92
Maternal education level‡										
Elementary school	34,095	35.1	20,683	31.1	0.89	0.87–0.91	0.84	0.81–0.87	0.81	0.78–0.84
High school	43,265	17.3	30,363	13.8	0.79	0.77–0.82	0.76	0.73–0.79	0.75	0.72–0.78
University	52,115	5.6	40,188	3.5	0.62	0.58–0.66	0.61	0.57–0.65	0.60	0.56–0.64
Total	129,738	17.3	91,431	13.2	0.76	0.75–0.78				

†n_{total} represents Norwegian women with registered smoking habits.
††Relative risk represents changes from period 1 to period 2.
⋆Odd ratio with period as independent variable.
⋆⋆Odds ratio with period and all other factors in the table as independent variables.
‡Among 581 women with unknown education level, 263 had registered smoking habits in 1999–2001, and 134 smoked daily. In 2002–2004, 197 had registered smoking habits, and 74 smoked daily.

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period to the second period, while university-educated women had a 40% reduction.

Sociodemographic variables and daily smoking at the end of pregnancy are presented in Table II. The daily smoking prevalence at the end of pregnancy increased with parity. Women with 3 or more previous births had almost twice the smoking prevalence of nulliparous. Smoking prevalence decreased with maternal age, except for women aged 35 years or more. Single women had about 4 times the smoking prevalence of married women. Women with elementary school only had about 8 times the smoking prevalence of university-educated women.

The OR for smoking at the end of pregnancy, adjusted for period and sociodemographic variables, increased with parity, while maternal age did not affect the risk for smoking when adjusted for other variables. Adjusted OR also established education as most influential for smoking during pregnancy.

More daily smokers quit smoking during pregnancy in the second period (31.8%) compared to the first period (23.4%) (Table III). Quitting smoking was defined as being daily smoker at the beginning of the pregnancy and non-smoker at the end of the pregnancy. Among those who remained daily smokers, cigarette consumption was constant during the study period (7.4 cigarettes per day). Cigarette consumption increased with rising maternal age and parity, and fell with maternal education level.

Occasional smoking was reported by 3,240 (1.7%) at the end of pregnancy. The prevalence of occasional smokers at the end of pregnancy decreased from 1.9% in the first period to 1.4% in the second period. Women with elementary school only had a higher prevalence of occasional smoking at the end of pregnancy compared to university-educated women.

For women born outside Norway ($n = 40{,}653$), we had information on smoking habits from 82%. These women had half the smoking prevalence of Norwegian-born women. Women aged 19 years or younger and single women had a higher proportion of smokers. Parity and education did not have as strong effect on smoking habits as for Norwegian-born mothers. In addition, among these women, smoking prevalence was reduced during the study period.

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Table II. Daily smoking at the end of pregnancy by sociodemographic variables ($n = 259{,}573$).

	n_{total}	Daily smokers (%)	OR_1†	95% CI	OR_2‡	95% CI
Parity						
0	104,333	13.9	1.00	Reference	1.00	Reference
1	94,227	15.2	1.11	1.08–1.14	1.33	1.29–1.37
2	44,363	17.8	1.34	1.29–1.38	1.64	1.58–1.71
3+	16,650	23.5	1.90	1.82–1.99	1.98	1.88–2.09
Maternal age						
<20	6,389	31.8	3.01	2.83–3.20	0.93	0.87–1.00
20–24	38,103	22.6	1.88	1.82–1.95	1.11	1.06–1.15
25–29	90,590	14.0	1.05	1.02–1.95	0.99	0.96–1.02
30–34	86,213	13.3	1.00	Reference	1.00	Reference
35+	38,278	15.2	1.17	1.13–1.22	0.98	0.94–1.02
Marital status						
Married	119,778	9.5	1.00	Reference	1.00	Reference
Cohabitant	120,201	18.6	2.21	2.15–2.27	2.06	2.01–2.13
Single	17,247	37.7	5.78	5.55–6.01	4.31	4.12–4.52
Other	2,347	31.8	4.53	4.09–5.01	3.17	2.84–3.53
Maternal education level*						
Elementary school	65,390	33.6	10.27	9.91–10.64	7.85	7.57–8.15
High school	85,965	15.9	3.85	3.72–4.00	3.34	3.22–3.47
University	107,637	4.9	1.00	Reference	1.00	Reference

†OR_1, Odds ratio with periods 1999–2001 and 2002–2004 as independent variables.
‡OR_2, Odds ratio with period and all other factors in the table as independent variables.
*Some 581 women had unknown education level.

Table III. Women reporting quitting smoking during pregnancy in relation to sociodemographic factors.

	Quitters 1999–2001		Quitters 2002–2004			
	$n_{smokers}$†	$\%_{quitters}$	$n_{smokers}$†	$\%_{quitters}$	RR	95% CI
Parity						
0	11,495	32.9	7,246	41.9	1.27	1.23–1.32
1	9,480	19.5	5,839	28.1	1.44	1.36–1.53
2	5,156	15.2	2,865	22.1	1.45	1.32–1.59
3+	2,354	10.8	1,356	14.5	1.34	1.13–1.59
Maternal age						
<20	1,502	29.8	946	35.3	1.18	1.05–1.33
20–24	6,210	26.2	3,863	34.8	1.33	1.25–1.41
25–29	9,432	24.7	5,277	34.4	1.39	1.32–1.47
30–34	7,823	21.3	4,727	29.7	1.40	1.31–1.49
35+	3,518	17.0	2,493	24.1	1.42	1.28–1.57
Marital status						
Married	8,203	22.2	4,453	31.6	1.42	1.34–1.51
Cohabitant	15,756	25.3	10,094	33.7	1.33	1.28–1.38
Single	4,109	19.4	2,477	25.3	1.31	1.19–1.43
Other	417	14.9	282	25.2	1.69	1.25–2.30
Maternal education level‡						
Elementary school	14,059	16.9	8,299	23.8	1.40	1.33–1.48
High school	9,913	26.6	6,313	35.5	1.33	1.27–1.40
University	4,372	37.4	2,606	48.7	1.31	1.23–1.38
Total	28,485	23.4	17,306	31.8	1.36	1.32–1.40

†Daily smokers at the beginning of the pregnancy.
‡Among women with unknown education level, 141 were daily smokers at the beginning of the pregnancy, and 8 quit smoking during pregnancy in 1999–2001. In 2002–2004, 88 women were daily smokers at the beginning of the pregnancy, and 15 quit smoking during pregnancy.

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The proportion of non-responders concerning smoking habits increased from 11.1 to 13.3% during the study period. There was no obvious trend in age, parity, marital status or education among the non-responders. Regional differences showed that Oslo and Finnmark had the highest proportion of non-responders (28.2 and 19.4%, respectively). The mean proportion of non-responders among all institutions was 12.0%.

The mean birth weight was 3,566 g (SD = 649 g). The birth weight of babies of non-smoking mothers, daily smokers (at the end of the pregnancy) or non-responders was 3,618 (624) g, 3,389 (630) g and 3,504 (719) g, respectively. Thus, babies of non-responders had a 114 g lower birth weight compared to babies of non-smokers, while smokers reduced the birth weight by 229 g. If this reduction is due to smoking, we estimated half of the non-responders to be daily smokers at the end of pregnancy. Adding these women to those with reported smoking habits gave a smoking prevalence of 20.2% in the first period and 17.9% in the second period. The estimated proportion of smokers among non-responders did not increase during the study period when comparing the birth weights of daily smokers and non-smokers.

On a national basis, large differences in smoking prevalence appeared. The county furthest north, Finnmark, had the highest reported proportion of smokers (24.3%) at the end of pregnancy. Oslo had the lowest reported proportion of smokers (9.0%) at the end of pregnancy. Including estimated smoking habits from non-responders, smoking prevalence at the end of pregnancy was 28.9% in Finnmark and 18.9% in Oslo.

Discussion

During the period 1999–2004, a substantial decline in smoking prevalence among Norwegian pregnant women was identified in all subgroups. During the 6-year study, a 24% decline in daily smoking at the end of pregnancy was observed. This is less than the percentage found in previous studies from Norway (35%) and Denmark (38%) (3,5).

The smoking prevalence increased with parity, and nulliparous quit smoking three times more often than multiparous (3+). Multiparous women who have smoked through earlier pregnancies without having experienced severe consequences may have a more relaxed attitude to smoking during pregnancy.

One-third of teenage mothers smoked daily at the end of pregnancy. In 1994/1995, a Norwegian study found a 46% smoking prevalence among women in the same age group (6). Similarly, studies carried out in Denmark and Finland found high proportion of smokers among young pregnant women (5,7). Single women had a four times higher smoking prevalence than married women. This is in accordance with findings from Finland (7).

The adjusted OR for smoking at the end of pregnancy established maternal education level as the strongest indicator for smoking at the end of the pregnancy (OR = 7.9). This is consistent with other studies (6,8). In 1994/1995, elementary school educated women had 5 times higher smoking prevalence compared to women with a university degree (6). It seems as though there is increasing social polarisation associated with smoking. While parity and marital status played a certain role, maternal age was not a decisive variable for smoking prevalence when adjusted for other variables.

Young age and high education are mutually exclusive. However, low education is associated with higher prevalence of daily smoking in all age groups. In our study, education data was last updated in 2002. Since it is uncertain which education level young women will achieve later in life, the education variable is incomplete.

From 1999 to 2001, about a quarter of the women quit smoking during pregnancy, compared to one-third during 2002–2004. In 1994/1995, 38% of pregnant women quit smoking during pregnancy (6). Women who continue to smoke during pregnancy are as aware of the health risks as non-smokers (9). Therefore, they might be more addicted to smoking, representing a 'hard core' of smokers. In an American study, more than half of the pregnant smokers met the criteria for nicotine dependence. The study suggested a strong association between mental disorders and nicotine dependence among pregnant smokers (10).

