SMOKING DURING PREGNANCY AND FETAL BRAIN DEVELOPMENT

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ABSTRACT

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Smoking during pregnancy and fetal brain development
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Background: Although the knowledge of adverse effects of smoking during pregnancy has increased in recent years, more research is needed to gain a better understanding of the effects of smoking during pregnancy. Smoking exposure is the most common preventable factor that causes adverse pregnancy outcomes.

Aims and Methods: First, data on smoking habits during pregnancy from the Nordic Medical Birth Registers was used to study the national differences in trends of smoking during pregnancy. Second, the effects of prenatal smoking exposure on fetal brain development, assessed by brain MRI at term age, were studied by using data from the multidisciplinary PIPARI Study consisting of a 6-year cohort of VLBW/VLGA infants (n = 232, of which 18.1% were exposed to prenatal smoking) born in Turku University Hospital, Finland. Third, the effects of prenatal smoking exposure on psychiatric morbidity and use of psychotropic medication were studied in a cohort of children born from 1987–1989 in Finland (n = 175,869, of which 15.3% were exposed). The data used were obtained from population-based longitudinal registers from the National Institute of Health and Welfare, the Statistics Finland, and the Finnish Social Insurance Institution.

Results: Smoking rates during pregnancy differed considerably between the countries. Smoking rates were highest among teenagers and women with lower socioeconomic positions. The smoking prevalence was found to be increasing among teenagers in both Finland and Norway. Prenatal smoking exposure was associated with smaller frontal lobe and cerebellar volumes in preterm infants. A clear association was found between prenatal smoking exposure and psychiatric morbidity treated with specialized hospital care and the use of various psychotropic medications.

Conclusions: Prenatal smoking exposure had adverse effects on fetal brain development. These effects might explain part of the association found between smoking exposure and psychiatric problems in later life. Our study suggests that prenatal smoking exposure is linked with both mild and severe psychiatric problems. This study emphasizes the importance of efforts to reduce smoking during pregnancy.

Key words: brain, child, epidemiology, mortality, offspring, pregnancy, prenatal exposure delayed effects, preterm infant, psychiatric diagnosis, psychotropic drugs, smoking, trends

TIIVISTELMÄ

Mikael Ekblad
Raskaudenaikainen tupakointi ja keskushermoston kehitys
Lastentautioppi, Tyks ja Turun yliopisto

Tausta: Vaikka tietoisuus raskaudenaikaisen tupakoinnin haitoista on lisääntynyt viime vuosina, lisätutkimukset aiheesta ovat tarpeen. Tupakointi on yleisin ehkäistävissä oleva raskauskomplikaatioita ja lapselle myöhempiä haittoja aiheuttava tekijä.

Tavoitteet ja menetelmät: Tutkimme Pohjoismaiden tupakoinnin trendien eroja Pohjoismaisten syntymärekisterien tiedoilla raskaudenaikaisesta tupakoinnista. Raskaudenaikaisen tupakka-altistuksen yhteyttä keskosten aivojen kehitykseen tutkittiin aivojen MRI-kuvauksella lasketussa ajassa. Aineisto koostui PIPARI-tutkimuksen 6-vuotiskohortin pikkukeskosista (n = 232, joista 18,1 % altistui tupakoinnille), jotka syntyivät Turun yliopistollisessa keskussairaalassa. Lisäksi tutkimme tupakka-altistuksen yhteyttä vuosina 1987–1989 syntyneiden nuorten (n = 175,869, joista 15,3 % altistui) psykiatriseen sairastuvuuteen ja psykiatristen lääkkeiden käyttöön. Aineisto muodostettiin Terveyden ja hyvinvoinnin laitoksen, Tilastokeskuksen ja Kansaneläkelaitoksen tiedoista.

Tulokset: Raskaudenaikaisen tupakoinnin esiintyvyys erosi selkeästi Pohjoismaiden välillä. Yleisintä tupakointi oli teineillä ja alhaisen sosiaalisen taustan omaavilla naisilla. Huolestuttavinta oli, että teinien tupakointi on lisääntynyt Suomessa ja Norjassa. Raskaudenaikainen tupakointi oli yhteydessä pienempiin etuaivolohko- ja pikkuaivotilavuuksiin pikkukeskosilla. Löysimme myös selkeän yhteyden tupakka-altistuksen ja nuorten psykiatrisen sairastuvuuden ja psykiatristen lääkkeiden käytön välillä.

Päätelmät: Raskaudenaikaisella tupakka-altistuksella on selkeitä haittoja sikiön aivojen kehitykseen. Nämä löydökset voivat selittää osan löydetystä yhteydestä tupakka-altistuksen ja psykiatrisen sairastuvuuden välillä. Tutkimuksemme perusteella tupakka-altistus on yhteydessä lieviin ja vaikeisiin psykiatrisiin häiriöihin. Tutkimustuloksemme korostavat, että on tärkeää ehkäistä ja vähentää raskaudenaikaista tupakointia.

Avainsanat: aivot, epidemiologia, kuolleisuus, lapsi, sairastuvuus, raskaus, raskaudenaikainen altistuminen, pikkukeskonen, psykiatrinen lääkitys, psykiatrinen sairastuvuus, trendit, tupakointi

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ABBREVIATIONS

ADHD	Attention deficit and hyperactivity disorder
AGA	Average birth weight (±2 SD) for gestational age according to the sex-specific reference values from the Finnish population
ATC	Anatomic Therapeutic Chemical classification system
CDC	Centers for Disease Control and Prevention, the United States
CI	95% confidence interval
ICC	Intraclass correlation coefficient
ICD-10	International Classification of Diseases and Related Health Problems, Tenth Revision
IVH	Intraventricular hemorrhage
LGA	Large birth weight (>2 SD) for gestational age according to the sex-specific reference values from the Finnish population
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
nAChR	Nicotinic acetylcholine receptor
OR	Odds ratio
PDA	Patent ductus arteriosus
SD	Standard deviation
SGA	Small birth weight (< -2 SD) for gestational age according to the sex-specific reference values from the Finnish population
T	Tesla
THL	The National Institute for Health and Welfare (in Finnish: Terveyden ja hyvinvoinnin laitos), Helsinki, Finland
VLBW	Very low birth weight (≤ 1,500g)
VLGA	Very low gestational age (< 32 gestational weeks)
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I–IV, and on some supplementary unpublished data.

I   Ekblad M, Gissler M, Korkeila J, Lehtonen L. Trends in Smoking during Pregnancy in the Nordic Countries. Submitted.

II   Ekblad M, Korkeila J, Parkkola R, Lapinleimu H, Haataja L, Lehtonen L, and The PIPARI Study Group. Maternal Smoking during Pregnancy and Regional Brain Volumes in Preterm Infants. J Pediatrics 2010;156(2):185–190.

III   Ekblad M, Gissler M, Lehtonen L, Korkeila J. Prenatal Smoking Exposure and the Risk for Psychiatric Morbidity into Young Adulthood. Arch Gen Psychiatry 2010;67(8):841–849.

IV   Ekblad M, Gissler M, Lehtonen L, Korkeila J. Relation of Prenatal Smoking Exposure and Use of Psychotropic Medication up to Young Adulthood. Am J Epidemiol 2011;174(6):681–690.

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1. INTRODUCTION

There have been a considerable number of studies investigating the substances in cigarette smoke that may be responsible for the adverse effects to health caused by smoking after the preliminary study which showed an association between smoking and lung carcinoma in the 1950s (Doll and Hill 1950). Nowadays it is known that cigarette smoke contains thousands of potentially toxic ingredients like nicotine, carbon monoxide, methanol, and different kinds of carcinogens for example nitrosamines and aromatic amines (Hoffmann and Hoffmann 1997). The awareness of the possible adverse effects of smoking during pregnancy arose as late as the end of the 1950s, when Lowe (1959) published a study showing a lower birth weight among infants exposed to prenatal smoking, when compared to unexposed infants. During the last decades, knowledge of the adverse effects of smoking exposure on the developing fetus has increased. Smoking exposure has been suggested to associate with for example preterm birth (Fantuzzi et al. 2007, Windham et al. 2000), and sudden infant death syndrome (McDonnell-Naughton et al. 2012). It has been further suggested that prenatal smoking exposure is associated with far-reaching consequences for the exposed offspring, such as an increased risk for obesity (Durmus et al. 2011, Suzuki et al. 2009), decreased lung function (Gilliland et al. 2000), and psychiatric problems (Ernst et al. 2001) in later life. There is a need for longitudinal studies to gain information on the burden of the effects of smoking exposure on national psychiatric morbidity. Psychiatric problems in offspring might be mediated through altered brain development, caused by smoking exposure. However, the effects of prenatal smoking exposure on fetal brain development have not yet been sufficiently studied.

While the awareness of the adverse effects of smoking during pregnancy has increased, the prevalence of smoking during pregnancy has been decreasing in most developed countries. A decreasing trend in smoking during pregnancy has also been seen in the Nordic countries, except for Finland where the prevalence of smoking has remained at 15% for over 20 years (Nordic Perinatal Statistics 2010). It would be important to gain a better understanding of the reasons behind the different trends of smoking during pregnancy in the Nordic countries in order to also successfully decrease smoking during pregnancy in Finland.

2. REVIEW OF THE LITERATURE

2.1 Epidemiology of smoking

2.1.1 Overall smoking

Smoking is still generally seen as a male problem, despite the fact that the worldwide prevalence of smoking among men is in a slow decline while smoking among women will probably reach its peak later in the 21st century (Mackay and Amos 2003). In addition, the prevalence of smoking among women rose later in the 20th century than it did with men (Harris 1983), however, men clearly smoke more often than women in Asian countries like China, India, and Thailand, as well as in Russia and Egypt (Giovino et al. 2012). The overall prevalence of smoking has been decreasing in many developed countries, such as the United States, the United Kingdom, Ireland, and Denmark (Centers for Disease Control and Prevention (CDC) 2009, Graham 1996). In the United States, a total of 22% of men and 17% of women smoked daily in 2010 (Centers for Disease Control and Prevention 2011a). In addition, a significant decrease in women's smoking was observed between 2001 and 2009 in the United States (Zhao et al. 2012).

Smoking rates for women and men have converged in developed countries during recent decades (Graham 1996). In New Zealand, smoking rates have been quite similar between men and women since the 1980s (The Social Report 2010). In the Basque region of Spain, smoking rates among men have been decreasing since 1986, whereas among women they have only decreased since 2002. In 2007, 36% of men and 32% of women in the Basque region smoked (Bacigalupe et al. 2012). In Finland, the prevalence of daily smokers among men has decreased from 35% to 22% since 1978, from when smoking rates have been collected. However, women's smoking increased until the mid 1980s, and did not start to decrease until 2006. Approximately 16% of women smoked daily in 2010 (Health Behaviour and Health among the Finnish Adult Population, Spring 2010).

Despite these decreasing overall trends in smoking, the prevalence of smoking among young people has increased in some of European countries in recent decades. Most worryingly, smoking among teenage girls has increased more rapidly than in teenage boys (Hublet et al. 2006). In a study between Canada and ten European countries, Canada was the only country where the prevalence of teenage girls' smoking had significantly decreased between 1990 and 2002 (Hublet et al. 2006). In some of the European countries, teenage girls were more likely to smoke daily than teenage boys (Griesbach et al. 2003, Raisamo et al.

2011, Schnohr et al. 2008). However, the prevalence of smoking among both Finnish teenage boys and girls has started to decline in recent years, according to the Finnish Adolescent Health and Lifestyle Survey (Raisamo et al. 2011).

2.1.2 Smoking during pregnancy

2.1.2.1 Trends

Globally, decreasing trends in smoking during pregnancy have been seen in recent decades. According to the CDC's report, smoking during pregnancy has decreased from 18% to 11% between 1990 and 2002 in the United States (Centers for Disease Control and Prevention 2004). Smoking during pregnancy has also continued to decrease in the United States during the 21st century, although the prevalence of smoking during pregnancy has still increased in four states (Tong et al. 2009). In New York City, the prevalence of smoking during pregnancy decreased significantly after a tobacco control program was begun in 2002 (Stein et al. 2009). However, according to a telephone survey exploring trends in behavioral risk factors in pregnancy, smoking during pregnancy remained stable between 2001 and 2009 in the United States, though overall smoking in women decreased (Zhao et al. 2012). In Japan, the prevalence of smoking during pregnancy remained stable between 1996 and 2006, (Suzuki et al. 2010) and in Australia decreased significantly, from 22% in 1994 to 14% in 2007, although there were no specially targeted public health efforts carried out to influence smoking during pregnancy (Mohsin et al. 2011).

Smoking during pregnancy has decreased in all the Nordic countries except in Finland (Egebjerg Jensen et al. 2008, Jaakkola et al. 2001a, Kvalvik et al. 2008, Moussa et al. 2009, Nordic Perinatal Statistics 2010). In Sweden, the prevalence of smoking during pregnancy was over 30% in the mid 1980s. However, it has been decreasing since 1982, since the smoking data has been collected (Moussa et al. 2009), and only 7% smoked during pregnancy in 2010 (Nordic Perinatal Statistics 2010). The information on smoking during pregnancy has been collected since 1987 in Finland, and the prevalence has remained stable at 15% over these years (Jaakkola et al. 2001a). Data on smoking during pregnancy has been collected since 1999 in Norway, where smoking in the end of pregnancy had decreased from 17% to 13% during the first 5 years of data collection (Kvalvik et al. 2008).

The proportion of women who stop smoking during pregnancy differs greatly between countries. In Norway, the proportion of women who stop smoking during pregnancy has been increasing significantly over the years, and a total of

32% stopped smoking in 2004 (Kvalvik et al. 2008). Between 20% and 40% of pregnant women stopped smoking during pregnancy in Sweden in the early 1990s (Lindqvist and Åberg 1992). In Australia, only 4% of pregnant smokers stopped smoking during pregnancy from 1999–2003, although the prevalence of smoking during pregnancy has been decreasing (Mohsin and Bauman 2005). One of the highest rates for stopping smoking during pregnancy is in Japan, where 67% of women stopped smoking during pregnancy, and where 10% smoked throughout pregnancy (Kaneko et al. 2008). A Spanish study showed that the proportion of women stopping smoking during pregnancy had decreased from 37% to 21% from 1998–2002. However, the prevalence of smoking during pregnancy remained stable because smoking prior to pregnancy also decreased (Palma et al. 2007).

2.1.2.2 Factors associated with smoking

Many maternal and paternal factors may be associated with smoking during pregnancy; for example women who smoke during pregnancy are more often young, single (Jaakkola et al. 2001a, Moussa et al. 2009), have a lower socioeconomic position, a lower level of education and lower incomes (Ergin et al. 2010, Mohsin and Bauman 2005), and have more unplanned pregnancies (Orr et al. 2008, Villalbí et al. 2007) than women who do not smoke during pregnancy. According to a study from the United Kingdom, pregnant women who smoke are less likely to engage in important health related behaviors, or to feel responsible for the health of their child (Haslam and Lawrence 2004). The differences in smoking rates have increased according to maternal age in Denmark (Egebjerg Jensen et al. 2008) as well as in Sweden, according to age, education, and marital status (Moussa et al. 2009). In Finland, the prevalence of smoking was higher among women with a lower occupational status than among women with a higher occupational status, a difference which had been increasing in the 1990s (Jaakkola et al. 2001a). The partner's smoking (Villalbí et al. 2007) and a lower level of education increased the probability of smoking during pregnancy for women (Ergin et al. 2010).

2.1.2.3 Who stops smoking during pregnancy?

Pregnancy might be an ideal time to stop smoking because being pregnant could act as a strong motivator for parents (Haug et al. 1992). It has been suggested that women who do stop smoking during pregnancy often started smoking at an older age (Lindqvist and Åberg 2001, Lu et al. 2001), are therefore, less addicted to nicotine (Lu et al. 2001), and are infrequently heavy smokers (Håkansson et al. 1999, Lu et al. 2001). These women are also more often older, more often their

pregnancies are planned, and they often have previous children (Lindqvist and Åberg 2001, Lu et al. 2001, Villalbí et al. 2007). Women with higher socioeconomic positions are more likely to stop smoking than those with lower socioeconomic positions (Lu et al. 2001, Villalbí et al. 2007). However, there have been controversial results of the effect of women's levels of education on their stopping smoking during pregnancy (Lindqvist and Åberg 2001, Villalbí et al. 2007). It has been shown that pregnant women were four times more likely to smoke in early pregnancy and over two times more likely to smoke throughout pregnancy if their partner also smoked (Villalbí et al. 2007). Nevertheless, pregnant women clearly stopped more often if their partner gave them positive support to stop smoking (Lindqvist and Åberg 2001).

2.2 Prenatal smoking exposure

2.2.1 Assessment

The assessment of actual smoking during pregnancy is a major problem concerning studies investigating the effects of prenatal smoking exposure. The World Health Organization (WHO) has published standardized guidelines for measuring the prevalence of general smoking (Centers for Disease Control and Prevention 2011b, WHO 1998). Generally, a smoker is a person who smokes either daily or occasionally, and a daily smoker is a person who smokes at least one cigarette a day. There are no guidelines for the measurement of smoking during pregnancy. Usually, studies group smoking during pregnancy into two categories 1) no smoking, and 2) smoking during pregnancy which includes women who smoke at least one cigarette per day during pregnancy. Recently, women who smoke have been further grouped into two categories, those who 1) smoked throughout pregnancy, and 2) stopped smoking during early pregnancy, usually during the first trimester.

The assessment of smoking during pregnancy by using questionnaires, or interview surveys based on maternal self-reporting, is the most widely used method, which makes it possible to collect large materials. These categorization and assessment methods are used, for example, in epidemiologic studies and in the routine collection of national birth registers, like in the Nordic countries (Jaakkola et al. 2001a, Kvalvik et al. 2008, Moussa et al. 2009). Some studies also collect other kinds of data on smoking during pregnancy, and may include occasional smoking (Ergin et al. 2010) or the number of cigarettes smoked daily during pregnancy (Lindqvist and Åberg 2001).