Among daily smokers, cigarette consumption was stable during the study period (7.4 cigarettes per day). In a previous Norwegian study, the mean cigarette consumption decreased from 8.6 cigarettes in 1987 to 7.0 cigarettes per day in 1994 (3). Cigarette consumption rose with parity and maternal age. Similarly, Wisborg et al. found a constant ratio between pregnant women who smoked lightly and heavily during the period 1989–1996 (5).

Occasional smoking was more frequent among women with low education compared to university-educated women. This is in contrast to the general population, where occasional smokers are more frequently highly educated (11).

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The study population comprises all Norwegian childbearing women during the period. The large study size carries small risk of selection bias. However, for 31,199 (12%) women, no smoking habits at the beginning or at the end of the pregnancy were registered. The stigma associated with smoking during pregnancy might reduce the reliance of self-reported smoking habits. Although several factors influence birth weight, smoking has been described as the most important single factor for reduced birth weight (12,13). Non-responders had babies with a 114 g lower birth weight than babies of non-smokers. If smoking is the most likely explanation for this reduction, our estimation changed the daily smoking prevalence at the end of pregnancy in period 2 from 13.2 to 18.5%.

Daily smoking was more prevalent in Finnmark (the most northern county), a rural part of Norway with a large area and low population. Smoking was least prevalent in Oslo, where more women have a university education, which might explain a lower smoking prevalence. On the other hand, Oslo also had the highest rates of non-responders.

Conclusion

Despite the decline presented, reducing smoking among pregnant women remains a challenge. Efforts are needed to further reduce the number of pregnant women smoking. Doctors and midwives should pay special attention to smoking during pregnancy among multiparous, teenage women, single women and women with low education. The suggested role of smoking habits of pregnant women with mental disorders (10) should be elaborated in order to obtain a further reduction in smoking habits during pregnancy.

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II

III


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50 doi: 10.1111/ppe.12164

Can 'Early Programming' Be Partly Explained by Smoking? Results from a Prospective, Population-Based Cohort Study

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Abstract

Background: Numerous studies have focused the association between low birthweight and later disease. Our objective was to study the association between birthweight and later adult smoking and thereby explore a possible mechanism for the association between low birthweight and later adult disease.

Methods: We studied associations between birthweight of women ($n = 247\,704$) born in 1967–1995 and smoking habits at the end of their pregnancy 13–42 years later in a prospective, population-based cohort study from The Medical Birth Registry of Norway. Similarly, the association between birthweight of men ($n = 194\,393$) and smoking habits of their partners were assessed. Finally, we studied the relation between smoking habits of the participating women and the cause specific death of their mothers ($n = 222\,808$).

Results: Twenty per cent of women with birthweight less than 2000 g were adult daily smokers compared with 11% with birthweight 4000–4499 g [relative risk = 1.8, 95% confidence interval 1.4, 2.2]. Similarly, we found an association between men's birthweight and their partners smoking habits. Mothers of smoking women had doubled risk of dying from lung cancer and from cardiovascular disease compared with mothers of non-smoking women.

Conclusions: Being born with low birthweight is associated with smoking in adulthood. Associations of adult smoking with partners' birthweight and mothers' smoking-related causes of death suggest a shared smoking environment, and may account for some of the established association between birthweight and later cardiovascular disease.

Keywords: *birthweight, fetal origin of adult disease hypothesis, maternal smoking, mortality, pregnancy, tobacco smoking.*

It has been proposed that undernutrition during pregnancy can lead to cardiovascular disease in adult life through early programming.[1] Numerous studies have focused the association between factors in early life, like low birthweight, and later disease.[2–5] The findings of associations between early life environment and later health and disease have evolved into the Developmental Origins of Health and Disease approach.[6]

The relation between low birthweight and adult cardiovascular disease may also be explained by common genetic and/or environmental factors related both to low birthweight and adult cardiovascular disease. Several environmental factors, including smoking, may act in addition to or instead of early programming. Smoking is well known to increase the risk of both low birthweight[7] and cardiovascular disease[8–10] and is, at least in recent decades, closely related to socioeconomic level.[7,10] Although studies claim that the association between low birthweight and adult cardiovascular disease persists even after adjusting for socioeconomic variables, residual confounding cannot be excluded.[2–5,11–13]

The aim of this study was to examine whether women born with low birthweight more often smoke as adults compared with women born with higher birthweights. To examine whether men born with low birthweight more often live in a smoking environment as adults, we also studied their partners' smoking habits in their pregnancies. Since partners often share smoking habits,[14] this would be an indication that also men born with low birthweight are likely to smoke as adults. Finally, we explored the possibility of smoking as a shared environmental exposure across generations, through the relation between

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women's smoking habits and their mothers' cause specific mortality.

We studied birth characteristics of women and men born from 1967 to 1995 who later were registered in The Medical Birth Registry of Norway (MBRN) as mothers and fathers in 1999–2009, when we had information on maternal smoking habits during pregnancy.

Methods

We used data from the MBRN, a population based-registry that has received compulsory notification of all births from at least 16 gestational weeks since 1967.[15] The notification form contains information on demographic variables, the mothers' health before and during pregnancy, complications during pregnancy and delivery, and pregnancy outcomes, as well as mothers', fathers' and infants' national identification numbers. These numbers allow linkage of mother–father–child units in generational data files. Women's smoking habits at the beginning and end of pregnancy have been registered since 1999. We chose to focus on smoking at the end of pregnancy since these women are more likely to stay lifelong smokers.[16] Smoking was dichotomised as non-smoking and daily smoking.

We included 293 237 singleton women born 1967–1995 and linked them to their first registered birth from 1999 to 2009. Women who were registered in the MBRN with more than one infant in this period were thus only counted once. We excluded 29 168 (9.9%) women with missing smoking habits and 3837 (1.3%) occasional smokers as well as women with missing birthweight ($n = 306$), birthweight less than 500 g or more than 6000 g ($n = 6$) and 11 918 (4.1%) women with missing gestational age. Gestational age was based on the first day of the last menstrual period and ranged from 13 to 48 weeks. To avoid mixing reduced birthweight due to growth restriction with that due to preterm delivery, we focused on women born at term (≥37 weeks) when studying absolute birthweight. Smoking has been shown to affect fetal growth in weight primarily in the third trimester of pregnancy.[17]

Z-scores for birthweight by gestational age were computed by applying Norwegian standards for birthweight by sex and gestational age.[18] We excluded absolute z-score values of 5 or more ($n = 298$) as misclassified gestational age. For z-score analyses, the remaining values were categorised into nine groups: from –4.9 to 4.99 as shown in Tables 1 and 2, with 0.50–1.49 as the reference group. A total of 247 704 singleton born women and 238 488 singleton term born women were thus the final study populations for birthweight z-score analyses and absolute birthweight analyses, respectively.

Table 1. Relative risks for women's daily smoking status at the end of pregnancy by their own birthweight by gestational age z-score among 247 704 singleton born women (both term and preterm), delivered in 1967–1995 and followed to their own pregnancy between 1999 and 2009 in Norway

Women's birthweight z-score	Total	Daily smoking by the end of pregnancy		Unadjusted model		Adjusted model[a]	
	No.	No.	%	RR	[95% CI]	RR	[95% CI]
–4.9, –3.51	214	50	23.4	2.02	[1.58, 2.57]	1.81	[1.42, 2.31]
–3.5, –2.51	2013	398	19.8	1.71	[1.56, 1.87]	1.61	[1.47, 1.76]
–2.5, –1.51	17 001	2970	17.5	1.51	[1.45, 1.57]	1.43	[1.37, 1.49]
–1.5, –0.51	69 785	10 102	14.5	1.25	[1.21, 1.29]	1.23	[1.19, 1.27]
–0.5, 0.49	94 669	12 046	12.7	1.10	[1.07, 1.13]	1.10	[1.07, 1.14]
0.5, 1.49	49 234	5702	11.6	1.00	Reference	1.00	Reference
1.5, 2.49	12 247	1 396	11.4	0.98	[0.93, 1.04]	0.96	[0.91, 1.02]
2.5, 3.49	2082	253	12.2	1.05	[0.93, 1.18]	0.99	[0.88, 1.11]
3.5, 4.99	459	64	13.9	1.20	[0.96, 1.51]	1.09	[0.86, 1.37]
Total	247 704	32 981	13.3				

[a]Adjusted for the women's mothers' education (low: <11 years, medium 11–14 years, high (reference): >14 years) and women's birth order (first born (reference), second born, third born, fourth or later born) and women's year of birth (1967–1976 (reference), 1977–1986, 1987–1995).

CI, confidence interval; RR, relative risk.

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Table 2. Relative risks for men having a smoking partner at the end of her pregnancy by the men's birthweight z-score among 194 393 singleton men delivered in 1967–1994 and followed to their partners' pregnancy between 1999 and 2009 in Norway

Men's birthweight z-score	Total	Partners daily smoking by the end of pregnancy		Unadjusted model	
	No.	No.	%	RR	[95% CI]
–4.9, –3.51	126	21	16.7	1.38	[0.94, 2.05]
–3.5, –2.51	966	158	16.4	1.36	[1.18, 1.57]
–2.5, –1.51	7428	1179	15.9	1.32	[1.25, 1.40]
–1.5, –0.51	38 117	5427	14.2	1.18	[1.14, 1.22]
–0.5, 0.49	73 434	9543	13.0	1.08	[1.05, 1.11]
0.5, 1.49	52 820	6359	12.0	1.00	Reference
1.5, 2.49	17 441	2063	11.8	0.98	[0.94, 1.03]
2.5, 3.49	3417	416	12.2	1.01	[0.92, 1.11]
3.5, 4.99	644	89	13.8	1.15	[0.95, 1.39]
Total	194 393	25 255	13.0		

CI, confidence interval; RR, relative risk.