Using biomarkers for smoking exposure might give more accurate and reliable information on the actual exposure of prenatal smoking, and therefore empower more accurate conclusions. Cotinine appears to be the best available biomarker for indicating smoking exposure (Benowitz 1996 and 1999) because cotinine is a primary metabolite of nicotine and so also shows the use of other nicotine containing tobacco products. The use of cotinine is suitable in fairly small studies but is not possible for use in larger epidemiological studies.

The use of cotinine as a biomarker is still challenging since overall cotinine cut-off levels among pregnant smokers has not yet been established. The nicotine cut-off levels for both smoking and non-smoking pregnant women varied widely between studies using nicotine as a biomarker (Kvalvik et al. 2012, Lindqvist et al. 2002, Shipton et al. 2009). The assessment of active smokers and non-smoking women is even more difficult because a proportion of non-smoking women may be exposed to environmental tobacco smoke during pregnancy. It would thus be important also to identify pregnant passive smokers because of the previously shown adverse effects on fetal outcomes and infant health (Leonardi-Bee et al. 2011, Salmasi et al. 2010).

2.2.2 Reliability of self-reporting

There are many studies investigating the reliability of self-reporting for smoking during pregnancy, using cotinine measurements. The results of these studies have been controversial. Many of the studies have concluded that data of self-reported smoking among pregnant women was inaccurate (Dietz et al. 2011, England et al. 2007, Ford et al. 1997, Pärna et al. 2005, Shipton et al. 2009, Walsh et al. 1996), whereas others showed that self-reported smoking data was highly accurate (George et al. 2006, Kvalvik et al. 2012, McDonald et al. 2005). In a study from Scotland, the United Kingdom, the self-reported smoking status among pregnant women underestimated their true smoking by 25% when smoking was verified by cotinine measurements (Shipton et al. 2009). However, a Norwegian study suggested that self-reported smoking was a valid marker (Kvalvik et al. 2012).

It has been shown that the information on self-reported smoking among pregnant women was more reliable if smoking habits were assessed repeatedly during pregnancy rather than with a single assessment (Bakker et al. 2011, George et al. 2006). A recent study has reported that the pregnant women who underreport their smoking habits are more often older, more highly-educated, married, employed full-time, and planning to breastfeed; although the prevalence of smoking during pregnancy was also significantly lower in these women (Land et

al. 2012). In addition, women who only smoke occasionally are more likely to underreport their smoking than those who smoke daily.

There have been concerns about the accuracy of self-reported smoking data in medical birth registers, as a study from the United States showed that interview data was of a higher quality than data obtained from medical birth records or birth certificates (Srisukhumbowornchai et al. 2012). On the other hand, a Finnish study showed excellent agreement between questionnaire-gathered information on smoking habits during pregnancy and the data from medical records in the Finnish Medical Birth Register (Jaakkola et al. 2001a). In addition, all of the Nordic Medical Birth Registers have been shown to be reliable for scientific research (Cnattingius et al. 1990, Gissler et al. 1995, Irgens 2000, Knudsen and Olsen 1998, Teperi 1993).

2.2.3 Mechanisms of fetal effects

Tobacco smoke contains over 4000 identified chemicals (Geiss and Kotzias 2007, Hoffmann and Hoffmann 1997), including many of which may interfere with brain development either alone or in concert with other chemicals (Dempsey and Benowitz 2001). The major components in cigarette smoke that threaten health are nicotine and carbon monoxide. The effects of the other potentially toxic ingredients of tobacco smoke on the development of fetal brain are less well known because most of the animal studies use nicotine exposure to model prenatal smoking exposure. Studies which use tobacco smoke exposure to model prenatal smoking exposure may give more reliable results. However, it has been suggested that animal lungs cannot absorb the components of tobacco smoke to the same extent as human lungs (Coggins 2007).

The major psychoactive component of tobacco smoke is nicotine (Dani and Harris 2005). Nicotine crosses the placenta during pregnancy (Luck et al. 1985, Berlin et al. 2010), and therefore has been strongly associated with negative effects on the growing fetus. A previous study showed that cotinine already accumulates in the fetal compartments at seven weeks of gestation both in pregnant passive and active smokers (Jauniaux et al. 1999a). Nicotine concentrations have been shown to be even higher in the fetuses than in their smoking mothers or in their mothers exposed to passive smoking (Jauniaux et al. 1999a, Luck et al. 1985).

Low concentrations of carbon monoxide are produced endogenously with normal physiologic functions like control of vascular tone (Wang 1998). Exogenous carbon monoxide originates from, among other things, tobacco smoke. Carbon

monoxide binds with hemoglobin with a 250 times higher affinity than oxygen (Benesch et al. 1972) producing carboxyhemoglobin, which limits the amount of circulating oxygen to the tissues. Carbon monoxide has been shown to cross the placenta and enter fetal circulation (Hill et al. 1977) and, therefore, may lead to hypoxia in the fetus and alter fetal brain development.

2.3 Consequences of prenatal smoking exposure

2.3.1 General

The first studies suggesting adverse effects of smoking during pregnancy for the developing fetus were published in the 1950s, when a study from the United Kingdom showed that the mean weight for infants of mothers who smoked throughout pregnancy was 170 grams less than infants of non-smoking mothers (Lowe 1959). Since then, the effects of prenatal smoking exposure have been increasingly studied. Smoking during pregnancy has been associated with pregnancy complications including ectopic pregnancies, placental abruption, placenta previa, and a premature rupture of membranes (Castles et al. 1999). Nowadays, the adverse pregnancy outcomes caused by prenatal smoking exposure for newborn infants, such as preterm birth (Fantuzzi et al. 2007, Windham et al. 2000) and low birth weight (England et al. 2001, Jaddoe et al. 2008), have also been well reported.

Raatikainen et al. (2007) found that the increased risk of fetal growth restriction and low birth weight caused by smoking throughout pregnancy could be avoided if mothers reduced their smoking to fewer than five cigarettes per day, although the increased risk for preterm birth and perinatal death remained significantly higher among smoke-exposed infants. When pregnant mothers stopped smoking during early pregnancy, no differences in the prevalence of low birth weights and preterm births were observed between exposed and unexposed newborns (Jaddoe et al. 2008, Lindley et al. 2000). However, if the mothers continued to smoke fewer than 10 cigarettes per day, a non-significant trend for an increased risk of low birth weight and preterm birth was seen, suggesting that smoking should be stopped completely during pregnancy (Jaddoe et al. 2008).

As the so-called Barker's hypothesis suggests, low birth weight has been shown to be a significant risk factor for obesity, hypertension, and type 2 diabetes (Barker and Clark 1997, Barker 1998). Significantly increased blood pressures were seen in healthy infants exposed to prenatal smoking, when compared to unexposed infants, until the age of 12 months and a dose-relationship was observed for smoking exposure (Beratis et al. 1996). Another study showed that

prenatal smoking exposure increased children's blood pressure until the age of six years, and that this effect was not mediated through low birth weight or other confounding factors (Blake et al. 2000). Recent studies have shown that children exposed to prenatal smoking were twice as likely to be obese as unexposed children (Durmus et al. 2011, Suzuki et al. 2009), and a clear dose-relationship for smoking exposure was observed (von Kries et al. 2002). In addition, according to a British longitudinal birth cohort study, prenatal smoking exposure was a true risk factor for early adult onset diabetes (Montgomery and Ekbom 2002).

Smoking during pregnancy has also been associated with sudden infant death syndrome (McDonnell-Naughton et al. 2012). Mitchell and Milerad (2006) conclude in their review article that about one-third of sudden infant death syndrome deaths might have been prevented if the fetuses would not have been exposed to prenatal smoking. One mechanism explaining this relationship may be that nicotine exposure alters the lung's mechanical response to hypoxia, as has been shown in lambs (Sandberg et al. 2007).

A variety of adverse pulmonary outcomes in human offspring have been associated with prenatal smoking exposure in recent studies. Decreased lung functions, such as peak expiratory flow rate and forced expiratory flow, were associated with prenatal smoking exposure in school-aged children (Gilliland et al. 2000). In addition, prenatal smoking exposure has been associated with an increased risk of wheezing from the first years of life (Duijts et al. 2012, Lannerö et al. 2006) to adolescence (Gilliland et al. 2001). In a Finnish population-based cohort study, the risk for asthma during the first seven years of life was increased independently by prenatal smoking exposure, although low birth weight and preterm birth also increased the risk of asthma (Jaakkola and Gissler 2004). Other studies have observed similar results (Gilliland et al. 2001). Prenatal smoking exposure was found to significantly increase the need for hospital care up to the age of 12 years (Yuan et al. 2001), and even mortality due to infectious diseases (Metzger et al. 2013).

2.3.2 Central nervous system in animals

There are only a few animal studies using tobacco smoke exposure instead of nicotine exposure during pregnancy. One study, which used tobacco smoke exposure on pregnant rats, showed that offspring exposed to tobacco smoke had lower birth weights and reduced growth, but that the exposure did not have adverse effects on developmental landmarks for example motor activity and learning (Gaworski et al. 2004). However, another study using tobacco-exposed

pregnant rats found that smoke exposure altered the development of the pedunculopontine nucleus in the brain, which modulated arousal and attention in the offspring (Garcia-Rill et al. 2007).

2.3.2.1 Effect of nicotine exposure

Nicotine has been shown to be neurotoxic in animal studies, using rats or mice, and in human studies (Ferrea and Winterer 2009, Shea and Steiner 2008, Wikström 2007). Nicotine involves the interactions with nicotinic acetylcholine receptors (nAChRs), which can be found in the central and peripheral nervous systems, and which are shown to involve the acetylcholine neurotransmission postsynaptically (Dani 2001). The nAChR proteins and gene transcripts have been shown to be present at a four to five week gestational age in human fetuses' brains and spinal cords (Hellström-Lindahl et al. 1998). The development of nAChRs is crucial for normal brain development because the nAChRs modulate, for example, axonal path finding and synapse formation (Role and Berg 1996, Slotkin 2004). In rodent studies the activation of nAChRs by nicotine has been shown to interfere with the immature and developing nervous system and alter brain development (Dwyer et al. 2008, Gold et al. 2009, Huang et al. 2007, Miao et al. 1998, Muhammad et al. 2012) and behavior (Eriksson et al. 2000). In addition, nicotine exposure has been shown to induce long-lasting changes in the expression of nAChRs (Chen et al. 2005).

The nAChRs also involves, presynaptically, the release of other catecholaminergic neurotransmitters, for example, dopamine, epinephrine, norepinephrine, and serotonin (Dani 2001), which are involved in several behavioral and cognitive functions (Arnsten 2006). Navarro et al. (1988) found suppressions of norepinephrine and dopamine levels and synaptic hypoactivity in nicotine-exposed rats. Prenatal nicotine exposure in rats has been linked with hyperactive behavior (Ajarem and Ahmad 1998). It has been suggested that the effect of nicotine exposure on later behavior may mediate via a negative influence on dopaminergic function in rats (Kane et al. 2004). Furthermore, nicotine exposure has been shown to alter serotonin turnover in rat brains (Muneoka et al. 1997). Alterations in the level of serotonin may interfere with normal brain development, and therefore may increase the risk for emotional disturbances (Shea and Steiner 2008).

Nicotine exposure has also been shown to directly alter cell differentiation and proliferation (Slotkin et al. 1986) and produce brain cell damage (Slotkin et al. 1987) on a fetal rat's brain. Another mechanism of alteration in brain development after nicotine exposure during pregnancy has been suggested to be

overexpression of c-Fos in rat brain (Trauth et al. 1999). C-Fos is a nuclear transcription factor that involves cell differentiation and death.

2.3.2.2 Effect of carbon monoxide exposure

In a study using guinea pigs, there was no difference in either length of gestation or birth weight after carbon monoxide exposure (McGregor et al. 1998, Venditti et al. 2011). However, carbon monoxide exposure in rats during pregnancy did alter the development of the cerebellum (Lopez et al. 2009) and hippocampus (Vaccari et al. 2001).

2.3.3 Central nervous system in humans

The knowledge of adverse effects of prenatal smoking exposure on brain development and function in humans has increased in recent years, as reviewed by Bublitz and Stroud (2012). Alterations on neurobehavior have been found among newborns who had been exposed to prenatal smoking (Godding et al. 2004, Law et al. 2003). A study including 27 exposed and 29 unexposed healthy newborn infants found that the infants exposed to prenatal smoking, verified by cotinine measurements, were more excitable and hypertonic, required more handling, and showed more stress signs than the unexposed infants, and a dose-relationship was also seen (Law et al. 2003). Another study showed that newborns exposed to prenatal smoking had significantly higher incidences of neurologic and withdrawal symptoms than unexposed newborns, although these symptoms decreased in the exposed newborns during the first five days of life (Godding et al. 2004). These studies suggest that newborns may experience clear withdrawal symptoms if exposed to prenatal smoking during pregnancy.

Some of the adverse effects of smoking exposure during pregnancy may be mediated through epigenetic mechanisms. Smoking exposure during pregnancy has been shown to increase the methylation of DNA, which may cause epigenetic changes in the human genome (Terry et al. 2008). Previously, smoking exposure during pregnancy has been shown to affect fetal and placental protein metabolism and enzyme activity (Jauniaux et al. 1999b). A recent human study found that smoking exposure during pregnancy increased the rate of methylation of a brain-derived neurotrophic factor, BDNF (Toledo-Rodriquez et al. 2010), which is an important gene for normal brain development (Martinowich et al. 2003). Other genes have also been suggested to modulate the adverse effects of smoking exposure on brain development (Paus et al. 2012) and later psychiatric problems (Cents et al. 2012, Lotfipour et al. 2010). Another mechanism of the adverse effects of smoking exposure could be the direct effect of hypoxia on the

brain by exposure to carbon monoxide. Verhagen et al. (2011) found that cerebral oxygen saturations were lower during the first week of life in preterm infants exposed to smoking, when compared to unexposed infants.

2.3.3.1 Head growth and circumference

Normal brain development usually leads to regular head growth and head circumference. In numerous studies reduced head growth during pregnancy (Jaddoe et al. 2007, Roza et al. 2007) has been identified in infants exposed to prenatal smoking, when compared to unexposed infants (Figure 1).
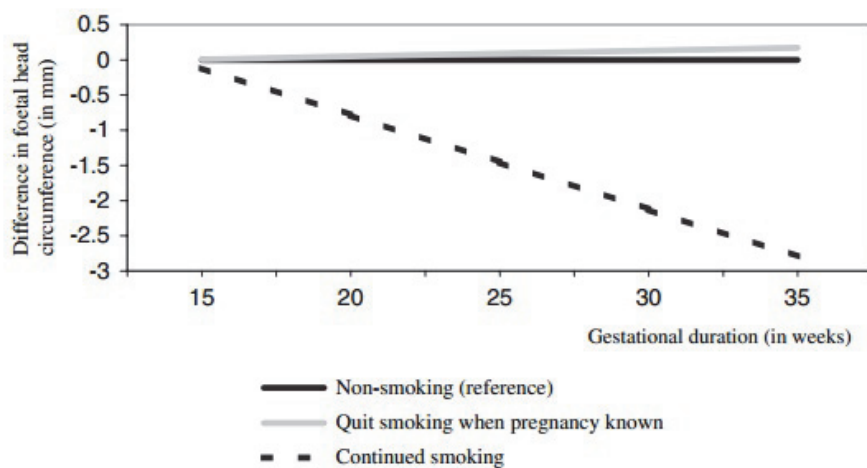
Figure 1. Estimated differences in fetal head circumference assessed with repeated ultrasound measurement during pregnancy according to prenatal smoking exposure. Modified from Roza et al. 2007.

The effect of prenatal smoking exposure on birth weight and head circumference at birth was studied more carefully in a meta-analysis in which study-specific estimates were pooled using random-effects meta-analysis and shown graphically by forest plots (Figure 2). The meta-analysis comprised nine studies that included information on birth weight and head circumference at birth, of which six included only full-term infants (Fenercioglu et al. 2009, Harrison et al. 1983, Himes et al. 2012, Ong et al. 2002, Wang et al. 1997). The studies were divided according to what the smoking information was based upon. Head circumference was on average 0.5 cm, and birth weight 200 grams, smaller in infants exposed to smoking throughout pregnancy than unexposed infants. A greater effect was seen in studies using cotinine verification of smoking exposure, although the study groups were smaller.
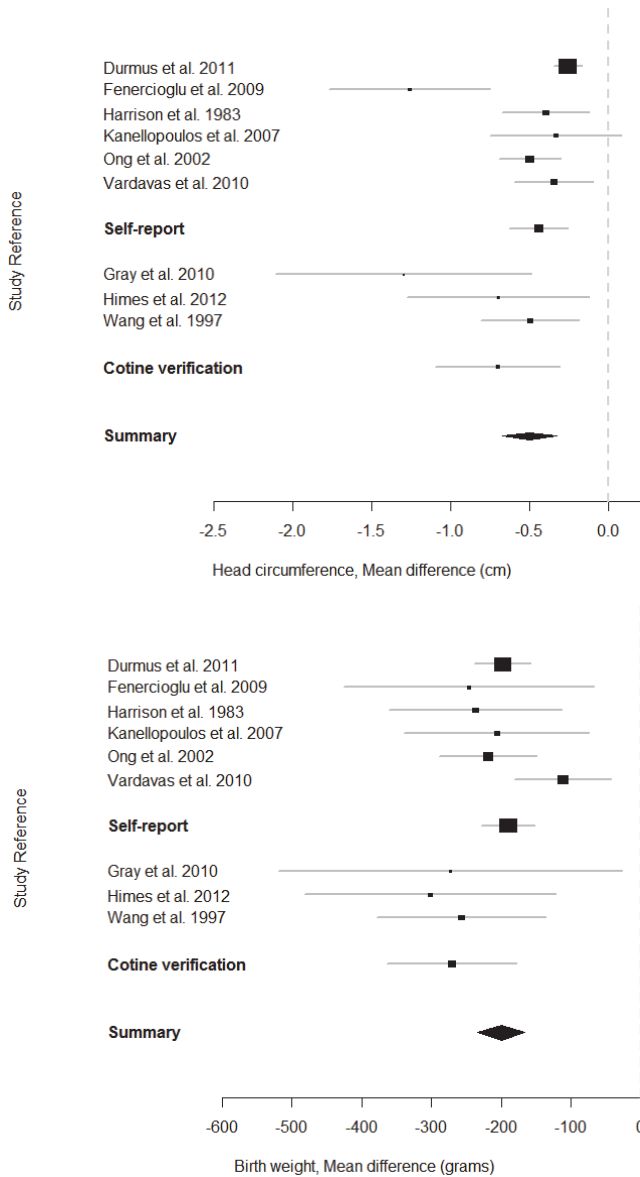
Figure 2. The mean differences of head circumference (cm) at birth and birth weight (grams) in newborn infants exposed to prenatal smoking, compared to unexposed infants (forest plot).

The infants exposed to smoking had a 1.5 times higher risk for a head circumference below -2 standard deviation (SD) (Källén 2000). Król et al. (2012) further evaluated the effects of smoking on cerebral mass by using a formula for calculating cerebral mass from newborns' head circumferences. They found that the risk for a significantly lower cerebral mass was almost four times higher in

newborns exposed to continued smoking. Another study showed that head circumferences and estimated brain-body weight ratios associated negatively to prenatal smoking exposure, but that there was no difference when smoking was stopped in early pregnancy (Lindley et al. 2000).

2.3.3.2 Brain structure

Studies using head circumference as a predictor for brain growth do not provide a proper insight into specific structural or functional alterations of the brain. Several studies have found an association between psychological development and prenatal smoking exposure as well as between psychological development and brain alterations in the offspring. However, there are only a few human studies investigating the effects of prenatal smoking exposure and brain development (Bublitz and Stroud 2012).

A study using repeated ultrasound examinations of the developing fetus during pregnancy found that fetuses exposed to smoking had a smaller atrial width of the lateral ventricle and transcerebellar diameter than did unexposed fetuses (Roza et al. 2007). Other studies have investigated the effects of prenatal smoking exposure on brain structure in childhood and adolescence with retrospective information on smoking during pregnancy (Haghighi et al. 2013, Jacobsen et al. 2007a, Lotfipour et al. 2009, Paus et al. 2008, Rivkin et al. 2008, Toro et al. 2008). Prenatal smoking exposure has been associated with smaller corpus callosum (Paus et al. 2008) and amygdala (Haghighi et al. 2013), thinner orbito-frontal, middle frontal, and parahippocampal cortices (Toro et al. 2008), increased fractional anisotropy in anterior cortical white matter (Jacobsen et al. 2007a), and reductions of cortical gray matter and total parenchymal volumes (Rivkin et al. 2008). Lotfipour et al. (2009) showed that smoking exposure during pregnancy modulates the development of the orbito-frontal cortex, which may increase the likelihood of drug use during adolescence. These findings provide some evidence for the impact of smoking exposure on later psychological problems.

There are some studies which demonstrate adverse effects of smoking exposure during pregnancy on brain function (Bennett et al. 2009, Jacobsen et al. 2006, Jacobsen et al. 2007b). Bennett et al. (2009) found, in a functional magnetic resonance imaging study, that 12-year-old children who had been exposed to prenatal smoking showed greater activation in a large and diverse set of brain regions than did unexposed children, which suggests altered brain function. In addition, two studies have suggested alterations in auditory brainstem-evoked responses, leading to greater auditory impairments in children exposed to

smoking during pregnancy, when compared to unexposed children (Kable et al. 2009, Peck et al. 2010).

2.3.4 Psychological development

Prenatal smoking exposure has been suggested to causally increase the risk of later behavioral problems (Cornelius and Day 2009), and psychiatric problems, in the offspring (Ernst et al. 2001). Most psychological problems are the result of complex causal chains involving genetic, environmental, and social risk factors (Kraemer et al. 2001). However, the length of time between prenatal exposure and the development of psychological problems in the offspring makes it difficult to evaluate the true effect of smoking during pregnancy (Knopik 2009).

A mother's young age, lower levels of education and psychiatric problems have been shown to increase the risk for psychiatric problems such as conduct disorders in her offspring (Hill 2002), and these children are more often exposed to smoking during pregnancy. In addition, negative parenting methods, like harsh and coercive discipline, may increase the risk for problems such as antisocial behavior in children (Fagot et al. 1998). Genetic factors play different roles, depending on the psychiatric problem, for example in conduct disorders, around half of the associations between smoking during pregnancy and conduct disorders was attributable to genetic effects and, with further controlling for familial factors, the effects of smoking was reduced, by between 75% and 100% of the effects (Maughan et al. 2004). The heritability has been suggested to be at around 30% for anxiety disorders (Bienvenu et al. 2011, Kendler et al. 1992), 40% for panic disorders (Bienvenu et al. 2011, Kendler et al. 1993), from 40 to 70% for substance abuse (Bienvenu et al. 2011), 80% for attention deficit and hyperactivity disorders (ADHD) (Coolidge et al. 2000), and from 60% to 85% for bipolar disorders and schizophrenia (Bienvenu et al. 2011, Wray and Gottesman 2012, Lichtenstein et al. 2009).

2.3.4.1 Behavioral problems

The negative effects of prenatal smoking exposure on behavioral function have even been found in young children. Orlebeke et al. (1997) assessed behavioral problems in 1,377 2- to 3-year-old children according to prenatal smoking exposure. A significant association was found between smoking exposure and externalizing problems, including aggressive and overactive behavior. Similar results were found in a Norwegian study with 22,545 three-year-old children (Stene-Larsen et al. 2009). Conversely, some studies have concluded that prenatal smoking exposure and behavioral problems in young children were not

associated after controlling for various parental factors (Lavigne et al. 2011, Roza et al. 2009). However, a prospective study with 318 children followed to 14 years of age found that children exposed to prenatal smoking had more externalizing problems at the age of six years when compared to unexposed children (Cornelius et al. 2011), and that this difference persisted to the age of 14 (Cornelius et al. 2012). These finding indicate that the effects of smoking on child behavior could be identified early.

2.3.4.2 Attention problems

There are several studies with controversial results investigating the effects of prenatal smoking exposure on the risk of ADHD in the offspring. Numerous studies have found everything from weak to strong associations between prenatal smoking exposure and hyperactivity and attention problems in children, including case-control (Linnet et al. 2005, Milberger et al. 1996, Schmitz et al. 2006) and cohort studies (Froehlich et al. 2009, Kotimaa et al. 2003, Markussen Linnet et al. 2006, Obel et al. 2009, Thapar et al. 2003).

There are also studies suggesting that the association between prenatal smoking exposure and hyperactivity and attention problems may be due to genetic and familial factors rather than a causal effect of smoking (Langley et al. 2012, Obel et al. 2011, Thapar et al. 2009). Obel et al. (2011) found, in a national register study, that prenatal smoking exposure was associated with hyperkinetic disorder in offspring, but there was no difference after sibling-matched analysis, suggesting smoking exposure had only a small effect. Another study compared the risk of smoking exposure on child ADHD symptoms in mother and offspring, for related and unrelated pairs, which found that the magnitude of the association was higher in related than in the unrelated pairs, suggesting the effects of inheritance (Thapar et al. 2009). In their previous study, with 1,452 pairs of twins aged 5–16 years, a clear association between smoking exposure and ADHD symptoms was found (Thapar et al. 2003). Furthermore, Obel et al. (2009) used three population-based pregnancy cohorts and found that the association between smoking exposure and ADHD in children cannot be entirely explained by genetic factors.

A positive dose-response relationship has been shown between prenatal smoking exposure and hyperactivity (Kotimaa et al. 2003) and attention problems (Koshy et al. 2011). As ADHD is more common in boys (Sciberras et al. 2011), studies with only boys (Milberger et al. 1996) give stronger results for the effects of smoking exposure on attention problems, compared to studies with both genders (Mick et al. 2002).

2.3.4.3 Conduct problems

Offspring exposed to prenatal smoking has been shown to have a 1.5 to 4 times greater risk for severe antisocial behavior, including conduct disorders, than unexposed offspring (Brion et al. 2010, Button et al. 2005, Fergusson et al. 1998, Wakschlag et al. 1997, Weissman et al. 1999). These findings have been more pronounced in males than in females (Fergusson et al. 1998, Wakschlag et al. 1997, Weissman et al. 1999).

The association between prenatal smoking exposure and antisocial behavior has been suggested to be moderate after considering the effects of prenatal and postnatal risk factors (Wakschlag et al. 2002). However, a British longitudinal twin study concluded that even the entire association between prenatal smoking exposure and childhood conduct problems might be explained by genetic and familial factors (Maughan et al. 2004), and other studies have suggested the same (Silberg et al. 2003). Many parental factors, such as maternal depression (Murray et al. 2010) and parental maladaptive behavior (Boden et al. 2010), and socioeconomic factors such as single and teenage mothers, and poor neighborhoods (Boden et al. 2010, Murray et al. 2010), have been shown to increase the risk of conduct problems in offspring.

The independent effects of prenatal smoking exposure on the increased risk for patterns of antisocial behavior have also been questioned because of the suggested increased risk for ADHD after prenatal smoking exposure, and the co-morbidity of ADHD and antisocial behavior, which may be mediated by the same genes (Coolidge et al. 2000, Silberg et al. 1996). In addition, it has been known that ADHD behaves as a risk factor for antisocial behavior (Fergusson and Horwood 1995, Taylor et al. 1996). However, a study using a population-based twin register data suggested that the association of smoking during pregnancy with antisocial behavior is not attributable to its association with ADHD (Button et al. 2005).

2.3.4.4 Substance abuse

There are only a few longitudinal studies investigating the effects of smoking during pregnancy on substance abuse in offspring, with controversial results. Nomura et al. (2011) found that in a sample of 1,625 individuals, followed for 40 years from pregnancy, the life time risk for alcohol use disorders was increased by 30% in individuals exposed to more than 20 cigarettes per day. In addition, results from a Danish study by Brennan et al. (2002), with a birth cohort of 8,112 children followed up to 40 years of age, indicate a dose-relationship between

prenatal smoking exposure and hospitalization due to substance abuse (psychoses due to alcohol or drugs, and alcohol/drug intoxication, withdrawal, abuse or dependence). In a study with only 147 children (34% exposed to prenatal smoking) between six and 23 years of age, followed for 10 years, an increased risk of drug abuse was found for exposed girls, but not for exposed boys, and no risk was found for alcohol abuse (Weissman et al. 1999).

2.4 Gaps in the current literature

The knowledge of the adverse effects of prenatal smoking exposure has increased over recent decades. Although several studies have demonstrated the effects of prenatal smoking exposure on emotional and behavioral development and attention and conduct disorders, the mechanisms of these effects are not yet well understood. Smoking exposure has also been linked to an increased risk for some psychiatric problems, but there are no population-based longitudinal studies which evaluate the effects of smoking exposure on a broad range of psychiatric morbidity. We need more knowledge of the differences in smoking during pregnancy between countries to develop ways to reduce prenatal smoking exposure.

3. AIMS OF THE STUDY

The main purpose of this thesis was to increase the knowledge of the adverse effects of smoking during pregnancy, to study the possible pathways of effects of prenatal smoking exposure, and to delineate target groups for interventions to reduce prenatal smoking exposure.

The specific aims in this thesis were:

1. To explore the differences of the trends in smoking during pregnancy in the Nordic countries (**I**).

2. To extend the knowledge of the maternal background factors affecting smoking during pregnancy in the Nordic countries in order to direct smoking cessation enlightenment to the populations with the most potential (**I**).

3. To evaluate the association between smoking during pregnancy and the brain volumes at term in very low birth weight (VLBW) and very low gestational age (VLGA) infants (**II**).

4. To investigate the effects of prenatal smoking exposure on psychiatric morbidity and use of psychotropic drugs among Finnish young adults by using a population-based longitudinal register data adjusted by severe maternal psychiatric morbidity (**III–IV**).

4. MATERIALS AND METHODS

4.1 Study design

This study consists of four original publications completed with unpublished data. Original publication I was based on statistics of smoking habits during pregnancy from the Nordic countries. Original publication II was part of the multidisciplinary PIPARI Study (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) in which a 6-year cohort of VLBW/VLGA infants is followed until school age in Turku University Hospital, Finland. Data in original publications III and IV were obtained from population-based longitudinal registers from the National Institute of Health and Welfare, Statistics Finland, and the Finnish Social Insurance Institution.

4.2 Nordic birth register study (I)

4.2.1 Data collection

A data request for detailed information on smoking during pregnancy in the five Nordic countries was sent to the heads of the birth registers in each country in January 2010. The register organizations were the Danish National Board of Health, the National Institute for Health and Welfare (THL) in Finland, the Public Health Institute in Iceland, the Norwegian Institute of Public Health, and the Swedish National Board of Health and Welfare. Iceland reported that their Medical Birth Register does not contain information on smoking.

The following data was requested: 1. Data on smoking during pregnancy by the year of birth of the child for the number of women who a) smoked during the first trimester of pregnancy, and b) smoked after the first trimester of pregnancy. 2. Data on smoking during pregnancy by background factor: maternal age, parity (none/one or more), marital status (married or cohabiting/single), and socioeconomic position.

The available data on overall smoking for females aged over 15 years by country were derived from the WHO European Health for All Database (http://data.euro.who.int/hfadb/). The data on overall smoking for Finnish teenagers aged 14–18 years was derived from the Adolescent Health and Lifestyle Survey (Raisamo et al. 2011).

4.2.2 Data sources

The Finnish Medical Birth Register includes data on both live-born and stillborn fetuses with a gestational age of 22 weeks or more, or with a birth weight of 500 grams or more. The register keeper, currently the THL, receives this data from all hospitals with a delivery unit and, in the case of home births, from the assisting health care personnel. The Register includes information on the mother's and child's identification numbers; maternal background, health care, and interventions during pregnancy and delivery; and the outcome of the newborn until 7 days of age. A midwife collects the information on smoking during pregnancy from the mothers during antenatal care (none/<10/>10 cigarettes per day between 1987 and September 1990, and since October 1990 information on smoking during the first trimester/after the first trimester of pregnancy). Most of the Medical Birth Register content corresponds well or satisfactorily with hospital record data according to two data quality studies (Gissler et al. 1995, Teperi 1993).

The Danish Medical Birth Register (the Danish National Board of Health, currently Statens Serum Institut) contains information on all deliveries since 1973. Data on smoking during pregnancy has been collected since 1991, with information on smoking after the first trimester of pregnancy collected separately since 1997. The database contains 99.8% of all deliveries in Denmark and the data quality has been shown to be reliable (Knudsen and Olsen 1998).

The Medical Birth Register of Norway (the Norwegian Institute of Public Health) contains information on all pregnancies after 12 weeks of gestation in Norway since 1967. The attending midwife or physician responsible for delivery records the background data on standardized notification forms shortly after the delivery. The information on smoking (smoking during the first trimester/after the first trimester) has been gathered since 1999. Contrary to the other Nordic countries, the mother's informed consent for collecting smoking data is required; permission has been received from 81% to 88% of mothers. The Medical Birth Register of Norway has frequently been used for scientific research and is deemed a reliable source (Irgens 2000).

The Swedish Medical Birth Register (the Swedish National Board of Health and Welfare) contains information on deliveries and newborn infants since 1973. Stillbirths were included from 28 weeks of gestation until 2006, and thereafter from 22 weeks of gestation. The register contains information on various maternal characteristics; information on smoking has been collected since 1983, with more detailed information (smoking during the first trimester/after the first

trimester) since 2000. Quality studies have reported that the Swedish Medical Birth Register includes information on 99% of all infants born in Sweden (Cnattingius et al. 1990).

Socioeconomic position (high/intermediate/low) was evaluated in Finland by occupational background (upper white-collar workers such as teachers, physicians, and journalists; lower white-collar workers such as secretaries, nurses, and shop assistants; blue-collar workers such as dressmakers, cooks, and cleaners), and in Norway by education (1–10 years of education, compulsory education; 11–13 years of education; at least 14 years of education, including at university level and higher). The women who only smoked during the first trimester of pregnancy are referred to as those who "smoked in early pregnancy", whereas women who smoked after the first trimester are referred to as those who "smoked in the end of pregnancy or throughout pregnancy".

The received data contained information on smoking during the first trimester and after the first trimester betwen 1991–2010 and 1997–2010 in Denmark, 1987–2010 and 1991–2010 in Finland, and 1983–2008 and 2000–2008 in Sweden, respectively, and for both categories during 1999–2009 in Norway. The other received data is shown by country in Table 1. The number of deliveries and the average prevalence of smoking in early pregnancy (number of smokers during pregnancy) during the included time period for smoking data by each country was: in Denmark 1,298,685 deliveries with an average of 21% (274,469) smoking prevalence; 1,432,969 and 15% (215,889) in Finland; 637,752 and 20% (107,103) in Norway; and 2,627,178 and 17% (450,290) in Sweden, respectively.