The women's and their mothers' highest achieved educational level was obtained from Statistics Norway in 2009. Education was divided in three levels, low (<11 years), medium (11–14 years) and high (college or university level: >14 years). There was missing information on education for 348 (0.14%) of the women and 907 (0.37%) of their mothers.

Our data also contained information on men born 1967–1994. We linked a total of 228 163 singleton born men to their first registered infant delivered in 1999–2009 to study the relation between the men's birthweights and their partners' smoking habits at the end of their pregnancies. We excluded 21 623 (9.5%) men whose partners had missing smoking habits and 2889 (1.4%) whose partners were occasional smokers. We further excluded men with missing birthweight ($n = 259$), birthweight more than 6000 g ($n = 4$) (none had birthweight less than 500 g) and missing gestational age ($n = 8736$; 3.8%), as well as 259 men whose birthweight by gestational age z-scores were 5 or more (absolute values). The final study populations were 194 393 singleton born men for birthweight z-score analyses, and 186 039 singleton, term born men for absolute birthweight analyses.

Our primary objective was to investigate the association between birthweight and later adult smoking. To examine if women's smoking was related to the smoking habits of their mothers, we looked at the association between women's smoking habits in pregnancy and smoking-related deaths in their mothers. We had information on cause-specific death of mothers to 222 808 women whose smoking habits at the end of pregnancy were registered. A secondary objective was therefore to study the cause-specific mortality among these mothers in relation to the smoking habits of their daughters, for deaths occurring at least 1 year after delivery. Data on cause of death were retrieved from the national Cause of Death Registry from 1969 until December 2009. Detailed description of this linkage has recently been published.[19] The study was approved by the regional ethics committee, REK VEST (2009/1868) and by the internal review board of the MBRN.

Statistical analyses

Analyses were carried out using STATA, version 12.1 (StataCorp, College Station, TX, USA) and IBM SPSS Statistics for Windows version 20 (IBM Corp., Armonk, NY, USA). Relative risks (RR) with 95% confidence intervals (CI) and *P*-values where calculated by using generalised linear models for the binominal family in STATA. Our data material consists of generations, and this warrants a restrictive attitude regarding adjustment for conventional confounding variables. We chose to adjust for the women's mothers' education as well as the women's year of birth and birth order, as these variables could be potential common causes for both the women's birthweight as well as the women's own smoking habits. Mothers who themselves where first born have been shown to smoke less than mothers who were later born.[20]

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We used Cox proportional hazards model in STATA to study the hazard ratios for women's mothers' death in strata of the women's smoking habits at the end of pregnancy. The proportionality assumption was verified by a log-log survival plot. We used the mothers' age as the underlying time variable with mothers entering follow-up at their daughters' year of birth. Outcomes were death from any causes, cardiovascular death (International Classification of Diseases (ICD) version 8 and 9: 410–414, 430–438; ICD-10: I20-I25, G45, I60-I65, I67, I69), death from lung cancer (ICD-8 and ICD-9: 162; ICD-10: C33-34) and death from all others causes combined. We adjusted for the mothers' education as a possible confounder.

Results

Among our study population of 247 704 singleton born women, 32 981 (13%) smoked daily at the end of their pregnancy. A comparison of the population of non-smoking and daily smoking women is provided in Table 3. Daily smoking women were more likely to be young, multiparous, less educated and more likely to be of higher birth order. The daily smoking prevalence decreased during the study period from 17% in 1999–2003 to 9.5% in 2004–2009. Women whose mothers were less educated were more often smokers.

Figure 1a shows smoking habits at the end of pregnancy by birthweight of singleton, term born women. Women born with birthweight less than 2000 g had a 75% higher risk of smoking daily at the end of their pregnancies than women whose birthweight was 4000–4499 g [RR = 1.8, 95% CI 1.4, 2.2]. There was a statistically significant trend between women's decreasing birthweight and increasing prevalence of adult smoking ($P < 0.001$).

Similarly, Figure 1b shows the relation between birthweight of singleton, term born men and smoking habits of their partners at the end of their pregnancies.

Table 3. Daily smoking at the end of pregnancy (13%) by various characteristics for 247 704 women born[a] in 1967–1995 and followed to their own year of delivery between 1999 and 2009 in Norway

	Non-smoking women		Daily smoking women		Total
Characteristic	No.	%	No.	%	No.
Total	214 723	87	32 981	13	247 704
Women's year of birth					
1967–1976	136 408	87	20 223	13	156 631
1977–1986	73 320	87	11 341	13	84 661
1987–1995	4995	78	1417	22	6412
Women's year of delivery					
1999–2003	109 125	83	21 845	17	130 970
2004–2009	105 598	90	11 136	9.5	116 734
Women's birth order					
First born	89 602	88	12 601	12	102 203
Second born	72 571	87	10 992	13	83 563
Third or later born	52 091	85	9300	15	61 391
Parity					
0	145 332	89	17 849	11	163 181
1	48 375	84	9446	16	57 821
2+	21 016	79	5686	21	26 702
Women's education					
Low (<11 years)	25 119	65	13 372	35	38 491
Middle (11–14 years)	76 494	84	14 745	16	91 239
High (>14 years)	112 903	96	4723	4.0	117 626
Women's mothers' education					
Low (<11 years)	57 962	80	14 875	20	72 837
Middle (11–14 years)	112 694	88	15 119	12	127 813
High (>14 years)	43 357	94	2790	6.1	46 147

[a]The women's birth order and education and the women's mothers' education were missing for 547, 348 and 907 individuals, respectively.

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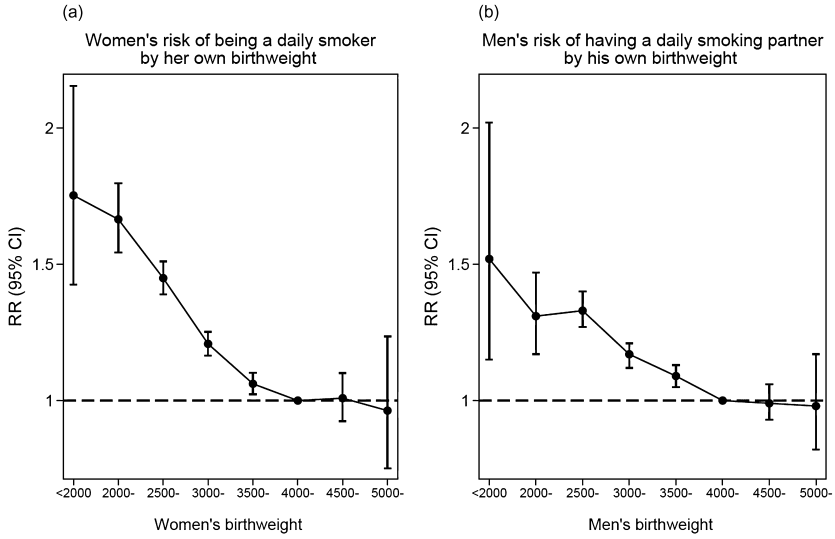

Figure 1. Relative risk (RR) of smoking status at the end of pregnancy by women's own birthweight among 238 488 term, singleton women (a) and among partners to 186 039 term, singleton men by the men's birthweight (b). Shown for women and men delivered in 1967–1995 and followed to the delivery of their own children from 1999 until 2009.

Men born at term with birthweight less than 2000 g had a 1.5 RR [95% CI 1.2, 2.0] of having a partner who smoked daily at the end of her pregnancy, compared with men whose birthweight was 4000–4499 g. There was a statistically significant trend between men's decreasing birthweight and increasing prevalence of adult smoking among partners ($P < 0.001$).

Daily smoking among pregnant women has decreased during the last decades.[21] We therefore repeated the analyses in two consecutive periods. During the first 5-year period (1999–2003), the RR of daily smoking was 1.6 [95% CI 1.2, 2.0] for women born at term with birthweight <2000 vs. 4000–4499 g, while in the last 6-year period (2004–2009), the corresponding RR was 2.0 [95% CI 1.4, 2.9].

Including preterm women, Table 1 shows the percentage of daily smoking at the end of pregnancy by women's own birthweight by gestational age z-scores. Among women in the lowest z-score category (–4.9 to –3.51), 23% were daily smokers as adults, compared with 12% of women in the reference category [z = 0.5 –1.49; RR = 2.0, 95% CI 1.6, 2.6]. Adjusting for the education of the women's mothers as well as the women's birth order and the women's year of birth slightly attenuated the results but did not change the pattern. Including women who reported daily smoking at the beginning of the pregnancy gave similar but weaker RR estimates.

The education level of the women's mothers did not seem to modify the results: In the highest level of mothers' education, women with birthweight z-scores –2 or less had a 1.41 RR [95% CI 0.96, 2.05] of being daily smokers as adults compared with women with z-score 0 or higher. In the lowest level of mothers' education, the corresponding RR was 1.5 [95% CI 1.3, 1.6]. However, the education level for the women and their mothers was associated with the women's smoking habits at the end of pregnancy. Even when women themselves had high education, their mothers' education level was associated with her smoking habits: Among women with high education, the proportions who smoked daily at the end of pregnancy was 2.8% and 6.1% when their mothers had high and low education, respectively, while the corresponding proportions among women with low education were 25% and 38%.

The relation between men's birthweight z-scores and smoking habits of their partners at the end of pregnancy is presented in Table 2. Among men in the lowest z-score category, 17% had a daily smoking partner, compared with 12% of men in the reference z-score category [RR = 1.4, 95% CI 0.9, 2.1].