Table 1. Received data from the Nordic countries

	Denmark	**Finland**	**Norway**	**Sweden**
Maternal age	x	x	x	x
Number of deliveries	-	x	x	x
Marital status	-	x	x	x
Socioeconomic position	-	x	x	-

"x" = Received data; "-" = No data available

4.3 Clinical study (II)

4.3.1 Data collection

The second study was a part of the multidisciplinary PIPARI Study which consisted of VLBW/VLGA infants born from 2001 to 2006 at Turku University Hospital. Inclusion criteria included a birth weight ≤1,500 gram in preterm infants (born below 37 gestational weeks) from 2001 to the end of 2003. From the beginning of the year 2004, the inclusion criteria were expanded to include all infants below the gestational age of 32 weeks at birth even if the birth weight exceeded 1,500g. In addition, at least one of the parents had to speak either Finnish or Swedish. A total of 293 VLBW/VLGA infants were born, and 40 (13.7%) of them died before discharge. Six infants (2.0%) were excluded because the language criteria were not fulfilled. Of the 247 infants that were invited to the study 11 families refused, and four families moved outside the hospital catchment area. Altogether, 232 (93.9%) eligible preterm infants participated in the study.

The background information, and the information about the smoking and alcohol consumption of the mothers during pregnancy, was collected from maternal antenatal follow-ups and hospital records. Questions about smoking during pregnancy are part of the neonatal follow-up, where the information is recorded and reported nationally, along with other prenatal data. In addition, before discharge, the mothers completed a questionnaire about their smoking habits during pregnancy (0/ 1–10/ 11–20/ >20 cigarettes per day), their use of alcohol and use of illicit drugs. Neonatal inflammatory diseases including chronic lung disease, necrotizing enterocolitis (NEC), and septicemia, were defined according to the Vermont Oxford Network definitions (Vermont Oxford Network Database 2005).

The background information of the studied infants (II) is shown in Table 2. A total of 42 (18.1%) mothers out of 232 smoked during pregnancy. The median number of cigarettes smoked per day was 10.

4.3.2 Head circumference and brain imaging

Head circumference was measured by using tape-measurement of the maximal occipito-frontal circumference at three different ages: at birth, at term and at two years of age, corrected for prematurity. The first measurement was performed at the hospital and the subsequent measurements were performed as part of a follow-up visit. Serial brain ultrasound examinations were performed by the attending neonatologist, trained to carry out brain ultrasound examinations, in the

neonatal intensive care unit at 3 to 5 days, at 7 to 10 days, at one month of age, and then monthly until discharge from the hospital.

Table 2. Background factors in premature infants exposed and unexposed to prenatal smoking (study II).

Characteristics	Exposed (n = 42)	Unexposed (n = 190)
Gender, male	28 (66.7)	103 (54.2)
Gestational age, wk x/7 d		
mean (SD)	29 1/7 (2 6/7)	29 0/7 (2 5/7)
min, max	24 0/7, 36 1/7	23 0/7, 35 6/7
SD of weight at birth		
mean (SD)	-1.43 (1.61)	-1.40 (1.50)
min, max	-4.70, 2.00	-4.90, 3.40
Neonatal inflammatory disease	10 (23.8)	60 (31.7)
PDA	5 (11.9)	24 (12.9)
IVH		
Mild	9 (21.4)	28 (14.9)
Severe	3 (7.1)	13 (6.9)
Cigarettes per day		
0	0 (0.0)	190 (100.0)
1–10	25 (65.8)	0 (0.0)
11–20	8 (21.1)	0 (0.0)
>20	5 (13.2)	0 (0.0)
Mother's alcohol use	7 (16.7)	11 (5.8)
Mother's illicit drug use	2 (4.8)	1 (0.5)
MRI equipment		
0.23 Tesla	22 (52.4)	103 (54.2)
1.5 Tesla	20 (47.6)	87 (45.8)

Values are given as numbers (%) of subjects unless stated otherwise. Only the mother's alcohol use ($P = 0.03$) differed significantly between the groups. Missing information for one (neonatal inflammatory diseases), two (IVH, intraventricular hemorrhage), and four (cigarettes per day and PDA, patent ductus arteriosus). Modified from Ekblad et al. 2010 (study II).

Magnetic resonance imaging (MRI) was performed at term age, corrected for prematurity. This imaging took place during postprandial sleep without pharmacological sedation or anesthesia. The infants were monitored by a nurse, or the parents, at the bedside during the imaging. Ear protection was used (3M Disposable Ear Plugs 1100, 3M, Brazil and Wurth Hearing protector, Art.-Nr. 899 300 232, Wurth, Austria). The MRI equipment was either an open 0.23 Tesla Outlook GP (Philips Medical Inc., Vantaa, Finland) for the first 126

investigations or 1.5 Tesla Philips Gyroscan Intera (Philips Medical Systems, Best, the Netherlands) for the remaining 106 infants. A total of 209 of 232 MRI investigations were successfully performed.

For volume measurements, at 0.23 Tesla (T) we obtained a T_1-weighted field echo sequence with a time repetition of 30 ms, a time echo of 10 ms, a flip angle of 45 degrees, a slice thickness of 5 mm, a field of view of 220 x 220 mm^2, and a matrix of 256 x 256 was obtained in the coronal plane. At 1.5 T we obtained a coronal T_1-weighted inversion recovery sequence with a time repetition of 3500 ms, a time echo of 400 ms, a time inversion of 15 ms, a flip angle of 90 degrees, a slice thickness of 4.8 mm, a field of view of 180 x 180 mm^2 and a matrix of 256 x 256. The sequences were optimized relative to the field strength of the equipment used.

The post acquisition volume measurements were performed on a GE workstation (GE AW1.0, GE Medical Imaging Systems, Milwaukee, USA). The coronal T_1-weighted images were loaded into Functool 1.0 post-processing software (GE Medical Systems, Milwaukee, USA). Volume measurement was manually performed, separating cerebrospinal fluid and the skull from brain tissue. Anatomical differentiation of the brain areas was based on both the anatomical landmarks and on signal intensity differences of the brain structures. In addition to the total brain volume (total brain volume excluding ventricle volumes), the regional brain volumes measured were the cerebral volume, the cerebellar volume, the frontal lobe volume, the combined volume of the medulla oblongata and the pons, and the combined volume of the basal ganglia and the thalami. The cerebellar volume included the cerebellar hemispheres, the vermis and the cerebellar pedunculi. The frontal volume included the frontal lobes anterior to the central sulcus excluding basal ganglia and lateral ventricles (Figure 3). The pons and medulla oblongata area was delineated together with the upper border being the lower border of the mesencephalon and the lower border, being the junction between the medulla oblongata and the cervical spinal cord. The basal ganglia and thalami were measured as a block and the anatomical border between these basal grey matter nuclei and unmyelinated deep white matter on both field strength images was easily delineated by visual inspection. The medial border of the basal ganglia and the thalami was formed by the third ventricle, the lateral border was formed by the external capsule and the inferior border was formed by the upper border of the mesencephalon. The classification of intraventricular hemorrhage (IVH) was done as described earlier in the literature (Papile et al. 1978). Structural brain pathology was categorized into normal, minor and major pathology groups (definitive brain pathology) according to the most pathological brain finding, either with ultrasound or MRI (Rademaker et al. 2005).
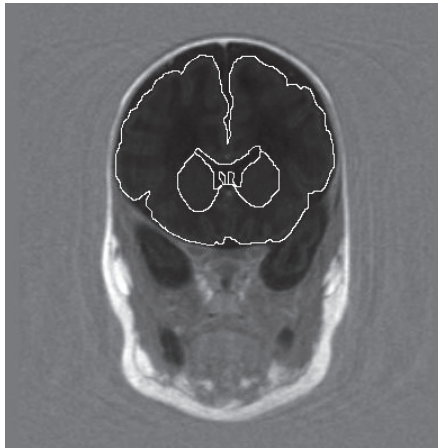
Figure 3. An example of the frontal volume measurement from the MRI image of one study infant.

The brain volume measurements of all the infants in this study were performed by one neuroradiologist blinded to the clinical data. The reproducibility of the brain volume measurements was assessed by repeated brain volume measurements for 20 infants, performed by another neuroradiologist who was blinded to the clinical data and to the results of the first volume measurement. The intraclass correlation coefficients (ICC[2,1]) (Shrout et al. 1979) were calculated to describe the reliability of the brain volume measurements. The ICC ranged from 0.93 to 0.99, except for the volume of brainstem for which the ICC was 0.78. The ICC was 0.95 for the volume of the cerebellum and 0.99 for the frontal lobe. In addition, we calculated the ICC of the volume of the frontal lobe and the cerebellum separately for the 0.23 T and 1.5 T MRI equipment. The ICC of the volume of the frontal lobe was 0.96 with the 0.23 T MRI equipment and 1.00 with the 1.5 T MRI equipment. The ICC of the volume of the cerebellum was 0.94 and 0.95, respectively.

4.4 Epidemiological studies on psychiatric morbidity (III, IV)

4.4.1 Data sources

The Finnish Medical Birth Register has been introduced previously, in paragraph 4.2.2 of this thesis.

The Hospital Discharge Register collects information on all episodes of inpatient care (including all hospitalizations requiring an overnight stay) in public and private hospitals (since 1969) and outpatient visits to public hospitals (since 1998). The register contains information on the patients' backgrounds, the hospitalization period, procedures, and the main diagnosis plus up to two other

diagnoses by International Classification of Diseases (ICD) code (Eight Revision [ICD-8] in 1969–1986, Ninth Revision [ICD-9] in 1987–1995, and Tenth Revision [ICD-10] since 1996). All hospitals send their data electronically to the THL. A 1986 data quality study reported that 99% of hospitalizations relating to mental disorders were registered under the correct ICD chapter and 98% of the main diagnoses had been correctly reported at the three digit ICD-code level (Keskimäki and Aro 1991).

The Finnish Cause-of-Death Register contains data from death certificates, written by the physician who took care of the patient or who performed the autopsy. All death certificates are checked by a physician in the provincial government and by medical experts at Statistics Finland, which is the register keeper. This register includes comprehensive information on all deaths of Finnish citizens and permanent residents who died in Finland and at least basic information on deaths of Finnish citizens that occurred abroad.

The Drug Prescription Register (1994–2007) is kept by the Finnish Social Insurance Institution. It comprises date of distribution and name of the drug, covering 97% of all reimbursed prescriptions in Finland. Nearly all prescription-only drugs deemed necessary for treatment of an illness are partly reimbursable. Prescription medication purchases were only reimbursed if the costs of one purchase exceeded 8.41 euro (1994–2002) or 10 euro (2003–2005). Among psychotropic drugs, virtually the only ones which were excluded from the database due to their low cost were small packages of diazepam. All reimbursed purchases have been registered since the year 2006. One purchase can cover a maximum of three months of medication and, therefore, medication used for one year should include at least four purchases.

4.4.2 Participants

The study population consisted of all children born in between1987 and 1989 in Finland (n = 186,246), as registered in the Medical Birth Register. We excluded multiple births (3,960 children [2.1%]) and children who had died during the first week of life (597 [0.3%]) from the study. Furthermore, we excluded children with major congenital anomalies (5,820 [3.2%]). Individual diagnoses of cryptorchism (n = 954), congenital dislocation of the hip (n = 943) or congenital partial dislocation of the hip (n = 845) were not considered major anomalies, and infants with these diagnoses were included in the study. After exclusions, the final study population consisted of 175,869 children, totalling 94.4% of all children born during the study years.

4.4.3 Background information

The information on smoking during pregnancy was assessed during the antenatal care of the mothers by a midwife (none/ <10/ >10 cigarettes per day). The questionnaire in the antenatal care categorized smoking as either "fewer than 10 cigarettes" or "more than10 cigarettes" per day, leaving it unclear as to which group the mothers who smoked exactly 10 cigarettes per day would be categorized. Other background factors were derived from the Finnish Medical Birth Register (the child's gender, gestational age, birth weight, and Apgar score at 5 minutes of age and maternal age, and parity) and from the Hospital Discharge Register (all the mother's psychiatric morbidity requiring inpatient hospital care before the birth of the child) for the period between 1969 and 1989.

4.4.4 Information on psychiatric morbidity

Information on psychiatric morbidity was obtained from the Finnish Hospital Discharge Register, and included all inpatient episodes in public and private hospitals between 1987 and 2007 and all outpatient visits to public hospitals between 1998 and 2007. Therefore, our data include all inpatient episodes from birth until 18–20 years of age and all outpatient visits of the children beginning from 9 to 11 years of age. For this study we included all episodes and visits with a psychiatric diagnosis (ICD-9 codes 290–319 in 1987–1995 and ICD-10 codes F00–F99 in 1996–2007) whether occurring as a primary or other diagnosis. We studied the following diagnostic groups separately by the ICD-10 F diagnosis:

1. F10–F19 psychiatric disorders due to psychoactive substance use (including ICD-9 codes 291, 292, 303, 305, and 304), subgroup F10 psychiatric disorders due to use of alcohol (ICD-9 codes 291, 303, and 3050A), and subgroup F11 through F19 psychiatric disorders due to use of other drugs (ICD-9 codes 292, 304, and 305, excluding 3050A);
2. F20 through F29, F31.2, F31.20, F32.3, and F33.3 psychosis (295, 296.xE, 297, and 298) and the subgroup of schizophrenias with F20 through F21 diagnoses (ICD-9 code 295);
3. F30 through F39 mood disorders (ICD-9 codes 296 and 3004A);
4. F40 through F59 behavioral syndromes, neurotic disorders, and stress-related disorders (ICD-9 codes 300 (excluding 3004A), 3071A, and 3075B) and subgroup F50.0 anorexia nervosa (ICD-9 code 3071A);
5. F60 through F61 disorders of adult personality and behavior (ICD-9 code 301),
6. F70 through F79 mental retardation (ICD-9 code 317);
7. F80 through F89 disorders of psychological development (ICD-9 codes 299 and 315); and

8. F90 through F99 behavioral and emotional disorders occurring in childhood and adolescence (ICD-9 codes 3072A–D, 313, and 314), subgroup F90 hyperkinetic disorders (ICD-9 code 314), and subgroup F91 through F92 disorders of conduct and emotions (ICD-9 codes 3072A–D, 313).

Information on the mother's psychiatric morbidity leading to inpatient care before the birth of the child was obtained from the Hospital Discharge Register. All inpatient episodes with a psychiatric diagnosis (ICD-8 and ICD-9 codes 290–319) were included, whether occurring as a primary or other diagnosis for the period between 1969 and 1989.

4.4.5 Information on drug prescriptions

The information on psychotropic medication was obtained from the Finnish Social Insurance Institution between 1994 and 2007 and included a cumulative use of psychotropic medication during a 13-year time period. Depending on the birth year, this time period ranged from 5–7 years of age to 18–20 years of age. Psychotropic medications were defined according to the Anatomic Therapeutic Chemical (ATC) classification system: all psychotropic medications (ATC groups N05, N06A, N06B, and N07B), antipsychotics (N05A), hypnotics/anxiolytics (N05B and N05C), antidepressants (N06A), stimulants (N06B), and medication used in addictive disorders (N07B). Purchases with the ATC-code N05BB01 (Hydroxyzine hydrochloride) were excluded from the data, as the drug is mostly used to alleviate itching in small children. In the year 1994, the ATC-code N05AC02, related to antipsychotics, also incorrectly included one antibiotic drug, and was therefore excluded from the data. Our data did not, however, contain any information concerning the indication for which drugs were prescribed.

We studied the continuity of consumption by the ATC-groups (N05A, N05B and/or N05C, N06A and N06B). The use of drug (N05A, N06A, and N06B) was categorized into four continuity groups: 1) no purchases during the follow-up; 2) sporadic use (one or more purchases in one three-month period); 3) moderate use (one purchase in at least two follow-up years or two to three purchases with an interval of over three months between the first and last purchase during the most severe one-year period); and 4) continuous use (four or more purchases of the drug during more than three months during the most severe one-year period). The continuity of drug use in hypnotics (N05B) and anxiolytics (N05C) was categorized into three groups according to the most severe one-year period

indicating misuse: 1) no purchases during the follow-up; 2) infrequent purchases (one to five purchases); and 3) frequent purchases (six or more purchases).

Single and multiple drug uses were defined as simultaneous use of several drug categories. The use of drugs (N05A, combined N05B and N05C, N06A, N06B and N07B) was categorized into three groups: 1) no purchases; 2) single drug consumption (purchases of drugs from one drug group in any follow-up year); 3) multiple drug consumption (use of drugs from two or more different drug groups in any follow-up year).

We further studied the effect of smoking exposure by comparing the incidence of children with: 1) use of psychotropic medication only (i.e. common psychiatric problems treated in primary healthcare, not requiring specialist psychiatric services); 2) psychiatric diagnosis given within specialized hospital care only; and 3) both psychotropic medication use and psychiatric diagnosis in specialized hospital care, to explore how far the groups with hospital care and medication overlap.

4.4.6 Information on mortality

The data were complemented by information on all deaths, and their causes, of children between 1987 and 2007 from the Cause-of-Death Register (Statistics Finland). Suicides and self-inflicted deaths (ICD-10 codes X60–X84) were analyzed separately.

4.4.7 Data combination

All data were combined by using both the child and mother's unique personal identification numbers. The statistical authorities performed the data linkages and therefore only unidentifiable data were delivered for the researchers working outside the THL. The combined data included complete follow-up information until December 31, 2007, or the death of the child. Our data did not include information on children migrating out of Finland. After data linkage to the Hospital Discharge Register, the Cause-of-Death Register, and The Drug Prescription Register, the Medical Birth Register is considered to be a complete record of all births and newborns in Finland. Two data quality studies showed that most of the register content corresponds well or satisfactorily with hospital record data (Gissler et al. 1995, Teperi 1993).

There were 5,487 (3.2%) children with unknown smoking exposure. Of exposed children, 34.0% were exposed to more than 10 cigarettes per day during

pregnancy (Table 3). Characteristics of the study groups by prenatal smoking exposure, subsequent psychiatric diagnoses, and use of psychotropic medication are shown in Table 4.

Table 3. Number of children exposed and unexposed to smoking during pregnancy by gender (studies III and IV).

	No smoking	<10 cigarettes/day	>10 cigarettes/day	Unknown	Total
Male	73,684	8,801	4,538	2,839	89,862
Female	70,615	8,413	4,331	2,648	86,007
Total	144,299	17,214	8,869	5,487	175,869

Table 4. Information of smoking during pregnancy and child's psychiatric diagnoses and use of psychotropic medication by the background factors (studies III and IV).

	Number	Smoking exposure (excl. unknown), %	Child's use of psychotropic medication, %	Child's psychiatric F-diagnoses, %
All Children	175,869	15.3	8.9	15.1
Maternal age				
Less than 20	5,320	37.8	13.1	24.9
20–39	166,199	14.7	8.7	14.7
40 or more	4,288	10.8	9.3	14.9
Unknown	62	8.6	0.0	0.0
Parity				
0	69,457	16.9	9.1	15.4
1	61,008	14.3	8.6	14.5
2–3	37,478	14.9	9.1	15.4
4 or more	5,535	9.8	8.4	14.4
Unknown	2,391	23.7	9.9	16.3
Mother's previous psychiatric diagnosis				
No	171,932	14.9	8.7	14.7
Yes	3,937	35.1	16.6	29.5
Gender				
Male	89,862	15.3	6.7	13.6
Female	86,007	15.3	11.2	16.6
Gestational age				
22–27	223	22.6	16.1	31.8
28–31	642	19.8	14.8	24.3
32–36	6,406	19.2	10.1	17.3
37 or more	166,094	15.1	8.8	14.9
Unknown	2,504	23.2	9.8	16.4

Table 4. cont. Information of smoking during pregnancy and child's psychiatric diagnoses and use of psychotropic medication by the background factors (studies III and IV).

	Number	Smoking exposure (excl. unknown), %	Child's use of psychotropic medication, %	Child's psychiatric F-diagnoses, %
Birth weight, grams				
Less than 1,500	666	22.1	14.1	29.3
1,500–2,499	3,757	26.8	12.3	20.1
2,500–3,999	133,322	16.5	9.0	15.2
4,000 or more	36,024	9.5	7.9	13.5
Unknown	2,100	10.5	10.1	16.5
Weight adjusted for gestational age				
SGA	3,115	31.4	11.9	22.2
AGA	163,858	15.3	8.9	14.9
LGA	6,392	8.3	8.5	14.9
Unknown	2,504	23.2	10.1	16.4
5 minutes Apgar score				
0–3	238	17.9	12.3	15.1
4–6	1,147	16.4	10.7	18.9
7–10	171,708	15.3	8.9	15.0
Unknown	2,776	20.7	10.2	17.1

If the 5 min Apgar score was missing, the 1 min Apgar score was used in case the score was 8, 9, or 10. Modified from Ekblad et al. 2011 (study IV).

4.5 Ethics

Permission of data delivery from the Nordic countries was granted by the register-keeping organizations. Only unidentifiable statistical data was received. In Norway, the Regional Committees for Medical and Health Research Ethics also approved the data request. For the second study, the PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of the South-West Finland. In addition, written consent was obtained from all parents. For the epidemiological studies (III and IV), the register-keeping organizations (THL, Statistics Finland, and the Finnish Social Insurance Institution) gave their permission to use their confidential health register data in this study, in accordance with the national data-protection legislation. The study protocol was reviewed by the statistical authorities (THL, Statistics Finland, and the Finnish Social Insurance Institution).

4.6 Statistical analyses

The data analysis was performed using commercially available software SAS (version 9.1; SAS Institute, Cary, North Carolina). A *P* value of <0.05 was considered statistically significant. Differences in the results were evaluated using 95% confidence intervals (III and IV). Non-overlapping confidence intervals were considered to be significant.

4.6.1 Nordic birth register study

The prevalence of smoking was analyzed separately, according to background factors in all countries. In addition, the smoking rates were analyzed more closely by age and marital status in Finland. The data on pregnant teenagers' smoking in Denmark was suspected to be unreliable because of a data discrepancy, showing 0.2–0.4% of all pregnancies to be teenage pregnancies while the WHO European Health for All Database showed a rate of 1.3–2.5% for the same period. Therefore, the Danish information on smoking among pregnant teenagers was excluded from Figure 5.

4.6.2 Clinical study

The independent samples t-test was used to compare brain volumes between the infants unexposed and exposed to prenatal smoking. Subsequently, analysis of covariance was used to further study associations between smoking and brain volumes, controlled for confounding factors. Associations between brain volumes and the number of cigarettes smoked were studied by the use of regression analysis. A mixed-model repeated-measures analysis with an unstructured covariance matrix was used to study associations between the head circumference and predictor variables. In the first model, the independent variables were age, smoking and the interaction between age and smoking. Then in the second model it was estimated in which the confounding variables were added to the first model. The effect of prenatal smoking exposure on the brain pathology of the infants (normal/ minor/ major) was analyzed with the Mantel-Haenszel Chi-Square test.

The confounding factors were considered to be the infant's gestational age at birth, the weight SD at birth, gender, patent ductus arteriosus (PDA), IVH, combined chronic lung disease, NEC, and septicemia as neonatal inflammatory disease, the MRI equipment, and the mother's alcohol consumption during pregnancy. IVH was categorized into mild (including grades I and II) and severe (including grades III and IV). The volumes of ventricles and brainstem were log transformed before the data analysis because they were positively skewed.

4.6.3 Epidemiological studies on psychiatric morbidity

Logistic regression analysis was used to compare the prevalence of any psychiatric diagnosis, inpatient and outpatient care, the type of psychiatric diagnosis, any psychotropic medication, the psychotropic medication by drug groups, the continuity of drug use, single and multiple drug use, both psychotropic medication use and psychiatric diagnoses, and mortality between the children exposed and unexposed to prenatal smoking. The survival probability was analyzed by calculating the probability of surviving without a psychiatric diagnosis in the study groups with 18-year Kaplan-Meier survival analyses. In addition, we assessed the overlap between those using psychiatric hospital care and using psychotropic medication with a special interest in children using medication without any diagnoses from specialized hospital care.

Having a teenage mother or low birth weight, or being premature, has been shown to be a risk for increased subsequent psychiatric problems in childhood and adolescence. Therefore, we analyzed the risk for psychotropic drug use for the following low-risk populations separately, by excluding: 1) children born to mothers under 20 years of age, 2) children born prematurely (gestational age less than 37 weeks), and 3) children with low birth weights (less than 2,500 g) using logistic regression analyses.

The analyses were adjusted by these background factors: the child's gender, gestational age, birth weight, and 5 minutes Apgar-score, as well as maternal age, parity, and psychiatric morbidity before the birth of the child.

5. RESULTS

5.1 Trends of smoking during pregnancy in the Nordic countries (I)

5.1.1 Smoking during pregnancy and overall smoking among women

The prevalence of smoking during early pregnancy has declined significantly in the Nordic countries, excluding Finland (Figure 4). The most rapid decline of smoking during early pregnancy was observed in Denmark and Sweden, even though the decline started 10 years later in Denmark than in Sweden. Smoking during pregnancy did not directly follow the decrease in overall smoking in women, especially in Finland where no change was seen in the prevalence of smoking during early pregnancy, even if overall smoking among women has been declining from 2004. However, the prevalence of smoking throughout pregnancy has been decreasing in all countries during the last decade. The proportion of women stopping smoking after the first trimester of pregnancy has increased in Finland from 10% to 36% in a decade, but decreased in Sweden from 45% to 27%.
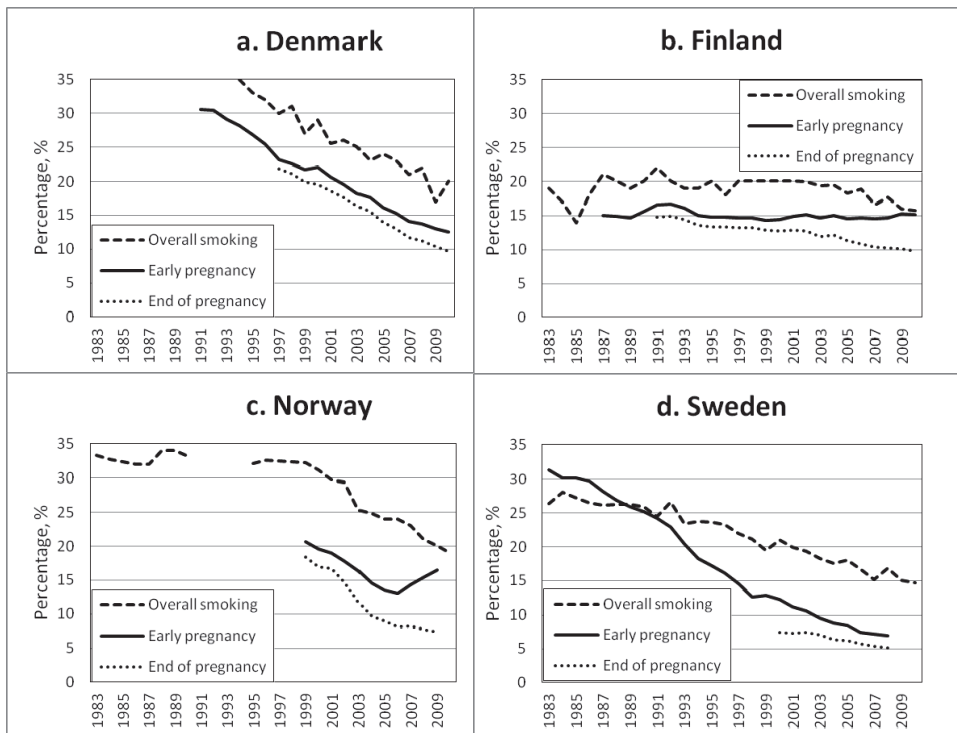
Figure 4. Trends of smoking in early and end of pregnancy and overall smoking among women according to the Nordic countries. Modified from Ekblad et al. Submitted (study I).

5.1.2 Smoking by maternal age

The highest smoking rates in early pregnancy in all countries were among teenagers (Table 5). Since 2000, smoking during early pregnancy among teenagers has decreased in Sweden from 32% to 24%, but increased in both Finland and Norway, from 41% to 49% and 43% to 49%, respectively (Figure 5). In 2010, only one in four Finnish teenagers stopped smoking after early pregnancy. However, more than one in two Norwegian teenagers stopped smoking.

Declining trends of smoking, both during early pregnancy and in the end of pregnancy, were seen among women over 25 years in all countries. Yet in Norway during the last five years, the smoking rates in early pregnancy have increased among women aged below 35 years, even though smoking rates had been previously decreasing for many years. Overall, the prevalence of smoking both during early pregnancy and in the end of pregnancy was 2.5–3 times higher among women below 25 years than among older women.

Table 5. The latest smoking rates (%) in early and the end of pregnancy and trends of smoking from year 2000.

	Denmark		Finland		Norway		Sweden	
	Early	End	Early	End	Early	End	Early	End
Age								
Teenagers	41	32	49	36	49	23	24	19
All below 25	28	22	32	22	32	15	15	11
25–34	10	8	12	7	14	6	5	4
35 or more	9	7	9	6	12	6	5	4
Marital status								
Single			35	24	35	19	21	15
Married/cohabiting			13	8	15	6	6	4
Parity								
0			18	10	20	7	7	5
One or more			13	9	14	7	7	5
Socioeconomic position								
High			5	2	6	2		
Intermediate			14	8	21	9		
Low			26	18	41	23		

Color codes: green indicates a declining trend, yellow a stable, and red an increasing trend.

A significant difference in smoking habits between pregnant teenagers aged 18 years or below and teenage girls aged 14–18 years in Finland was seen (Figure 6). This difference has even been on the increase during the last 15 years; approximately 20% of teenage girls smoke, whereas up to 55% of pregnant teenagers smoke.
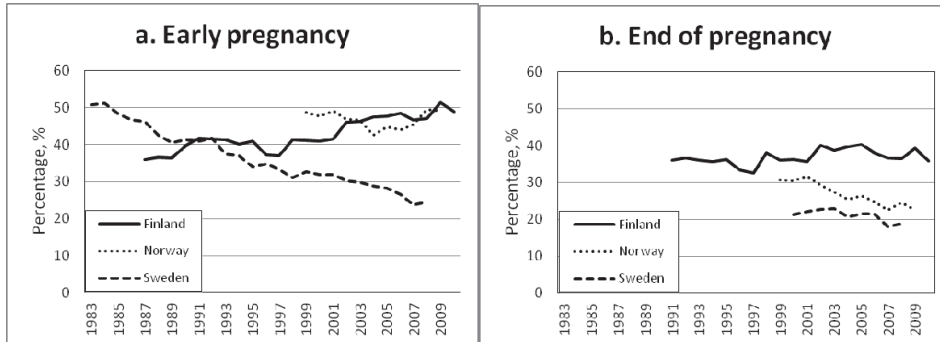
Figure 5. Trends of smoking among pregnant teenagers (under 20 years old) in (a) early and (b) end of pregnancy by country. Modified from Ekblad et al. Submitted (study I).
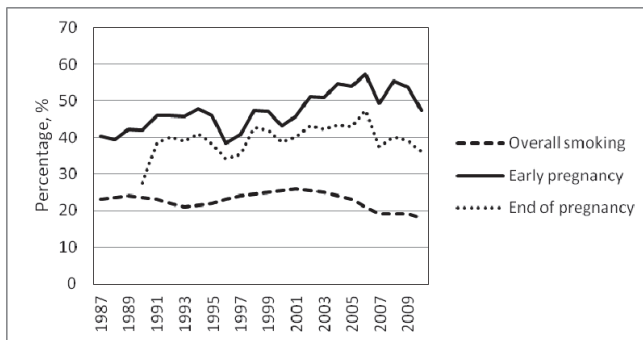
Figure 6. Trends of smoking in early and end of pregnancy among women 18 years or below and overall smoking among women aged 14–18 years in Finland.

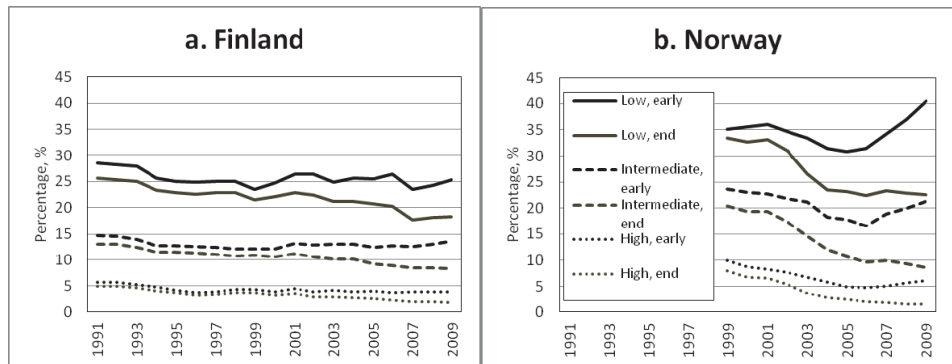### 5.1.3 Smoking by socioeconomic position, parity, and marital status

Women with the lowest socioeconomic positions were 6–7 times more likely to smoke, and women with intermediate positions were 3–3.5 times more likely to smoke, than women with the highest positions in early pregnancy (Figure 7 and Table 5). These differences were even greater in the end of pregnancy.

In Finland and in Norway, women who had not had a previous delivery were more likely to smoke during early pregnancy compared to women who had had previous deliveries (Table 5). However, the prevalence of smoking in the end of pregnancy evened out between pregnant women who had not had and had had

previous deliveries both in Finland (9–10%) and Norway (both 7%). In Sweden, no difference was observed at any time of pregnancy.

Single women were 2–3 times more likely to smoke both during early pregnancy and in the end of pregnancy compared to married women in all countries (Table 5). The proportion of Finnish single women who smoke throughout pregnancy has remained stable, at the level of 24–30%, for the last decade. A decreasing trend was found in all pregnant women in Norway and Sweden, including single women.

Figure 7. The trends of smoking during early and end of pregnancy according to socioeconomic position in (a) Finland and (b) Norway. Modified from Ekblad et al. Submitted (study I).

Smoking rates by marital status were calculated separately for teenagers and women over 20 years of age in Finland. Smoking rates of pregnant single women over 20 years of age were at the same level as all single pregnant women (Figure 8). However, smoking rates among single pregnant teenagers were high, remaining between 50% and 60% during the last decade.
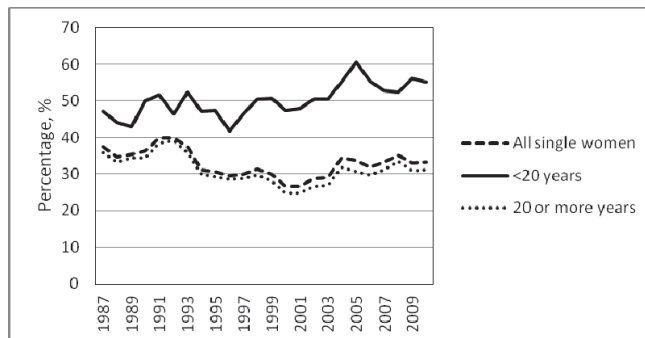
Figure 8. Trends of smoking during pregnancy among single women aged <20 years and 20 or more years and among all single pregnant women in Finland.

5.2 Regional brain volumes and head circumference (II)

The study infants exposed to prenatal smoking had significantly smaller frontal lobe volumes when compared to unexposed infants, and this difference remained significant after adjusting for the confounding factors ($P = 0.01$). The cerebellar volumes were significantly smaller after adjusting for the confounding factors ($P = 0.03$). There were no differences in the other measured volumes according to prenatal smoking exposure (Table 6). No significant dose-relationship between the number of cigarettes smoked and the brain volumes was observed.