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Table 4. Hazard ratios for death of mothers by comparing mothers who had smoking daughters to mothers with non-smoking daughters (reference) among 222 808 mothers followed from 1967–2009

	Women's smoking habits by the end of pregnancy									
	Non-smoking women			Daily smoking women						
	Maternal deaths		Total	Maternal deaths		Total	Unadjusted model		Adjusted model[a]	
Mothers' cause of death	No.	%	No.	No.	%	No.	HR	[95% CI]	HR	[95% CI]
Death from any causes	11 073	5.8	191 836	2617	8.5	30 972	1.7	[1.6, 1.7]	1.5	[1.4, 1.6]
Cardiovascular death	1453	0.76	191 836	423	1.4	30 972	2.1	[1.9, 2.3]	1.8	[1.6, 2.0]
Death from lung cancer	990	0.52	191 836	321	1.0	30 972	2.3	[2.1, 2.7]	2.0	[1.7, 2.2]
Death from all other causes combined	8647	4.5	191 836	1881	6.1	30 972	1.5	[1.5, 1.6]	1.4	[1.3, 1.5]

[a]Adjusted for the women's mothers' education (low <11 years, medium 11–14 years, high (reference) >14 years).
CI, confidence interval; HR, hazard ratio.

We observed a statistically significant trend between birthweight z-scores and adult smoking habits for women and between birthweight z-scores and partners' adult smoking habits for men ($P < 0.001$). The correlation between women's and men's birthweight was low and could not explain this similarity [Pearson correlation coefficient 0.023, 95% CI 0.018, 0.027]. Among singleton men born at term with low birthweight the RR of having a partner who also was born singleton, at term with low rather than high birthweight was 1.2 [95% CI 0.9, 1.7]. When excluding partners with birthweight less than 2500 g, the relation between men's birthweight and partners' smoking habits remained similar.

Finally, we looked at cause-specific death among 222 808 of the women's mothers in strata of the women's smoking habits at the end of their pregnancies (Table 4). For lung cancer, cardiovascular, total death and death from all other causes combined, the respective hazard ratios of cause specific death were 2.3 [95% CI 2.1, 2.7], 2.1 [95% CI 1.9, 2.3], 1.7 [95% CI 1.6, 1.7] and 1.5 [95% CI 1.5, 1.6] if the women were daily smokers rather than non-smokers at the end of pregnancies. Adjusting for the mothers' education slightly weakened the results. When dividing the period into 1999–2003 and 2004–2009, the hazard ratio estimates for all four cause-of-death categories increased from the first to the second period but CIs were overlapping.

Comment

In this cohort study, we have shown that women who were born at term with a low birthweight are more often smokers at the end of their pregnancies than women with higher birthweights. The same was true for growth restricted women at all gestational ages. Similar associations were found between men's birthweight and their partners' smoking habits in their pregnancies. Further, mothers whose daughters smoked throughout pregnancy had approximately twice the risk of dying from both lung cancer and cardiovascular disease compared with mothers whose daughters did not smoke as adults.

Strengths and weaknesses of the study

An important strength of the present study is the large size of the cohort, enabling detailed birthweight by gestational age stratification, which showed a dose–response relation between birthweight by gestation and later daily smoking. Also, due to the prospective design, there was no retrospective recall bias of birthweight, gestational age or smoking habits. The population-based compulsory notification of births made selection bias minimal. In Tables 1 and 2, we use the complete material (term and preterm born women and men), while in Figure 1, we use only data for term born women and men. Gestational age itself was, however, hardly related to later smoking (results not shown). Preterm birth is associated with maternal smoking, but not as strongly as low birthweight is. Smoking-related risks for preterm birth have been shown to be in the range 1.2–1.6 while risks for small-for-gestational-age has been shown to be 1.5–2.9.[22]

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Our population had a relatively high proportion of missing smoking habits (9.9%). However, missing smoking habits was only weakly associated with low birthweight [RR = 1.1, 95% CI 1.03, 1.2].

Among women where smoking information was missing, mean birthweight of their singleton infants was reported to be 114 g lower than among non-smoking women, compared with 229 g lower among daily smoking women, which indicates that approximately half of the women with missing smoking habits were smokers.[21] In a sensitivity analysis, we assigned all women with missing information on smoking habits to be daily smokers. This reclassification did not change the dose–response pattern although it attenuated the results. We excluded occasional smokers from analyses as a previous study found that 66% of women reporting occasional smoking had cotinine values suggesting daily smoking.[23]

Maternal smoking during pregnancy has only been registered in the MBRN since 1999. Therefore, we could not study the smoking habits of the women's mothers directly. However, previous studies have shown that maternal smoking is linked through generations.[24–26] A recent Norwegian study found an inverse association between offspring birthweight and grandparental cardiovascular mortality, but this was considerably weakened after adjusting for maternal smoking during pregnancy.[27] They also showed an inverse association between birthweight and lung cancer and chronic obstructive pulmonary disease. Recently, Smith *et al.*[28] concluded that so far there is no study that includes medical records of birthweight and gestational age, that appropriately takes life style habits and socioeconomic status into account and that includes disease incidence or cause of death as end points. We have focused a factor that has not been available when studying the relation between low birthweight and adult cardiovascular disease: smoking habits passed on through generations. By using smoking-related mortality among mothers as a proxy for their smoking habits, we suggest that maternal smoking is a common cause of offspring low birthweight as well as offspring's smoking habits in adulthood. The latter will be an important risk factor for cardiovascular disease, and accordingly, transgenerational smoking habits could explain parts of the association between low birthweight and later cardiovascular disease. Thus, studies describing this relation need to be able to adjust appropriately for smoking habits.

Comparisons to other studies

It has been argued that the early programming hypothesis is too general and has inconsistent support.[29] Also, it has been suggested that socioeconomic factors and smoking are possible mediators that may explain the association.[30,31] Low birthweight is related to socioeconomic level both at birth[32] and later in life[33] and adjusting for adult deprivation have been shown to weaken the relation between infant and adult mortality rates.[34] Low childhood socioeconomic position has been shown to predict later smoking, an association partly explained by educational level.[35] However, several 'early origin studies' state that adjustment for smoking has been done.[2–5,12,13,36] Besides the Nurses' Health Study,[3] these studies have below 1500 participants. In the Nurses' Health Study with 70 297 participants, the authors adjust for smoking as a confounding factor both for the nurse and the nurse's mother without a considerable change in the inverse association between the extremes of self-reported birthweight and cardiovascular disease.[3] However, adjusting for an intermediate variable using traditional statistical models is questionable and biased associations cannot be excluded.[37,38]

In our study, we found that birthweight was related to adult smoking habits both directly and indirectly through partners' smoking habits in pregnancy. A previous study from the MBRN showed low correlation between mothers' and fathers' birthweight.[39] Given this low correlation and the persistent association after excluding partners whose own birthweight was very low, this may reflect spousal selection on smoking status.[14] Since smoking in pregnancy is associated with intrauterine growth restriction, these findings indicate that children born with low birthweight seem to share environmental risk factors that are culturally dependent. This suggests smoking as a shared environmental exposure across generations, and that the mothers' smoking contributed to low birthweight in their offspring. The birthweight–smoking association among women was observed in both the highest and the lowest level of their mothers' education, and indicates that smoking habits are 'inherited' irrespective of socioeconomic status. In an adjusted model where we consider women's own education as a proxy for their socioeconomic status and included it as an adjustment variable, the RRs somewhat attenuated, but the pattern remained evident (data not shown).

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Some studies have claimed no association between birthweight and adult smoking.[3,12,13] However, the association between birthweight[40] and weight at 1 year of age[41] and later adult smoking habits has previously been mentioned. Some of these studies are commenting on the association between birthweight and smoking habits among men only.[12,41] Others have information on birthweight only from self-report[3] and do not have data on gestational age.[13,40] The relation between birthweight and adult smoking is influenced by different overall smoking prevalences between populations as well as different time periods within a population. Different birth cohorts appear to have dissimilar patterns of smoking habits[42] and Great Britain and the US experienced both an earlier tobacco epidemic as well as higher consumptions than Norway.[43]

We studied women born in 1967–1995 and their smoking habits between 1999 and 2009. Thus, our cohort of women is younger than women in most other studies.[3,4,13,40,44–46] Among pregnant women in the Norwegian Mother and Child Cohort Study, 20% of those born in 1954–1965 reported being exposed to cigarette smoke in utero, compared with 32% among those born in 1981–1992.[47] For the general female population in Norway, the peak smoking prevalence was 10% for the early 1890s cohort, 52% for the early 1940s cohort and 41% for the early 1960s cohort.[42]

In this study, we had the opportunity to quantify the association between z-scores for birthweight by gestational age and adult smoking habits in a large material. This study shows that birthweight is associated with smoking habits in adulthood. It is therefore essential that research relating birthweight to later health outcomes provide a proper control for smoking habits both of the mother during pregnancy and in adulthood for the individual under study. The women in our study were too young to allow us to study the relation between their birthweight and their own long-term cardiovascular morbidity and mortality with adequate power. Future studies will be able to look at a person's whole lifetime and could study how birthweight and later smoking habits are related to cardiovascular disease.

Conclusion

In conclusion, being born with low birthweight is associated with smoking in adulthood. Associations of adult smoking with partners' birthweight and mothers' smoking-related causes of death suggest a shared smoking environment, and may account for some of the established association between birthweight and later cardiovascular disease.

Conflict of interest: The authors declare that they have no conflict of interests.

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IV


Paediatric and Perinatal Epidemiology

doi: 10.1111/ppe.12333

Maternal Smoking Status in Successive Pregnancies and Risk of Having a Small for Gestational Age Infant

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Abstract

Background: Smoking during pregnancy is linked to having a small for gestational age (SGA) baby. We estimated SGA risk among women who smoked persistently, quit smoking or started smoking during their first two pregnancies.

Methods: Data from the population-based Medical Birth Registry of Norway was used to evaluate self-reported smoking at the beginning and end of two successive pregnancies among 118 355 Nordic women giving birth 1999–2014. Relative risks (RR) with 95% confidence intervals (CI) of SGA in the second pregnancy were estimated using adjusted generalised linear models with non-smokers during both pregnancies serving as referent category.

Results: Daily smokers throughout both pregnancies had almost threefold increased SGA risk in the second pregnancy (RR 2.9, 95% CI 2.7, 3.1). Daily smokers in the first pregnancy, who abstained in the second, had a 1.3-fold increased risk (95% CI 1.1, 1.5). Intermediate risks were found among persistent daily smokers who quit by the end of the second pregnancy (RR 2.0, 95% CI 1.6, 2.4) and non-smokers in first pregnancy who smoked daily throughout their second (RR 1.8, 95% CI 1.4, 2.3). Persistently smoking women without SGA in first pregnancy, had a 2.7-fold increased risk of SGA in second pregnancy (95% CI 2.5, 3.0).

Conclusions: Smoking throughout two successive pregnancies was associated with the greatest increased SGA risk compared with non-smokers, while cessation before or during the second pregnancy reduced this risk. Women who smoked in the first pregnancy without experiencing SGA are not protected against SGA in second pregnancy if they continue smoking.

Keywords: *pregnancy, infant small for gestational age, risk factors, perinatal, smoking.*

Small for gestational age (SGA) is most commonly defined as birthweight below the 10th percentile for gestational age and sex[1,2] and is a marker for restricted fetal growth. SGA infants have an increased risk of morbidity[3] and mortality.[4,5] SGA can represent underlying pathology such as pregnancy complications or maternal conditions associated with placental dysfunction.[6] Smoking is one of the most important modifiable risk factors for SGA[7,8] and a causal relationship between smoking and fetal growth restriction is well established.[7] The Medical Birth Registry of Norway (MBRN) has since 1999 registered maternal smoking status at the beginning and end of pregnancy, allowing us to characterise smoking status at four time points across two subsequent pregnancies. Having two measures of smoking (one at the beginning and one at the end of pregnancy) is important because some women are unable to quit smoking immediately and others may quit but resume smoking before the end of the pregnancy. Reliance on one measure, therefore, inevitably leads to some misclassification of exposure among women attempting to quit. To the extent that misclassification occurs, estimates between maternal smoking and outcomes may be obscured. More detailed knowledge of the timing of maternal smoking and SGA risk would be informative for advising pregnant smokers and guiding smoking cessation campaigns. To our knowledge, the risk of SGA associated with early and late maternal smoking across two pregnancies has not yet been reported.

The main aim of our study was to estimate risk of SGA in a second pregnancy among women who

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smoked persistently, quit smoking, or started smoking during the first two pregnancies compared to non-smokers. A secondary aim was to assess if daily smoking women throughout the first pregnancy, without a growth restricted infant, were 'protected' against growth restriction in the next pregnancy if they continued smoking.

Methods

Data source and study population

The MBRN is a mandatory nationwide population-based registry of all births from 16 weeks' gestation.[9] Starting at the first antenatal visit a midwife or a doctor fills in an antenatal chart that follows the woman throughout her pregnancy. The chart contains information about demographic data, reproductive history, medical conditions, complications during pregnancy, and lifestyle habits. Self-reported smoking status at the beginning and at the end of pregnancy is obtained through interview. At the time of delivery a midwife transfers information from the antenatal chart to the MBRN notification form. On this form, maternal smoking status is registered by checkboxes as non-smoker, occasional smoker (less frequent than daily), or daily smoker. For daily smokers the number of daily smoked cigarettes is recorded. Checkboxes transfer more valid information to registries than written text.[10] Maternal age at first birth, marital status, mothers' country of birth, and gestational age were available from the MBRN. Gestational age was based on the first day of the last menstrual period (LMP). If LMP was missing or the difference between LMP and ultrasound was more than 10 days, gestational age was based on second trimester ultrasound measurements. Maternal education in 2009 was derived from the National education database at Statistics Norway through record linkage in a subset of the study population, using the mother's unique national identification number.

Study population

Our study population consisted of 220 413 women having their first and second singleton birth in 1999 to 2014 (Figure S1). The two births were linked to their mother using the mother's unique national identification number (included in the MBRN notification forms for all births), and the mother with her successive pregnancies was the observation unit. Our study included only women born in Norway, Sweden, Denmark, Finland, and Iceland, excluding 33 503 women. The offspring of women born outside these Nordic countries weighed an average of 119 g less than babies born to Nordic women (*t*-test $P < 0.005$), and they would therefore more likely be classified as SGA using Norwegian standards even without intrauterine growth restriction. We further excluded women with missing data on infant sex, birthweight, or gestational age and women with spontaneous abortion (<22 weeks and birthweight <500 g) ($n = 2012$). After exclusion of women with missing data on smoking at the end of pregnancy ($n = 59\,909$) or occasional smokers at the end of pregnancy ($n = 2510$), our main analyses included 122 479 women with valid smoking status at the end of each of the two pregnancies (Tables 1 and 2). For the analyses on smoking status early and late in two pregnancies, exclusions were women with missing smoking status for these time points ($n = 60\,431$), occasional smokers ($n = 5805$), and women with unusual smoking trajectories ($n = 307$), leaving 118 355 women with valid smoking status at the beginning and end of the two pregnancies (Table 3, Figure 1).

Giving birth to an SGA infant is a strong risk factor for recurrent SGA. To avoid mixing the effect of smoking with other causes of recurrent SGA, we did additional analyses restricted to women without SGA in the first pregnancy ($n = 106\,468$ women, Table 3), and analysed separately women with SGA in their first pregnancy ($n = 11\,087$).

Maternal education was only available for mothers giving birth during 1999–2010, which amounted to 76 161 women with available birthweight, gestational age, and smoking status. Analyses evaluating a possible different effect of smoking on SGA by level of education were done in this subset, while the main analyses were done on the total study population (1999–2014).

Statistical analyses

Generalised linear models for the binominal family were used to compute relative risks (RR) with 95% CI for the association between smoking status in two pregnancies and the risk of SGA in the second. SGA was defined as birthweight by gestational age below the 10th percentile based on Norwegian gender specific birthweight standards.[2] We first examined

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Table 1. Maternal characteristics of the 122 479 women born in the Nordic countries, having two successive singleton pregnancies in the period 1999–2014

	Total number		SGA in second pregnancy (10th percentile)			
Maternal Characteristics	*n*	%	*n*	% within poplulation	% with category	*P*-value[a]
Total	122 479	100	5972	100%	4.9	
Smoking status at the end of first pregnancy & second pregnancy						
No & No	110 189	90.0	4765	79.8	4.3	<0.01
Daily & No	4253	3.5	269	4.5	6.3	
No & Daily	1865	1.5	171	2.9	9.2	
Daily & Daily	6172	5.0	767	12.8	12.4	
Maternal age first pregnancy						
<20	6044	4.9	395	6.6	6.6	<0.01
20–24	31 430	25.7	1649	27.6	5.3	
25–29	52 177	42.6	2329	39.0	4.5	
30–34	27 261	22.3	1304	21.8	4.8	
35+	5567	4.6	295	4.9	5.3	
Marital status first pregnancy						
Married	36 012	29.4	1655	27.7	4.6	<0.01
Cohabiting	76 374	62.4	3680	61.6	4.8	
Single	8608	7.0	552	9.2	6.4	
Widow/other/missing	1485	1.2	85	1.4	5.7	
Previous SGA in first pregnancy [b]	11 458	9.4	2149	36.3	18.8	<0.01
Maternal education[c]						
Low education (<11 years)	10 261	13.5	738	18.6	7.2	<0.01
High education (≥11 years)	65 900	86.5	3231	81.4	4.9	

[a]*P*-values refer to testing of independence between the respective factor and SGA status (second pregnancy) using Pearson's chi square test(χ^2).

[b]845 (0.7%) women had no information on prior SGA, of these 49 women had SGA in the second pregnancy.

[c]Highest achieved education was obtained in 2009. Education was missing for 504 (0.7%) women in subset of the study population with available information on education 1999–2010.

Table 2. The Risk of small for gestational age (SGA) (10th and 2.5th Percentile) in the second pregnancy among Nordic born women with two successive singleton pregnancies by smoking status at the end of both pregnancies. Norway, 1999–2014

		SGA 10th percentile in second pregnancy				SGA 2.5th percentile in second pregnancy			
Smoking status end of first & second pregnancy	Total	*n*	%	RR (95% CI)	aRR[a] (95% CI)	*n*	%	RR (95% CI)	aRR[a] (95% CI)
No & No	110 189	4765	4.3	1.0 (Reference)	1.0 (Reference)	847	0.8	1.0 (Reference)	1.0 (Reference)
Daily & No	4253	269	6.3	1.5 (1.3, 1.6)	1.5 (1.3, 1.7)	49	1.2	1.5 (1.1, 2.0)	1.5 (1.1, 2.0)
No & Daily	1865	171	9.2	2.1 (1.8, 2.5)	2.1 (1.8, 2.5)	46	2.5	3.2 (2.4, 4.3)	3.1 (2.3, 4.2)
Daily & Daily	6172	767	12.4	2.9 (2.7, 3.1)	2.9 (2.7, 3.1)	191	3.1	4.0 (3.4, 4.7)	3.9 (3.3, 4.6)
Total	122 479	5972	4.9			1133	0.9		

[a]Adjusted for maternal age, marital status and year of first birth.

categories of smoking based on the status at the end of two successive pregnancies; persistent non-smokers (*No-No*), quitters from first to second pregnancy (*Daily-No*), starters from first to second (*No-Daily*), and persistent smokers (*Daily-Daily*) (Table 2). We then examined more complex categories taking into account status at the beginning and at the end of the two successive pregnancies (Table 3). Women who were non-smokers throughout both pregnancies were the referent group. Based on causal diagrams and directed acyclic graph (DAG) theory,[11] maternal age at first birth (<20, 20–24, 25–29, 30–34, 35 + years), marital status at first birth (married, cohabitating, single, widow/other/missing), year of first birth (1999–

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Table 3. The risk of small for gestational age (SGA) (10th percentile) in the second pregnancy, all second and term infants among Nordic born women by detailed smoking habits in with two successive singleton pregnancies. Norway 1999–2014