Table 6. Prenatal smoking exposure and regional brain volumes at term (study II).

Brain region (ml)	Exposed (n = 38)		Unexposed (n = 171)		Adjusted
	mean (SD)	min, max	mean, (SD)	min, max	*P* value
Cerebrum	361.7 (47.2)	271.0, 464.9	367.6 (48.3)	233.0, 479.8	0.13
Frontal lobe	117.9 (18.9)	85.0, 160.0	127.3 (24.7)	67.0, 194.1	0.01
Basal ganglia and thalami	24.4 (3.8)	17.1, 33.9	25.3 (4.9)	13.0, 42.8	0.17
Cerebellum	23.1 (5.3)	9.0, 34.0	24.5 (5.0)	5.7, 37.80	0.03
Brainstem	6.0 (2.2)	3.9, 12.1	6.4 (2.6)	2.5, 14.9	0.63
Total brain volume (excl. ventricles)	390.8 (51.3)	289.0, 498.9	398.4 (51.2)	254.0, 514.9	0.09
Ventricles	17.0 (35.2)	3.0, 222.9	14.1 (14.5)	2.3, 138.30	0.78

Adjusted for the confounding factors that are described in Table 2. Modified from Ekblad et al. 2010 (study II).

The subgroup analysis of infants below 32 gestational weeks did not affect the main results. However, in a subgroup analysis of infants with a birth weight at or below 1,500 grams, the frontal lobe volume remained significantly smaller in infants exposed to prenatal smoking but the cerebellar volumes were not statistically significantly different according to smoking exposure ($P = 0.06$).

No association was observed between prenatal smoking exposure and 1) structural brain pathology ($P = 0.75$), and 2) head circumference ($P = 0.10$, Table 7) at any of the age points in the study infants after adjusting for confounding factors.

Table 7. Head circumference at birth, term and two years of corrected age by smoking exposure (study II).

Age	Exposed			Unexposed			Adjusted
	n	mean (SD), cm	min, max, cm	n	mean (SD), cm	min, max, cm	*P* value
At birth	42	26.3 (2.8)	20.7, 31.1	190	26.5 (2.6)	20.0, 32.0	
At term	42	34.3 (1.9)	29.5, 37.5	188	34.6 (1.6)	29.0, 39.5	0.10
At 2 years of CA	38	48.4 (2.1)	42.0, 53.1	185	48.9 (1.7)	44.3, 53.8	

Adjusted for the confounding factors that are described in Table 2. Modified from Ekblad et al. 2010 (study II).

5.3 Psychiatric morbidity and psychotropic drug use

5.3.1 Inpatient and outpatient care (III)

The prevalence of psychiatric morbidity by age and prenatal smoking exposure is shown using the Kaplan-Meier method (Figure 9). The prevalence of hospital care (inpatient and outpatient care) with any psychiatric diagnosis until the age of 18 was 12.7% in unexposed children, 19.5% in children exposed to fewer than 10 cigarettes per day, and 23.0% in children exposed to more than 10 cigarettes per day. There was a significant group difference beginning at 6 years of age. A statistically significant difference according to prenatal smoking exposure in any psychiatric diagnoses as well as separately in inpatient and outpatient care diagnosis after adjusting for background factors was seen (Table 8). A dose-response to smoking was also seen. There were no significant differences between males and females according to the type of hospital care and smoking exposure.
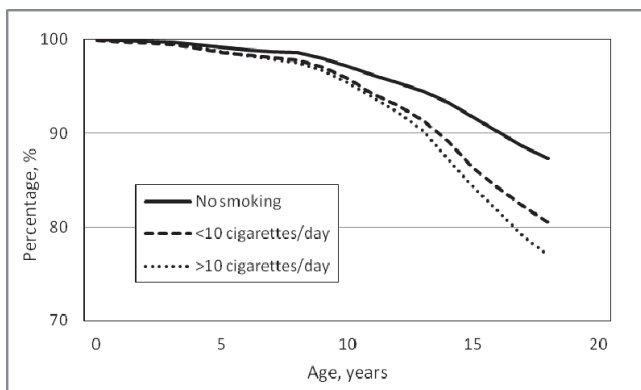
Figure 9. Psychiatric-morbidity-free survival by age and prenatal smoking exposure. Modified from Ekblad et al. 2010 (study III).

The study population had a total of 510,685 psychiatric treatment episodes, including 24,579 (4.8%) episodes in inpatient care, with the remainder in outpatient care. The mean number of all inpatient and outpatient treatment episodes per child was 19.3 (16.1 in males and 22.0 in females) for those with at least one psychiatric care episode. The mean number of inpatient treatment episodes per child was 2.7 (2.7 in males and 2.6 in females) and of outpatient treatment episodes was 20.1 (17.0 in males and 22.6 in females). Smoking exposure did not affect the number of treatment episodes per child in children with psychiatric care.

Table 8. Children with psychiatric diagnosis by prenatal smoking exposure and gender (study III).

	No smoking	<10 cigarettes/day	>10 cigarettes/day	Total
Any psychiatric diagnosis				
Males	9,099 (12.3)	1,681 (19.1)	1,031 (22.7)	12,232 (13.6)
Females	10,685 (15.1)	1,934 (23.0)	1,160 (26.8)	14,245 (16.6)
Total	19,784 (13.7)	3,615 (21.0)	2,191 (24.7)	26,245 (15.1)
Crude OR (95% CI)	1	1.44 (1.39–1.50)	1.64 (1.57–1.72)	
Adjusted OR (95% CI)	1	1.53 (1.47–1.60)	1.85 (1.74–1.96)	
Inpatient care psychiatric diagnosis				
Males	3,431 (4.7)	700 (8.0)	442 (9.7)	4,739 (5.3)
Females	3,246 (4.6)	640 (7.6)	358 (8.3)	4,390 (5.1)
Total	6,677 (4.6)	1340 (7.8)	800 (9.0)	9,129 (5.2)
Crude OR (95% CI)	1	1.63 (1.54–1.74)	1.87 (1.73–2.02)	
Adjusted OR (95% CI)	1	1.65 (1.55–1.75)	1.91 (1.76–2.07)	
Outpatient care psychiatric diagnosis				
Males	8,025 (10.9)	1,483 (16.9)	909 (20.0)	10,792 (12.0)
Females	10,052 (14.2)	1,813 (21.5)	1,093 (25.2)	13,396 (15.6)
Total	18,077 (12.5)	3,296 (19.1)	2,002 (22.6)	24,188 (13.8)
Crude OR (95% CI)	1	1.44 (1.39–1.50)	1.65 (1.57–1.74)	
Adjusted OR (95% CI)	1	1.55 (1.48–1.61)	1.87 (1.77–1.97)	

Results are given as numbers (%) of subjects unless stated otherwise. Adjusted for the background factors that are described in Table 4. The total number includes children with unknown smoking exposure (n = 5,487). Modified from Ekblad et al. 2010 (study III).

5.3.2 Effect of maternal psychiatric morbidity (III)

The children whose mothers had no psychiatric diagnoses before the birth of the child had a probability of 0.86 (Kaplan-Meier 95% CI, 0.86–0.87) of remaining without psychiatric diagnosis until the age of 18 years. Contrary to which, the children born to mothers with previous psychiatric diagnosis had a lower probability (0.72, CI 0.71–0.74). A statistically significant difference was seen from 5 years of age onwards.
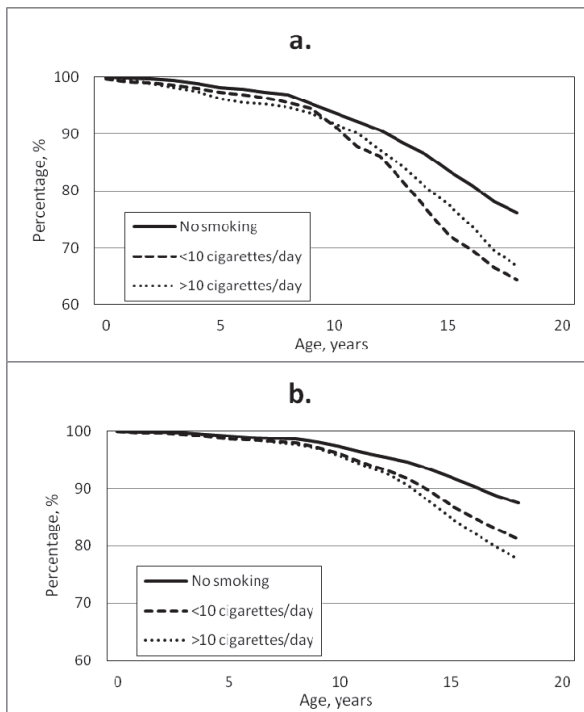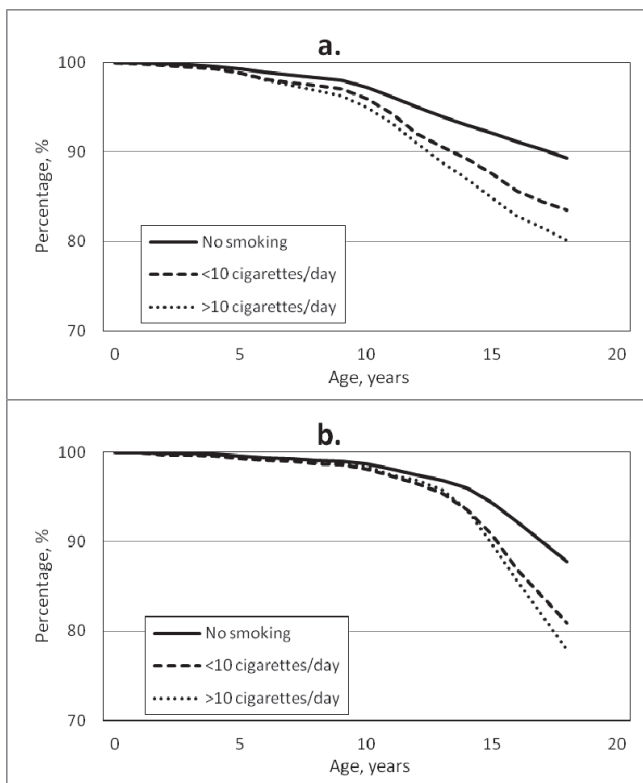

Figure 10. Psychiatric-morbidity-free survival by age and prenatal smoking exposure among children born to mothers (a) with and (b) without previous psychiatric morbidity. Modified from Ekblad et al. 2010 (study III).

The effect of prenatal smoking exposure was further examined by maternal psychiatric morbidity (Figure 10). Smoking exposure had a significant effect on the probability of remaining without psychiatric diagnosis until the age of 18 in children born to mothers with psychiatric morbidity, ranging between 0.76 for the unexposed children (CI 0.74–0.78), 0.64 for the children exposed to fewer than 10 cigarettes per day (CI 0.60–0.69), and 0.67 for the children exposed to more than 10 cigarettes per day (CI 0.62–0.71). The effect of smoking exposure was also significant in children born to mothers without psychiatric morbidity probabilities, ranging from 0.87 (CI 0.87–0.88) to 0.81 (CI 0.81–0.82) and 0.78 (CI 0.77–0.79), respectively.

5.3.3 Effect of gender (III)

The effect of prenatal smoking exposure was found to significantly associate with psychiatric morbidity separately in males and females (Figure 11). The probability of remaining without a psychiatric diagnosis until the age of 18 ranged from 0.88 (Kaplan-Meier 95% CI 0.88–0.89) in unexposed males to 0.82 (CI 0.81–0.83) in those exposed to fewer than 10 cigarettes per day and 0.79 (CI 0.77–0.80) in those exposed to more than 10 cigarettes per day. The probabilities in females ranged from 0.86 (CI 0.86–0.86) to 0.79 (CI 0.78–0.80) and 0.75 (CI 0.74–0.77), respectively. There was a significant group difference from the age of seven in males, and from the age of 12 in females.

Figure 11. Psychiatric-morbidity-free survival by age and prenatal smoking exposure separately among males (a) and females (b). Modified from Ekblad et al. 2010 (study III).

5.3.4 Type of psychiatric diagnoses (III)

Prenatal smoking exposure increased the risk for psychiatric morbidity including all groups of psychiatric diagnoses (ICD-10), except for that of schizophrenia group where the adjusted odds ratio [OR] was 1.17 (95% CI 0.80–1.73, n = 29) in the children exposed to fewer than 10 cigarettes per day, and OR was 1.26 (CI 0.76–2.09, n = 16) in those exposed to more than 10 cigarettes per day (Table 9).

A dose-response to smoking exposure was seen in the risk for mood disorders and behavioral and emotional disorders occurring in childhood and adolescence, and for disorders of conduct and emotions. The risk for mental retardation (F70–F79) was only significantly increased in males: OR 1.44 (CI 1.07–1.94) in the children exposed to fewer than 10 cigarettes per day and OR 1.67 (CI 1.15–2.44) in those exposed to more than 10 cigarettes per day. The risk for disorders of psychological development (F80–F89) was not increased in females exposed to more than 10 cigarettes per day, although the risk was increased in those exposed to fewer than 10 cigarettes per day. Smoking exposure seemed to be protective against anorexia nervosa (F50.0) in females exposed to fewer than 10 cigarettes per day (n = 57, OR 0.70, CI 0.54–0.92). The adjusted odds ratios for other diagnoses did not differ between males and females.

A total of between 70% and 95% were female children who had been diagnosed with disorders related to adult personality and behavior, behavioral syndromes, neurotic disorders, and stress-related disorders (including anorexia nervosa), mood disorders, and psychoses. The highest amount of males was seen in disorders for psychological development (71%) and the subgroup of hyperkinetic disorders (83%). The amount of males in the other diagnostic groups varied between 50% and 60%.

5.3.5 Psychotropic drug use (IV)

A total of 8.9% of children born between 1987 and 1989 had used psychotropic medication during the 13-year follow-up period (Table 10). Prenatal smoking exposure significantly increased the risk of the use of psychotropic drugs even after adjusting for background factors including severe maternal psychiatric illness ($P < 0.001$). A dose-response to smoking was also seen. Prenatal smoking exposure was associated with all psychotropic medication categories when the groups were analyzed separately. The risk was most profoundly increased in the use of stimulants (ATC group N06B) and drugs for treating addiction (N07B). Disulfiram (ATC-code N07BB01) prescriptions represented a total of 98% of the drugs for treating addiction. A dose-relationship was seen between smoking

Table 9. Psychiatric diagnoses by prenatal smoking exposure (study III).

ICD-10 Diagnosis	No smoking	<10 Cigarettes/day	>10 Cigarettes/day	Total
F10–F19 due to psychoactive substance use				
n (per 1,000)	1,417 (9.8)	406 (23.6)	232 (26.2)	2,135 (12.1)
Adj. OR (95% CI)	1	2.40 (2.15–2.68)	2.66 (2.32–3.05)	
F10 due to use of alcohol				
n (per 1,000)	1,239 (8.6)	344 (20.0)	195 (22.0)	1,845 (10.5)
Adj. OR (95% CI)	1	2.33 (2.07–2.62)	2.56 (2.20–2.97)	
F11–F19 due to use of other drugs				
n (per 1,000)	389 (2.7)	130 (7.6)	76 (8.6)	621 (3.5)
Adj. OR (95% CI)	1	2.80 (2.30–3.41)	3.18 (2.49–4.06)	
F20–29, F31.2, F31.20, F32.3, and F33.3 psychosis				
n (per 1,000)	2,375 (16.5)	453 (26.3)	284 (32.0)	3,218 (18.3)
Adj. OR (95% CI)	1	1.60 (1.45–1.76)	1.94 (1.72–2.19)	
F30–F39 Mood disorders				
n (per 1,000)	4,881 (33.8)	960 (55.8)	580 (65.4)	6,635 (37.7)
Adj. OR (95% CI)	1	1.65 (1.54–1.76)	1.93 (1.78–2.10)	
F40–F59 behavioral syndromes, neurotic, and stress-related disorders				
n (per 1,000)	5,458 (37.8)	873 (50.7)	498 (56.2)	7,057 (40.1)
Adj. OR (95% CI)	1	1.34 (1.25–1.44)	1.48 (1.36–1.62)	
F60–F69 Disorders of adult personality and behavior				
n (per 1,000)	410 (2.8)	88 (5.1)	54 (6.1)	571 (3.2)
Adj. OR (95% CI)	1	1.80 (1.43–2.26)	2.14 (1.16–2.84)	
F70–F79 Mental retardation				
n (per 1,000)	509 (3.5)	82 (4.8)	50 (5.6)	661 (3.8)
Adj. OR (95% CI)	1	1.35 (1.07–1.70)	1.60 (1.20–2.13)	
F80–F89 disorders of psychological development				
n (per 1,000)	3,788 (26.3)	611 (35.5)	329 (37.1)	4,918 (28.0)
Adj. OR (95% CI)	1	1.35 (1.24–1.47)	1.41 (1.26–1.58)	
F90–F99 behavioral and emotional disorders occurring in childhood and adolescence				
n (per 1,000)	4,605 (31.9)	998 (58.0)	636 (71.7)	6,473 (36.8)
Adj. OR (95% CI)	1	1.82 (1.70–1.94)	2.25 (2.07–2.43)	
F90 subgroup of hyperkinetic disorders				
n (per 1,000)	729 (5.1)	184 (10.7)	122 (13.8)	1,073 (6.1)
Adj. OR (95% CI)	1	2.11 (1.80–2.48)	2.72 (2.25–3.29)	
F91–F92 subgroup of disorders of conduct and emotions				
n (per 1,000)	2,025 (14.0)	566 (32.9)	395 (44.5)	3,097 (17.6)
Adj. OR (95% CI)	1	2.34 (2.14–2.57)	3.17 (2.85–3.53)	

Adj. for the background factors described in Table 4. The total number incl. children with unknown smoking (n = 5,487). Modified from Ekblad et al. 2010 (study III).

exposure and the use of antidepressants (N06A). There was no difference observed in the effect of smoking exposure between males and females in any psychotropic drug category. A total of 62% of the children with any psychotropic drug use were females. According to the psychotropic drug categories, females were more likely to use antipsychotics (55%), hypnotics/anxiolytics (59%), and antidepressants (68%) than were males, who were more likely to use stimulants (75%) and drugs for addiction (63%).