			SGA in second pregnancy						
	Smoking status		Total material					Only term born	Only non-recurrent
Category number	First Pregnancy	Second Pregnancy	Total	*n*	%	RR (95% CI)	aRR[a] (95% CI)	RR[a](95% CI)	aRR[a](95% CI)
1	No-No	No-No	99 733	4274	4.3	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2	Daily-No	No-No	5185	254	4.9	1.1 (1.0, 1.3)	1.2 (1.0, 1.3)	1.2 (1.0, 1.3)	1.1 (0.9, 1.3)
3	Daily-Daily	No-No	2790	156	5.6	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	1.3 (1.1, 1.6)	1.2 (1.0, 1.5)
4	No-No	Daily-No	1025	52	5.1	1.2 (0.9, 1.5)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.4 (1.0, 1.9)
5	Daily-No	Daily-No	936	47	5.0	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.3 (1.0, 1.7)	1.3 (0.9, 1.8)
6	Daily-Daily	Daily-No	1087	92	8.5	2.0 (1.6, 2.4)	2.0 (1.6, 2.4)	2.0 (1.6, 2.5)	2.0 (1.5, 2.5)
7	No-No	Daily-Daily	739	57	7.7	1.8 (1.4, 2.3)	1.8 (1.4, 2.3)	1.9 (1.5, 2.5)	1.7 (1.3, 2.4)
8	Daily-No	Daily-Daily	901	99	11.0	2.6 (2.1, 3.1)	2.6 (2.1, 3.1)	2.7 (2.2, 3.3)	2.4 (1.9, 3.1)
9	Daily-Daily	Daily-Daily	5959	740	12.4	2.9 (2.7, 3.1)	2.9 (2.7, 3.1)	3.0 (2.8, 3.3)	2.7 (2.5, 3.0)
	Total		118 355	5771	4.9				

[a]Adjusted for maternal age, marital status and year of first birth.

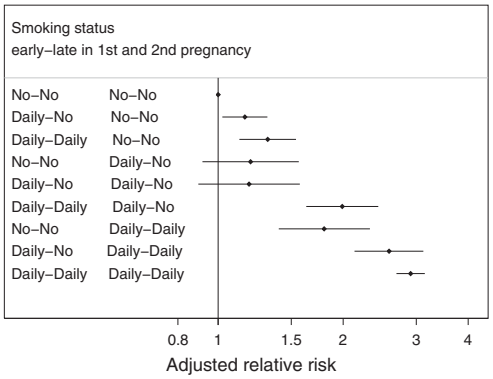

Figure 1. The Adjusted Relative Risk for SGA (10th Percentile) in second pregnancy among women born in the Nordic countries with two successive pregnancies with singleborns in the period 1999–2014. Persistent non-smokers as reference group.

2007, 2008–14) and maternal education (highest achieved education: ≤10 years and ≥11 years) were considered possible confounders for the association between maternal smoking and SGA in the second pregnancy (DAG in Figure S2). We adjusted for maternal age, marital status, and year of first birth.

We repeated analyses defining SGA as birthweight below the 2.5th percentile, and performed separate analyses examining term pregnancies (≥37 gestational weeks). Analysing term deliveries alone excluded an important possible selection bias as the proportion of missing smoking information at the end of the second pregnancy was higher in preterm than term gestations (41%, 25% and 18% in 23 weeks, 30 weeks, and term gestations respectively).

To evaluate smoking dosage in different smoking categories, two sample *t*-tests comparing group means (number of cigarettes smoked daily) were performed. Pearson's chi square test *P*-values were used to test the independence between the respective factors and SGA status in second pregnancy. In separate analyses investigating patterns of missing smoking information, SGA risk in second pregnancy was estimated among women with missing values for any of the four registration points of their two first pregnancies.

All analyses were performed with STATA, version 14.0 Intercooled for Windows (StataCorp LP, College Station, Texas).

The study was approved by Regional Ethical Committee (2009/1868 and 2015/1728).

Results

Maternal characteristics

Among 122 479 women, 4.9% had an SGA infant in their second pregnancy. Most women had their first child at the ages of 20–34 years and were married or cohabiting (Table 1). Of women with registered smoking status, 90% were non-smokers at the end of both

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pregnancies, 5% were persistent daily smokers at the end of both pregnancies, 3.5% quit smoking from the first to the second pregnancy and 1.5% were non-smokers at the end of first pregnancy and daily smokers at the end of second pregnancy. Being younger than 30 years and not married when delivering the first child were both associated with being a persistent smoker (data not shown). Comparing women with and without SGA in the second pregnancy, those with an SGA infant were more likely to smoke, were younger, were more often single and with low education. Women with SGA in first pregnancy had increased risk of giving birth to an SGA infant also in the second compared to women without SGA in the first pregnancy (RR 5.5, 95% CI 5.2, 5.8).

Smoking status at the end of pregnancies only

Compared to women who did not smoke at the end of their first two pregnancies, women who smoked daily at the end of two successive pregnancies (persistent smokers) had an almost threefold increased risk of having a SGA baby (10th percentile) in the second pregnancy (Table 2). Adjustment for maternal age, marital status, and year of first birth resulted in a similar estimate. Women who reported non-smoking at the end of the first pregnancy and daily smoking at the end of second pregnancy (starters) also had a higher risk compared with non-smokers, although the risk ratio was smaller than persistent smokers. Women who smoked daily at the end of the first pregnancy but were non-smokers at the end of their second pregnancy (quitters) had a significantly smaller increase in risk of SGA in the second pregnancy. When defining SGA below the 2.5th percentile, quitters had a similar risk of SGA in the second pregnancy, while persistent smokers and starters had an even higher relative risk (Table 2).

Smoking status at the beginning and end of the two pregnancies

Women who smoked throughout the first pregnancy, but were non-smokers throughout their second pregnancy (Category 3), had a modestly increased risk of SGA in the second pregnancy. Women who were daily smokers at the beginning of each pregnancy and quit smoking by the end of each (Category 5) did not have significantly increased risk of SGA in the second pregnancy compared to persistent non-smokers (Category 1), while those who were non-smokers in first pregnancy, but smoked daily throughout their second (Category 7), had a 80% increased risk of a SGA infant in the second pregnancy. Women who smoked daily throughout their first pregnancy and at the beginning, but not the end of the second pregnancy (Category 6), had a twofold risk of SGA in the second pregnancy, however, this risk was significantly smaller than persistent smokers (Category 9). Relative risks were similar when restricting analyses to only term births in the second pregnancy. Among women without SGA in their first pregnancy, persistent daily smokers (Category 9) had 2.7 times the risk of SGA in the second pregnancy, compared to persistent non-smokers (Category 1). The risk for SGA in second pregnancy in Category 2 and 3 was no longer statistically significant among women without SGA in the first pregnancy. Among women with SGA in the first pregnancy (data not shown), persistent smoking was also associated with an increased risk of SGA in the second pregnancy, but the RR estimate was smaller than among those whose first birth was not SGA (RR 1.8, 95% CI 1.6, 2.0), although the baseline risk was higher for these women. In a sensitivity analysis we excluded women with preeclampsia in the second birth and the results were essentially unchanged.

Number of daily cigarettes

In Table 3 three smoking trajectories had daily smoking at the end of second pregnancy. The mean number of daily cigarettes smoked at the end of the second pregnancy in the *Daily-Daily-Daily-Daily* category was 7.8 (95% CI 7.6, 7.9), while it was 6.3 (95% CI 6.1, 6.6) in the *Daily-No-Daily-Daily* category and 5.8 (95% CI 5.5, 6.1) in the *No-No-Daily-Daily* category, being significantly higher among the persistent smokers than in each of the other categories. The mean number was also significantly higher in the *Daily-No-Daily-Daily* category than in the *No-No-Daily-Daily* category ($P < 0.05$).

Education

There was a strong association between persistent smoking and SGA in the second pregnancy both among women with low and high education (Table S1). Using non-smoking women with high

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education as the common reference, the highest point estimate RR was found for persistent smokers with low education. However, we found no interaction effects between smoking and maternal education on the risk for SGA in second pregnancy. The results remained similar when further adjusting for education in the main analyses (as of Table 3). Although the differences in educational level in the proportion of women with SGA in second pregnancy were small for several of the smoking categories, the proportion of women in categories of daily smoking were much higher in low than in high education; 18.6% of all women with low education were in category 9 (Daily-Daily-Daily-Daily), while only 3.3% of women were present with high education.

Missing smoking status

For the 184 898 women with two successive singleton births in the period 1999–2014, a total of 9820 (5.3%) had missing smoking status at the end of both pregnancies, while 50 089 (27.1%) had missing in one of the pregnancies. Compared to persistent non-smokers, women who were daily smokers in the first pregnancy and had missing smoking status in the second had a twofold increased risk of SGA in the second pregnancy (aRR adjusted relative risk) 2.2, 95% CI 1.9, 2.6) (Table S2, Figure S3). The risks in other trajectories are also reported.

Among women who did not have SGA in second pregnancy, 17.6% had missing smoking data for the end of second pregnancy, while this percentage was 18.8% among those with SGA in second pregnancy (RR 1.1, 95% CI 1.0, 1.1).

SGA and potential changes in smoking habits

We explored the possibility that smoking followed by SGA in the first pregnancy may have reduced the probability of smoking in the second pregnancy. Among women who smoked at the end of the first pregnancy and gave birth to an SGA infant, 64.5% continued to smoke throughout the end of second pregnancy, compared to 58.2% of daily smokers in the first pregnancy without SGA in the first pregnancy (RR 1.1, 95% CI 1.1, 1.2). Experiencing SGA in the first pregnancy was therefore not associated with a higher probability of smoking cessation. We did find that daily smoking women who experienced SGA in first pregnancy, smoked a higher average number of cigarettes daily than daily smoking women without SGA in first pregnancy: 7.1 (95% CI 6.9, 7.3) vs. 6.5 (95% CI 6.5, 6.6) ($P < 0.05$).