Table 10. Children's use of psychotropic medication by smoking exposure (study IV).

	No smoking	<10 Cigarettes/day	>10 Cigarettes/day	Total
All psychotropics (N05–N07)				
n (per 1,000)	11,967 (82.9)	1,952 (113.4)	1,207 (136.1)	15,644 (89.0)
Adj. OR (95% CI)	1	1.36 (1.29–1.43)	1.63 (1.53–1.74)	
Antipsychotics (N05A)				
n (per 1,000)	2,578 (17.9)	420 (24.4)	260 (29.3)	3,395 (19.3)
Adj. OR (95% CI)	1	1.25 (1.12–1.39)	1.43 (1.25–1.63)	
Hypnotics/anxiolytics (N05B and N05C)				
n (per 1,000)	4,522 (31.3)	705 (41.0)	428 (48.3)	5,861 (33.3)
Adj. OR (95% CI)	1	1.25 (1.15–1.36)	1.44 (1.29–1.59)	
Antidepressants (N06A)				
n (per 1,000)	8,636 (59.9)	1,486 (86.4)	913 (103.0)	11,406 (64.9)
Adj. OR (95% CI)	1	1.42 (1.34–1.51)	1.67 (1.55–1.80)	
Stimulants (N06B)				
n (per 1,000)	289 (2.0)	65 (3.8)	49 (5.5)	415 (2.4)
Adj. OR (95% CI)	1	1.75 (1.33–2.30)	2.57 (1.89–3.50)	
Drugs for addiction (N07B)				
n (per 1,000)	83 (0.6)	24 (1.4)	15 (1.7)	128 (0.7)
Adj. OR (95% CI)	1	2.17 (1.36–3.45)	2.58 (1.47–4.53)	

Adjusted for the background factors that are described in Table 4. The total number includes children with unknown smoking exposure (n = 5,487). Modified from Ekblad et al. 2011 (study IV).

The main results remained unchanged when the risk for psychotropic drug use was analyzed, excluding the following high-risk populations separately: 1) teenage mothers, 2) preterm children, and 3) low birth weight children. Exposure to fewer than 10 cigarettes per day was associated with an increased use of any psychotropic medications by adjusted OR 1.36 (95% CI 1.29, 1.43), 1.36 (CI 1.29, 1.44), and 1.37 (CI 1.30, 1.44), respectively. Exposure to more than 10 cigarettes per day was associated with an increased use of any psychotropic medications by 1.61 (CI 1.51, 1.73), 1.65 (CI 1.54, 1.76), and 1.63 (CI 1.53, 1.74), respectively.

5.3.6 Continuity of psychotropic drug use (IV)

Exposure to more than 10 cigarettes per day was associated with an increased risk in all consumption categories for psychotropic drug use, when compared to unexposed children (Table 11). The effect of smoking exposure was most profound in continuous use of stimulants, where smoking exposure increased the risk threefold when compared to unexposed children.

Table 11. Continuity of psychotropic drug use according to drug groups by prenatal smoking exposure (study IV).

	No smoking	<10 Cigarettes/day	>10 Cigarettes/day	Total
Antipsychotics (N05A)				
No purchases	141,721	16,794	8,609	172,474
Sporadic use	1,008 (7.0)	157 (9.1)	106 (12.0)	1,325 (7.5)
Adj. OR (95% CI)	1	1.22 (1.03–1.45)	1.55 (1.26–1.90)	
Moderate use	348 (2.4)	81 (4.7)	40 (4.5)	495 (2.8)
Adj. OR (95% CI)	1	1.68 (1.31–2.15)	1.53 (1.10–2.14)	
Continuous use	1,222 (8.5)	182 (10.6)	114 (12.9)	1,575 (9.0)
Adj. OR (95% CI)	1	1.15 (0.98–1.35)	1.32 (1.08–1.60)	
Antidepressants (N06A)				
No purchases	135,663	15,728	7,956	164,463
Sporadic use	5,474 (37.9)	1,006 (58.4)	610 (68.8)	7,311 (41.6)
Adj. OR (95% CI)	1	1.52 (1.42–1.63)	1.79 (1.64–1.95)	
Moderate use	1,371 (9.5)	230 (13.4)	148 (16.7)	1,814 (10.3)
Adj. OR (95% CI)	1	1.34 (1.16–1.54)	1.60 (1.34–1.91)	
Continuous use	1,791 (12.4)	250 (14.5)	155 (17.5)	2,281 (13.0)
Adj. OR (95% CI)	1	1.15 (1.01–1.32)	1.35 (1.14–1.60)	
Stimulants (N06B)				
No purchases	144,010	17,149	8,820	175,454
Sporadic use	166 (1.2)	32 (1.9)	26 (2.9)	231 (1.3)
Adj. OR (95% CI)	1	1.55 (1.05–2.27)	2.48 (1.63–3.79)	
Moderate use	52 (0.4)	8 (0.5)	9 (1.0)	71 (0.4)
Adj. OR (95% CI)	1	1.07 (0.50–2.26)	2.29 (1.12–4.71)	
Continuous use	71 (0.5)	25 (1.5)	14 (1.6)	113 (0.6)
Adj. OR (95% CI)	1	2.77 (1.74–4.42)	3.01 (1.68–5.41)	

The values are numbers and (per 1,000) if not stated otherwise. Adjusted for the background factors that are described in Table 4. The total number includes children with unknown smoking exposure (n = 5,487). Modified from Ekblad et al. 2011 (study IV).

Table 11. cont. Continuity of psychotropic drug use according to drug groups by prenatal smoking exposure (study IV).

	No smoking	<10 Cigarettes/day	>10 Cigarettes/day	Total
Hypnotics (N05B)				
No purchases	141,152	16,777	8,590	171,868
Infrequent purchase	2,648 (18.4)	350 (20.3)	204 (23.0)	3,314 (18.8)
Adj. OR (95% CI)	1	1.07 (0.96–1.20)	1.16 (1.00–1.34)	
Frequent purchase	499 (0.5)	87 (1.5)	75 (1.6)	687 (0.6)
Adj. OR (95% CI)	1	1.31 (1.04–1.65)	2.17 (1.70–2.79)	
Anxiolytics (N05C)				
No purchases	142,491	16,864	8,661	173,420
Infrequent purchase	1,497 (10.4)	288 (16.7)	167 (18.8)	2,020 (11.5)
Adj. OR (95% CI)	1	1.53 (1.35–1.74)	1.70 (1.45–2.01)	
Frequent purchase	311 (2.2)	62 (3.6)	41 (4.6)	429 (2.4)
Adj. OR (95% CI)	1	1.60 (1.22–2.12)	2.05 (1.47–2.86)	

The values are numbers and (per 1,000) if not stated otherwise. Adjusted for the background factors that are described in Table 4. The total number includes children with unknown smoking exposure (n = 5,487). Modified from Ekblad et al. 2011 (study IV).

5.3.7 Single and multiple drug use (IV)

A total of 2.2% (n = 11,708) of the children used multiple drugs and 6.7% (n = 3,936) used drugs from only one group in any year during the follow-up years including children with unknown smoking exposure. Smoking exposure associated significantly with an increased risk for single drug use in children exposed to fewer than 10 cigarettes per day (n = 1,430; adjusted OR 1.31, 95% CI 1.24–1.39) and in those exposed to more than 10 cigarettes per day (n = 893; 1.59, CI 1.47–1.71), when compared to unexposed children (n = 9,014, *P* < 0.001). The risk for multiple drug use was also increased in exposed children (n = 522; 1.41, CI 1.28–1.55 and n = 314; 1.59, CI 1.41–1.80, respectively), when compared to unexposed children (n = 2,953, *P* < 0.001).

5.3.8 Psychiatric morbidity and psychotropic drug use (IV)
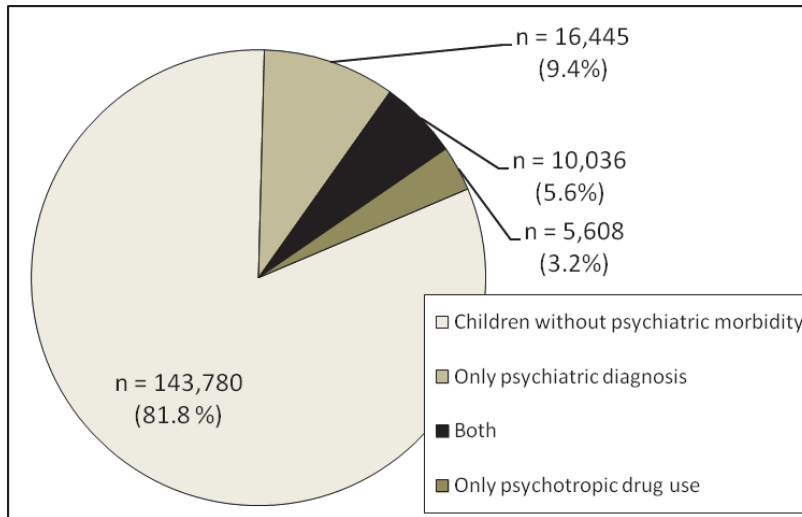
Figure 12. Study population by psychiatric morbidity and psychotropic drug use including children with unknown smoking exposure (study IV).

Figure 12 shows the overlap between the children who have got a psychiatric diagnosis in psychiatric hospital care, and those using psychotropic medication. Prenatal smoking exposure was associated with an increased risk for psychiatric morbidity and psychotropic drug use together, when compared to unexposed children (n = 7,497). The adjusted OR was 1.44 (95% CI 1.36–1.53, n = 1,335) for those children exposed to fewer than 10 cigarettes per day and 1.83 (CI 1.70–1.97, n = 877) for those exposed to more than 10 cigarettes per day. The adjusted OR was 1.36 (CI 1.29–1.43, n = 617) and 1.63 (CI 1.53–1.73, n = 330) for children with only psychotropic drug use and 1.51 (CI 1.44–1.59, n = 2,281) and 1.69 (CI 1.59–1.80, n = 1,314) in children with only psychiatric diagnoses, respectively. The number of children treated with psychotropic medication without a diagnosis from specialized hospital care, of all children with psychiatric problems, categorized by drug group is shown in Table 12.

Table 12. Prevalence of children using psychotropic medication without diagnosis by drug groups (study IV).

All medication (N05–N07)	17.5 (5608)
Antipsychotics (N05A)	14.1 (479)
Hypnotics/anxiolytics (N05BC)	44.1 (2583)
Antidepressants (N06A)	29.1 (3316)
Stimulants (N06B)	13.7 (57)

The values are percentages and (numbers)

5.4 Mortality (III)

There were a total of 927 deaths (5.3 per 1,000 person) in the study population including 66 (7.1%) suicides. Prenatal smoking exposure to over 10 cigarettes per day significantly increased total mortality after adjusting for the background factors (Table 13). The risk for suicide did not differ between the unexposed children (n = 51 suicides and 0.4 per 1,000), the children exposed to fewer than 10 cigarettes per day (n = 9 and 0.5 per 1,000; OR 1.42 [95% CI, 0.68–2.95]), and those exposed to more than 10 cigarettes per day (n = 4 and 0.5 per 1,000; 0.91 [0.28–2.96]) after adjusting for the background factors.

Table 13. Mortality among children by prenatal smoking exposure (study III).

	No smoking	<10 cigarettes/day	> 10 cigarettes/day	Total
Males	414 (5.6)	69 (7.8)	56 (12.3)	567 (6.3)
Crude OR (95% CI)	1	1.39 (1.08–1.80)	2.18 (1.65–2.89)	
Females	266 (3.8)	40 (4.8)	25 (5.8)	360 (4.2)
Crude OR (95% CI)	1	1.26 (0.90–1.76)	1.53 (1.01–2.31)	
Total	680 (4.7)	109 (6.3)	81 (9.1)	927 (5.3)
Crude OR (95% CI)	1	1.34 (1.08–1.80)	1.93 (1.53–2.43)	
Adj. OR (95% CI)	1	1.17 (0.93–1.45)	1.69 (1.31–2.19)	

The values are numbers and (per 1,000) if not stated otherwise. Adjusted for the background factors that are described in Table 4. The total number includes children with unknown smoking exposure (n = 5,487). Modified from Ekblad et al. 2010 (study III).

6. DISCUSSION

6.1 Smoking during pregnancy as a public health problem

Our study, based on a large-scale nationwide register data from the Nordic birth registers, showed that smoking throughout pregnancy has been decreasing in all of the Nordic countries. Similar trends have been seen in several other countries, such as the United States (Centers for Disease Control and Prevention 2004), and in most of the European countries (WHO European Health for All Database). However, the smoking rates during pregnancy differ considerably between the Nordic countries, as smoking rates in early pregnancy have remained stable for over 20 years in Finland, contrary to the other countries. In addition, very few Finnish women stop smoking before pregnancy, as 15% of Finnish women smoked in early pregnancy and overall smoking in Finnish women was 16% in 2010. In contrast, overall smoking in Swedish women was 15% and only 7% smoked in early pregnancy. This highlights the need for smoking cessation intervention for women planning pregnancies in Finland. Globally, the proportion of women who stop smoking during pregnancy has varied greatly – as evidenced in earlier studies -- as only 4% of women stop smoking in Australia (Mohsin and Bauman 2005) yet 67% of women stop in Japan (Kaneko et al. 2008).

Despite this stable rate of smoking in early pregnancy, an increasing number of women are stopping smoking during pregnancy in Finland. The proportion of Swedish women who stop smoking during pregnancy has, however, decreased in recent years, possibly due to the decreasing rate of overall smoking during pregnancy. Smoking during pregnancy did not directly follow the decreasing trend of overall smoking in women, suggesting that there may be specific issues related to smoking during pregnancy.

6.1.1 Maternal age

Previous studies have identified more prevalent smoking during pregnancy among young, single women (Jaakkola et al. 2001a, Moussa et al. 2009), in women with a lower level of education, and those with a lower socioeconomic status (Ergin et al. 2010, Mohsin and Bauman 2005). Moreover, women who smoke during pregnancy also have unplanned pregnancies more often than those that do not smoke (Orr et al. 2008, Villalbí et al. 2007). In our study, the highest smoking rates were seen in pregnant teenagers who were 4–5 times more likely to smoke than older women in every country. This difference between teenagers and older women was slightly lower in an Australian study (Mohsin and Bauman

2005). Significant differences were observed between the Nordic countries in the prevalence of smoking during pregnancy among teenagers. Teenagers were more than twice as likely to smoke in early pregnancy in Norway and Finland, than in Sweden.

Most worryingly, the findings of our study show that smoking during pregnancy among Finnish and Norwegian teenagers has increased during recent years, which raises a concern for the health-behavior of the teenagers who become pregnant. Smoking during pregnancy as a teenager may be a marker for the risk of marginalization.

Although the smoking rates in early pregnancy were equal between Finland and Norway, Norwegian teenagers stopped smoking during pregnancy more frequently. Therefore, teenagers in Finland were almost twice as likely to smoke throughout pregnancy when compared to those in Norway and Sweden. In Norway, therefore, antenatal care might have better succeeded with its smoking cessation interventions during pregnancy.

Teenage pregnancies are rarely planned (Finer and Henshaw 2006). The known risk factors for teenage pregnancy include alcohol and drug abuse (Cavazos-Regh et al. 2011), disrupted family structures, low socioeconomic backgrounds, and lower levels of education (Imamura et al. 2007, Olausson et al. 2001, Vikat et al. 2002). In our study, the smoking rate in early pregnancy among teenagers in Finland was high (49%) compared to overall smoking among teenagers (16%) in 2011 (Raisamo et al. 2011). Similar rates were also seen in Norway (49% and 14%, respectively), but not in Sweden, where 24% of all teenagers smoke compared to 21% of pregnant teenagers, and these rates have been decreasing (Hibell et al. 2011). The lack of difference in smoking rates in Sweden suggests that Sweden has succeeded in decreasing the rate of unplanned pregnancies, as the prevalence of teenage pregnancies has also been decreasing (WHO European Health for All Database).

Maternal health care is quite similar in all the Nordic countries, but there are significant differences in national health policies related to the availability and price of contraceptives. In Sweden, teenagers have received a discount for oral contraceptives since 1975, or have been given totally free contraceptives in recent years. These benefits have decreased the rates of both teenage pregnancies and abortions (Edgardh 2002, Santow and Bracher 1999), although the rate of abortions has been seen to rise again in recent years (Edgardh 2002). In Finland, where there are no such benefits, the rate of teenage pregnancies which result in delivery has remained stable (WHO European Health for All Database),

termination of pregnancies has increased over 21% in 20 years (Leppälahti et al. 2012), and smoking among pregnant teenagers has risen in recent years. Approximately 40% of Finnish teenagers with an unplanned pregnancy which ended in an induced abortion reported not having used any contraception (Leppälahti et al. 2012).

6.1.2 Socioeconomic position

The strongest association was observed between smoking during pregnancy and socioeconomic position in Finland and in Norway, where the information was available. A 6–7 times higher prevalence of smoking was seen among women with the lowest socioeconomic position compared to the highest, and this difference has been slowly increasing. Previous studies have also shown lower, but significant, differences in smoking according to socioeconomic background (Ergin et al. 2010, Mohsin and Bauman 2005, Villalbí et al. 2007). Contrary to Finland and Norway, the rate of smoking during pregnancy has also been decreasing in the lowest social group in Australia during recent years (Mohsin et al. 2011).