Comment

Main findings

We found the highest relative risks of SGA in the second pregnancy in trajectories with smoking in the second pregnancy. We found that women who smoked throughout two pregnancies had close to threefold higher risk of SGA in the second pregnancy than non-smokers. Quitting smoking at any time before the end of the second pregnancy was associated with smaller risk increases. Even women who smoked throughout the first pregnancy and in the beginning of the second, but quit before the end, had a significantly smaller increased risk than persistent smokers, although twice the risk of non-smokers. Women who smoked daily in the first pregnancy, but not in the second had a modestly increased risk of SGA in the second pregnancy. Women who smoked in the first pregnancy without experiencing SGA had a more than twofold risk of SGA in the second pregnancy if they continued smoking. We found heterogeneous risk patterns in the different smoking trajectories throughout two successive pregnancies, suggesting that smoking information across four time points better characterised risk of SGA in the second pregnancy than using information only in the beginning or end of the pregnancy. The average number of cigarettes smoked daily at the end of the second pregnancy also differed significantly between women with different smoking trajectories; persistent smoking in two pregnancies having the highest dose. The association between persistent smoking and recurrent SGA was slightly weaker than associations in the total study population, suggesting that in women with previous SGA other factors causing SGA dilute the effect of smoking.

Comparisons with other studies

Smoking is a risk factor for SGA as well as for the morbidity in SGA infants.[3] Baba *et al*.[12] found similar associations between smoking during one pregnancy and term SGA (OR 3.2, 95% CI 3.0, 3.4) as we found among women smoking throughout two pregnancies (RR 3.0, 95% CI 2.8, 3.3). They studied changes in smoking habits within one pregnancy, and found that

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women who quit smoking early in pregnancy had lower risk of SGA than women who quit late. Our results based on smoking information at two time points in two successive pregnancies is consistent with Baba's finding: Women who smoked daily in their first pregnancy and in the early stage of their second, had a significantly smaller increase in risk of SGA in the second pregnancy than persistent daily smokers, although twice the risk compared to non-smokers. Women who smoked at the beginning of pregnancy, but managed to quit by the end in both pregnancies did not have a significantly increased risk of SGA in the second pregnancy.

Nordström *et al.*[13] looked at smoking in two successive pregnancies and differences in sibling birthweight. Using smoking data from the first antenatal visit in two pregnancies, they reported an increased birthweight in the second infant among women who smoked heavily in first pregnancy and then quit smoking. Our study using smoking across four time points in two pregnancies shows that women who smoked at the beginning of the first pregnancy could have several different smoking trajectories throughout the first and second pregnancy. These trajectories differed in risk of SGA in the second pregnancy; the women in the category *Daily-Daily-No-No* had a 30% increased risk of having an SGA baby, while women in the category *Daily-Daily-Daily-No* had a twofold risk. We also found that women who reported non-smoking at the end of first pregnancy and daily smoking at the end of second pregnancy differed in the risk of SGA according to the four time point trajectories.

Strengths and limitations

The mandatory reporting of all births to the MBRN diminished the possibility of selection bias. Data on smoking status were prospectively collected which minimises recall bias. We used family-based data (sib-files) and had information on smoking status in two successive pregnancies (early and late in each gestation), giving a unique depiction of women's smoking trajectories throughout the two pregnancies.

We have previously found self-reported smoking status to be a valid marker for tobacco exposure by comparing self-reported smoking status against plasma cotinine in a subset of a large Norwegian cohort study.[14] However, the hazards of smoking during pregnancy are well known and women may wish to portray themselves in a better light and underestimate how much they smoke. Women may also refuse to report their smoking status. The risks of SGA in second pregnancy were increased in several of the trajectories where missing smoking status was combined with daily smoking at least once across the four time points, suggesting that the presented risk of SGA associated with smoking is a conservative estimate. Although the percentage of women with missing data on smoking habits in second pregnancies were slightly higher when the infant was SGA than not, the difference was so small that it should not have biased our results by much.

Although we were able to adjust for important potential confounders like maternal education, residual confounding cannot be ruled out. Information on maternal height and pre-pregnancy weight were not available. The modestly increased risk among women who were daily smokers in the first pregnancy and non-smokers in the second pregnancy, raises the question whether tobacco smoke has a direct toxic effect only during the pregnancy exposed or if it persists to the next pregnancy. Although we cannot rule out a tobacco effect, these women who smoked during pregnancy likely differ from non-smokers in other health-related behaviours associated with SGA.

When restricting analyses to women who did not give birth to an SGA infant in the first pregnancy, we may open a backdoor path through the unmeasured genetic factors that are causally related to SGA in the first and second pregnancy and introduce bias to the estimate.[15] However, the estimates remained similar after stratification suggesting that the amount of bias was minimal.

Conclusions

Quitting smoking from one pregnancy to the next reduced the risk of SGA in the second pregnancy. Even quitting before the end of the second pregnancy reduced the risk compared to persistent smokers, although the risk was still almost twice the risk of non-smoking women. Women who smoked in two successive pregnancies were at higher risk of having an SGA baby in their second pregnancy compared to women who smoked in only the second pregnancy. Women who smoked in the first pregnancy without experiencing SGA are not protected against SGA in the second pregnancy if they continue to smoke.

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Acknowledgements

Rolv Skjærven has received research support from The Research Council of Norway (Project 214129). Corresponding author Liv Kvalvik is supported with a PhD grant from University of Bergen, Norway. The authors declare that they have no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. The risk for SGA (10th Percentile) in second pregnancy among Nordic women with two successive pregnancies with singleborns in the period 1999–2010. Non-smokers with high education as reference group.
Table S2. The risk for SGA (10th Percentile) in second pregnancy and smoking status missing in either first or second pregnancy among women with two successive pregnancies with singleborns in the period 1999–2014.
Figure S1. Flow chart of the Study Population of Women with Two Successive Singleton Pregnancies in Norway, 1999–2014.
Figure S2. Proposed Directed Acyclic Graph (DAG) exploring the causal pathways in the study.
Figure S3. The adjusted relative risk for SGA (10th Percentile) in second pregnancy among women born in the Nordic countries with two successive pregnancies with singleborns in the period 1999–2014. Persistent non-smokers as reference. Adjusted for maternal age and marital status at first birth

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Maternal smoking status in successive pregnancies and risk of having a small-for-gestational-age infant

Appendix

Table S1. The risk for SGA (10th Percentile) in second pregnancy among Nordic women [a] with two successive pregnancies with singleborns in the period 1999-2010. Non-smokers with high education as reference group.

			Low education				High education			
			SGA in 2nd pregnancy				SGA in 2nd pregnancy			
Category number	Smoking status 1st pregnancy	2nd pregnancy	Total	n	%	aRR[b] (95% CI)	Total	n	%	aRR[b] (95% CI)
1	No-No	No-No	5,614	274	4.9	1.1 (1.0, 1.2)	56,616	2,545	4.5	1.0 (Reference)
2	Daily-No	No-No	729	34	4.7	1.0 (0.7, 1.4)	2,860	150	5.2	1.2 (1.0, 1.4)
3	Daily-Daily	No-No	496	27	5.4	1.2 (0.8, 1.8)	1,292	88	6.8	1.5 (1.2, 1.9)
4	No-No	Daily-No	348	24	6.9	1.5 (1.0, 2.2)	1,010	48	4.8	1.1 (0.8, 1.4)
5	Daily-No	Daily-No	310	21	6.8	1.5 (1.0, 2.3)	700	28	4.0	0.9 (0.6, 1.3)
6	Daily-Daily	Daily-No	350	30	8.6	1.9 (1.3, 2.7)	524	38	7.3	1.6 (1.2, 2.2)
7	No-No	Daily-Daily	241	26	10.8	2.4 (1.6, 3.4)	348	26	7.5	1.7 (1.2, 2.4)
8	Daily-No	Daily-Daily	267	30	11.2	2.4 (1.7, 3.5)	362	45	12.4	2.8 (2.1, 3.7)
9	Daily-Daily	Daily-Daily	1,906	272	14.3	3.1 (2.8, 3.6)	2,188	263	12.0	2.7 (2.4, 3.1)
	Total		10,261	738	7.2		65,900	3,231	4.9	

Abbreviations: CI, confidence interval; aRR, adjusted relative risk

[a] Nordic women in this subset means if the women were born in Norway but their mother was born outside the Nordic countries they were also excluded.

[b] Adjusted for maternal age, marital status and year of first birth.

Table S2. The risk for SGA (10th Percentile) in second pregnancy and smoking status missing in either first or second pregnancy among women with two successive pregnancies with singleborns in the period 1999-2014.

		SGA in 2nd pregnancy			
Smoking status					
1st pregnancy	**2nd pregnancy**	Total	n	%	aRR[a] (95% CI)
No-No	No-No	99,733	4,274	4.3	1.0 (Reference)
Miss-Miss	Miss-Miss	7,496	385	5.1	1.2 (1.1, 1.3)
Daily-Daily	Miss-Miss	1,436	134	9.3	2.2 (1.9, 2.6)
No-No	Miss-Miss	15,215	741	4.9	1.1 (1.1, 1.2)
Total		123,880	5,534	4.5	

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; SGA, small for gestational age

[a] Adjusted for maternal age, marital status and year of first birth.

Figure S1 Flowchart of the Study Population of Women with Two Successive Singleton Pregnancies in Norway, 1999-2014.

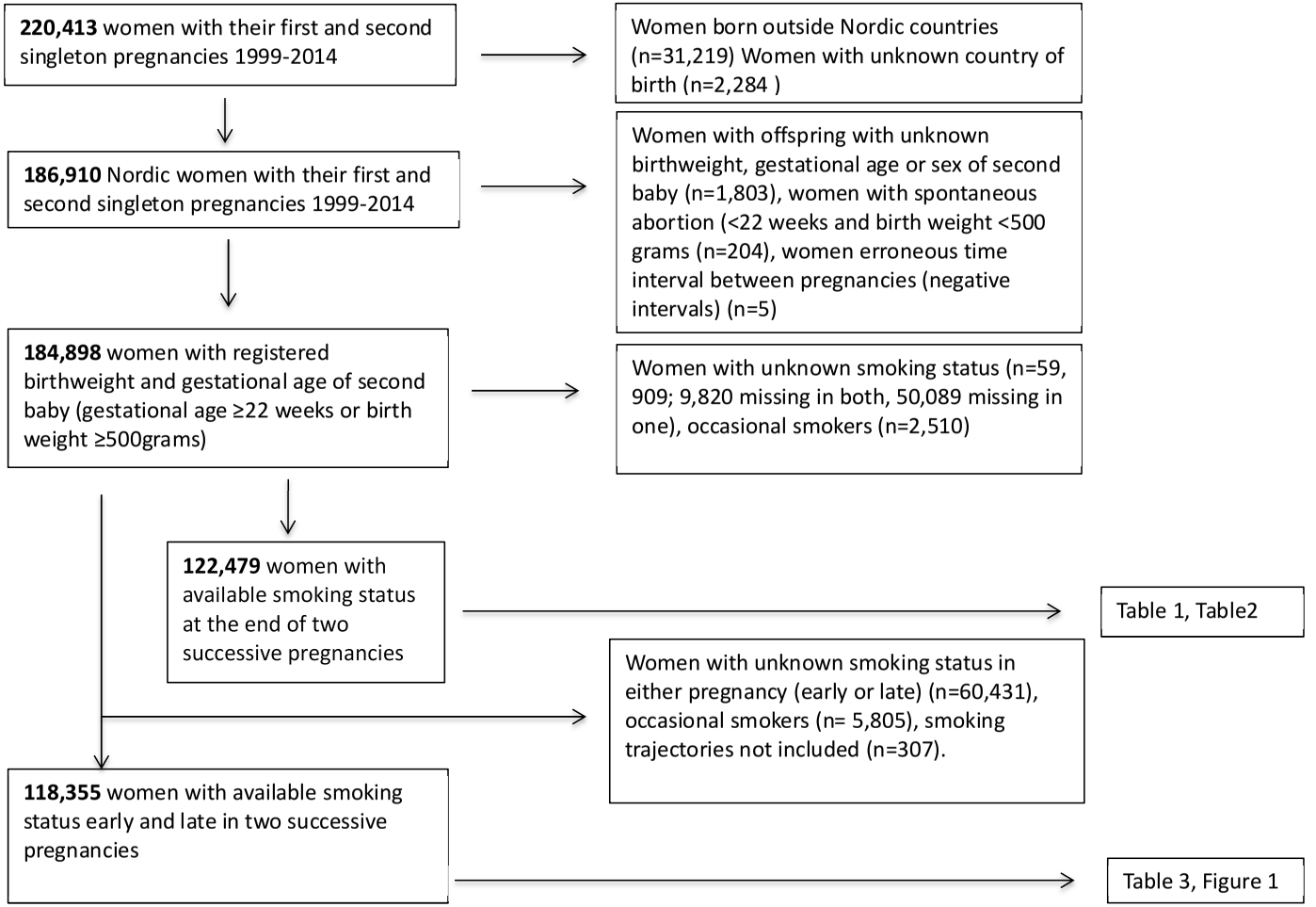


Figure S2 Proposed Directed Acyclic Graph (DAG) exploring the causal pathways in the study.

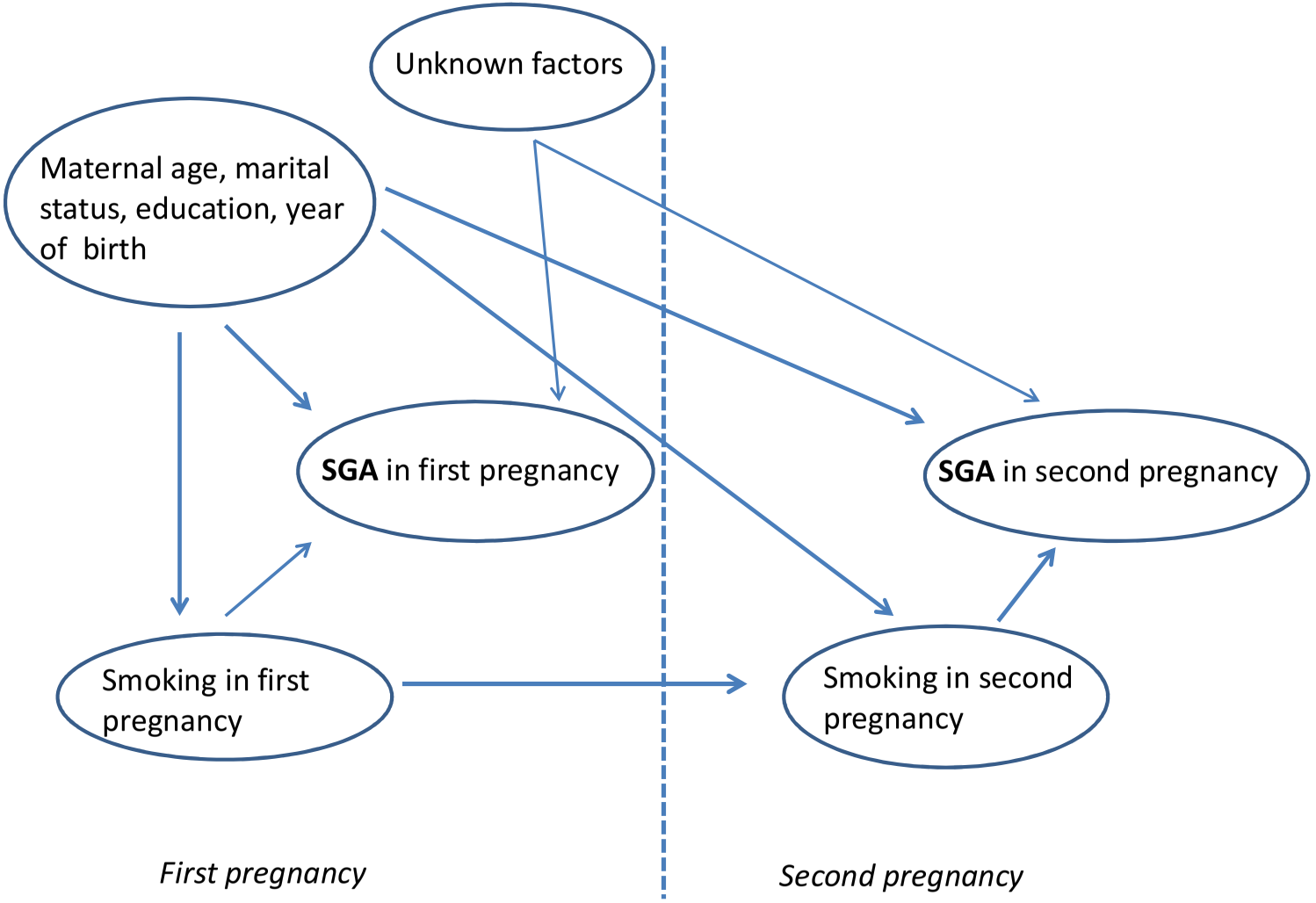
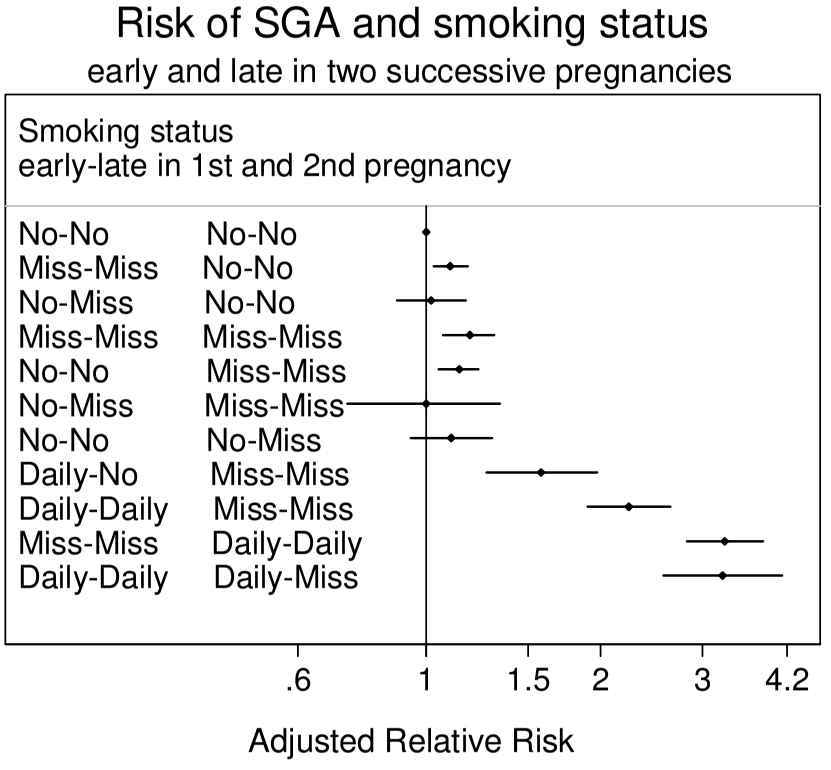


Figure S3 The adjusted relative risk for SGA (10th Percentile) in second pregnancy among women born in the Nordic countries with two successive pregnancies with singleborns in the period 1999-2014. Persistent non-smokers as reference. Adjusted for maternal age and marital status at first birth.



Grafisk design: Kommunikasjonsavdelingen, UiB / Trykk: Skipnes Kommunikasjon AS

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ISBN: 978-82-308-3794-8