6.1.3 Marital status and parity

Living without a partner seemed to be an independent risk factor for smoking during pregnancy, although single women are more often also younger. In a previous study, women who had had previous deliveries were more likely to smoke daily during pregnancy than those who had not had a previous delivery, but no association was found between daily or occasional smoking throughout pregnancy and parity (Ergin et al. 2010). Our study showed, however, that women who had not had previous deliveries, both in Finland and in Norway, were more likely to smoke in early pregnancy than those with previous deliveries, although no difference was observed in the end of pregnancy.

Women who have had previous deliveries may smoke less during early pregnancy because they may stop prior to the pregnancy, or smoke less overall due to their increased knowledge of the risks of smoking during pregnancy from their antenatal care visits in previous pregnancies. Women who had not had a previous delivery may encounter the smoking-cessation intervention for the first time during their antenatal care, and therefore tend to stop more often during pregnancy. Therefore, smoking-cessation interventions should be aimed towards women who had not had a previous delivery, because if they succeed in stopping smoking, they may smoke less in future pregnancies, as well as generally.

6.1.4 Smoking cessation

Stopping smoking is never easy, although pregnancy could act as a strong motivator for the pregnant woman, and for her partner, to stop smoking (Haug et al. 1992). Smoking-cessation interventions have been shown to have some effect on smoking during pregnancy (Table 14). Results of studies on the effectiveness of nicotine replacement therapy on pregnant women have been controversial. The most effective strategy has been suggested to be financial incentives (Lumley et al. 2009). This strategy may be most effective especially in those for whom the prevalence of smoking is highest, for example teenagers and women with low incomes. Our study offers more knowledge about the groups of women to whom smoking-cessation intervention could be specifically aimed during pregnancy.

Some women have such a strong nicotine addiction that pharmacological therapies should be considered. The efficacy of nicotine replacement therapy during pregnancy is unclear, but a recent Cochrane-analysis showed that pharmacotherapy had a significant effect on smoking cessation during pregnancy (Coleman et al. 2012). However, there have been concerns about the safety of nicotine replacement therapy during pregnancy (Pauly and Slotkin 2008) because nicotine is held as one of the major components in tobacco smoke which has adverse effects on the fetus. Theoretically, with nicotine replacements a fetus may be exposed for a longer time at a steady level, or even to a higher level of nicotine, than from actual smoking. The assessment of the safety of nicotine replacement therapy during pregnancy needs further study (Murin et al. 2011) as one previous study had to be terminated prematurely due to the high number of adverse birth outcomes in the group using a nicotine replacement therapy (Pollak et al. 2007). The best way to decrease smoking during pregnancy would be to prevent teenagers from initially starting smoking with new national legislations (Rimpelä and Rainio 2004), or promoting to parents the benefits of strict home-smoking bans (Rainio and Rimpelä 2008).

6.2 The effects of the smoking exposure

6.2.1 Brain volumes

Previous studies have shown smaller brain volumes in various brain regions at term age in preterm infants when compared to full-term infants (Limperopoulos et al. 2005, Peterson et al. 2003, Thompson et al. 2007), but the etiology of these reductions is not well known. The possible mediating factors for reduced brain volumes might be low gestational age (Inder et al. 2005, Limperopoulos et al. 2005), treatments used in neonatal care (Thompson et al. 2008), and brain

Table 14. Effectiveness of interventions promoting smoking cessation in pregnancy.

		Method	Effectiveness
Coleman et al. 2012	Cochrane Database Syst Rev.	Pharmacological interventions: nicotine replacement therapy (NRT), varenicline, and bupropion	No statistically significant difference for smoking cessation with NRT, risk ratio 1.33, 95% CI 0.93–1.91. No studies on other medications.
Lumley et al. 2009	Cochrane Database Syst Rev.	Various interventions: cognitive behavior therapy, feedback of fetal health, financial incentives for stopping smoking, and pharmacotherapies	A significant reduction in smoking following all interventions was observed, risk ratio 0.94, CI 0.93–0.96, and also separately in different interventions. Most effective strategy was financial incentives with a risk ratio 0.76, CI 0.71–0.81.
Naughton et al. 2008	A systematic review and meta-analysis	Comparison of routine care and self-help (self-help interventions without cessation counseling)	A total of 4.9% stopped with routine care compared to 13.2% with self-help. There was a significant difference observed, odds ratio 1.83, CI 1.23–2.73.
Hajek et al. 2001	Original report	Randomized controlled trial of comparison of routine care and midwife-delivered brief intervention with feedback on expired-air carbon monoxide levels	No statistically significant difference in smoking at birth of child.
Acharya et al. 2002	Original report	Randomized survey of the effectiveness of antismoking counseling during the first visit for the antenatal care in the United Kingdom.	A total of 84% of smokers did not change smoking habits, 11% reduced number of cigarettes smoked, and almost 5 % stopped smoking. No effect on partners' smoking habits.
Jaakkola et al. 2001b	Original report	Controlled intervention study including women who smoked during pregnancy. Nurses following the intervention group had had a one-day training session on smoking cessation interventions. No structured individual based intervention.	A total of 19.0% in intervention group and 14.5% in control group stopped smoking during pregnancy. The difference was no statistically significant.

pathology (Inder et al. 2005, Limperopoulos et al. 2005, Thompson et al. 2007,Thompson et al. 2008). In addition, preterm infants are more often exposed to prenatal smoking than full-term infants (Fantuzzi et al. 2007, Windham et al. 2000). Our study, with VLBW/VLGA infants, showed smaller cerebellar and frontal lobe volumes in infants exposed to prenatal smoking when compared to unexposed infants. However, no difference was observed in structural brain disease or IVH between the exposed and unexposed infants.

To our knowledge, only one previous human study has investigated the relationship between prenatal smoking exposure and brain volumes in late gestation. There are no other studies from early infancy. Roza et al. (2007) found smaller sizes in both brain regions that were measured, transcerebellar diameter and atrial width of lateral ventricle, in fetuses exposed to prenatal smoking when compared to unexposed fetuses. Various regions were affected by prenatal smoking exposure in older children (Jacobsen et al. 2007a, Paus et al. 2008, Rivkin et al. 2008), for example the frontal lobe volume was found to be smaller in children aged 12 to 18 years exposed to prenatal smoking, than in the unexposed children (Toro et al. 2008).

Several animal studies have shown robust associations between prenatal nicotine exposure and brain development (Roy et al. 1998, Slotkin 1998). Prenatal nicotine exposure has been suggested to increase the expression of an important nuclear transcription factor, c-fos, in the rat forebrain, cerebellum, and brainstem (Trauth et al. 1999). C-fos is involved in cell death and differentiation in the brain. These findings suggest that the cerebellum and the frontal lobe might be the most vulnerable brain regions for prenatal smoking exposure.

6.2.2 Head circumference

Numerous studies have documented smaller head circumferences at birth in full-term infants exposed prenatally to smoking, when compared to unexposed infants (Fenercioglu et al. 2009, Harrison et al. 1983, Himes et al. 2012, Ong et al. 2002, Wang et al. 1997). In our study consisting of preterm infants, smaller brain volumes were found in specific brain regions, and no association between prenatal smoking exposure and head circumference was observed. This might be explained by the fact that full-term infants are exposed to prenatal smoking for a longer period of time during pregnancy, and therefore could be even more vulnerable to smoking exposure. This assumption is supported by findings which show that stopping smoking between the first prenatal care visit and week 32 of pregnancy prevents the adverse effects of smoking on head circumference (Lindley et al. 2000).

In a study consisting of mostly full-term infants, in which prenatal smoking exposure was evaluated by maternal cotinine measurements and questionnaire information, Król et al. (2012) found that infants exposed to prenatal smoking had a smaller head circumference and smaller cerebral mass than did unexposed infants. Cerebral mass was calculated according to a equation: cerebral mass (g) = 0.037 x head circumference $(cm)^{2.57}$ (Lindley et al. 2000). Therefore, a smaller head circumference in full-term infants exposed to smoking throughout pregnancy might be due to a more global brain volume reduction after prolonged prenatal smoking exposure.

6.2.3 Psychiatric morbidity

Our nationwide epidemiological study showed that children exposed to prenatal smoking had a significantly higher risk, ranging from 1.5 to 1.9 times, for psychiatric morbidity treated in specialized hospital care when compared to unexposed children, and a strong dose-response was observed. There are no previous large-scale epidemiological studies of this kind that have controlled for maternal severe psychiatric morbidity. Previous studies have focused on only some psychiatric problems concurrently (Fergusson et al. 1998, Weissman et al. 1999), or on only one outcome like hyperkinetic disorders (Koshy et al. 2011, Linnet et al. 2005, Milberger et al. 1996) or conduct disorders (Maughan et al. 2004, Wakschlag et al. 1997).

Our results, showing an association with smoking exposure and various types of psychiatric morbidities, are in contrast to earlier studies with various outcomes (Fergusson et al. 1998, Weissman et al. 1999). Fergusson et al. (1998) found an association between smoking exposure and conduct disorders, but not with other psychiatric problems including anxiety, major depression, and substance abuse. Weissman et al. (1999) showed an increased risk for conduct disorders in boys and for drug dependence in girls exposed to prenatal smoking when compared to unexposed children, but no association was found for mental disorders, anxiety disorders, ADHD, or alcohol dependence. The difference in these results might be explained by the previous studies having been limited by the size of the study population. The largest study investigating the effects of smoking on psychiatric problems includes no more than 22,545 children (Stene-Larsen et al. 2009). In addition, the follow-up of the children had often only been carried out until early childhood (Thapar et al. 2009), despite the occurrence of psychiatric problems increasing with age. Furthermore, some studies assessed psychiatric problems retrospectively with questionnaires or interviews (Button et al. 2005, Weissman et al. 1999) and focused only on symptoms (Kotimaa et al. 2003, Langley et al.

2012, Markussen Linnet et al. 2006, Thapar et al. 2003) and not on diagnosed psychiatric problems.

6.2.3.1 ADHD

The effect of prenatal smoking exposure on ADHD has been studied the most. The findings of these studies have been somewhat controversial; however, the general understanding is that prenatal smoking exposure increases the risk for attention problems in children (Froehlich et al. 2009, Kotimaa et al. 2003, Linnet et al. 2005, Markussen Linnet et al. 2006, Milberger et al. 1996, Obel et al. 2009, Schmitz et al. 2006, Thapar et al. 2003). Similarly, in our study the strongest associations between prenatal smoking exposure and psychiatric morbidity were observed for behavioral and emotional disorders including hyperkinetic disorders with a 2.1 to 2.7 times increased risk, and disorders of conduct and emotion with a 2.3 to 3.2 times increased risk in children exposed to smoking when compared to unexposed children. A similar magnitude of the effect of smoking has been seen in previous studies investigating smoking and ADHD diagnoses (Froehlich et al. 2009, Linnet et al. 2005, Koshy et al. 2011, Schmitz et al. 2006) and symptoms (Kotimaa et al. 2003, Markussen Linnet et al. 2006), with the risk ranging from between 1.3 and 3.4 times increase. A positive dose-response was seen in our study, as in a few other previous studies (Koshy et al. 2011, Kotimaa et al. 2003).

6.2.3.2 Antisocial behavior and conduct problems

The association between exposure to prenatal smoking and antisocial behavior or conduct problems has also been widely studied. Smoking exposure has been suggested as having an independent effect on the increased risk for conduct problems (Button et al. 2005, Fergusson et al. 1998, Murray et al. 2010, Wakschlag et al. 1997 Weissman et al. 1999), although genetic and environmental factors also have an important role (Bor et al. 2004, Maughan et al. 2004).

In our study, the risk for conduct disorders was increased 2.3 times in children exposed to fewer than 10 cigarettes per day, and 3.2 times in children exposed to more than 10 cigarettes per day, when compared to unexposed children. Contrary to our study, earlier studies have usually only shown a significantly increased risk in children exposed to more than 10 cigarettes per day, and often this association was significant only in boys (Fergusson et al. 1998, Wakschlag et al. 1997). These differences may be explained by the smaller study populations in these studies. However, a similar risk as found in our study for children exposed

to more than 10 cigarettes per day when compared to unexposed children, was observed in a study with 177 clinic-referred boys followed up to 18 years of age with 4.4 times the risk for conduct disorders (Wakschlag et al. 1997).

6.2.3.3 Substance abuse

Our study found a clear association between prenatal smoking exposure and the prevalence of psychiatric diagnoses due to psychoactive substance abuse including alcohol and other drugs with a dose-response. Earlier studies have shown similar results but the association has been smaller, as Nomura et al. (2011) found with a 30% increased risk for alcohol-use disorders in individuals exposed to more than 20 cigarettes per day, compared to unexposed individuals. A study using a Danish birth cohort of 4,169 males and 3,943 females showed that psychiatric hospitalization due to substance abuse was increased both in males and females exposed to prenatal smoking (Brennan et al. 2002), although they found no association between smoking exposure and psychiatric hospitalization due to other psychiatric reasons. However, a 21-year longitudinal study found no association between smoking exposure and alcohol problems in children (Baer et al. 2003).

6.2.3.4 Psychosis

Only two studies have previously investigated the effects of prenatal smoking on psychotic symptoms in children, with controversial findings. The first found no association between prenatal smoking exposure and hospitalization due to psychoses (Dombrowski et al. 2005). The second study, by Zammit et al. (2009), comprised a longitudinal study of 6,356 children at 12 years of age who completed an interview for psychotic symptoms. Prenatal smoking exposure was associated with a 20% increased risk for suspected or definitive psychotic symptoms but they concluded that these findings might reflect lifestyle markers or secondhand smoke exposure. There was no association between smoking exposure and schizophrenia in our study. However, the risk for psychoses in our study was seen to significantly increase in exposed children, when compared to unexposed children. This finding is interesting because of the low incidence of psychoses in young adults, as psychoses starts to increase in young adulthood.

6.2.3.5 Effect of gender

The magnitude of the increased risk from smoking was increased almost equally for males and females for different psychiatric morbidities in our study. However, the occurrence of psychiatric morbidities differed between males and

females. Psychiatric morbidities often occur earlier in males; for example males have a higher incidence of hyperkinetic disorders, which usually occur in early childhood. Conversely, females tend to have more problems with later manifestation, for example behavioral syndromes, neurotic disorders, and stress-related disorders. Our study showed the broad effects of smoking exposure on psychiatric morbidity, which clarifies the impact of prenatal smoking exposure on the burden for psychiatric morbidity in a nationwide population.

6.2.4 Psychotropic drug use

The use of psychotropic medication has been increasing among children in recent years (Clavenna et al. 2007, Delate et al. 2004, Martin and Leslie 2003, Schirm et al. 2001). The most commonly prescribed psychotropic medications in children were stimulants, anxiolytics, and antidepressant (Clavenna et al. 2007, Schirm et al. 2001). Of these, anxiolytics and antidepressant are mostly prescribed in primary health care, and therefore are not included in hospital-based psychiatric morbidity. This highlights the importance of also using pharmacy data. There are significant differences in psychotropic medication use between countries, as the annual prevalence of psychotropic medication was 6.7% in the United States, 2.9% in the Netherlands, and 2.0% in Germany (Zito et al. 2008). The cumulative prevalence of the use of psychotropic medication was 8.9% in our study. A cumulative approach provides a comprehensive picture of the utilization pattern, and therefore yields a higher percentage.

To our knowledge, our study was the first to investigate the associations between prenatal smoking exposure and the cumulative use of all psychotropic medications into early adulthood. Previously, a Swedish register-based study with 982,856 children aged 6–19 years found a 2.9 times increased risk for ADHD medication in children exposed to prenatal smoking, when compared to unexposed children. However, when two pregnancies of the same mother were analyzed, no significant difference was observed according to smoking exposure (Lindblad and Hjern 2010). In our study, the strongest association between smoking exposure and the use of stimulants, which are commonly used to treat ADHD was seen. In addition, we found associations between prenatal smoking exposure and all psychotropic medication categories, all continuity categories, and in both single and multiple drug consumption categories. As all the results of psychotropic medication use were in accord, we suggest that prenatal smoking exposure is linked with both mild and severe psychiatric problems.

6.2.5 Mortality

Previous studies have shown that infants exposed to prenatal smoking had a 1.4 to 1.8 times higher risk for mortality during the first year of life, compared to unexposed infants (Salihu et al. 2003, Wisborg et al. 2001). There was no difference in mortality during the first eight years of life between children exposed to prenatal smoking and those unexposed (Hofvendahl 1995). However, another study from Sweden indicated that deaths related to traumas were increased in males exposed to prenatal smoking (Nilsson et al. 2006). Males exposed to prenatal smoking, and also females exposed to more than 10 cigarettes per day during pregnancy, had an increased risk for mortality in our study. The prevalence of suicides did not differ according to the exposure to smoking. The prevalence of mortality may be increased in exposed children because common causes of death in children and adolescents are usually related to injuries and accidents, which may be more prevalent in individuals with psychiatric problems.

6.3 Strengths and limitations of the thesis

The strength of this thesis is that it consists of studies with different types of approaches to prenatal smoking exposure. In the clinical study with VLBW/VLGA preterm infants, exposure to prenatal smoking was associated with smaller frontal lobe and cerebellar volumes. These brain regions are important for normal psychological development, and might explain part of the association between prenatal smoking exposure and later behavioral problems. In two nationwide epidemiological birth register studies, including 94% of all children born between 1987 and 1989, we found that prenatal smoking exposure was associated with an increased risk for various mild and severe psychiatric problems in the resulting offspring. The different approaches in these current studies have a clear synergy, and the results of the adverse effects of smoking exposure are parallel with each other, which makes the results more robust.

The major concern in this thesis is the accuracy of the smoking data. It is suggested that the most reliable way to assess prenatal smoking exposure is to measure cotinine levels, usually from maternal blood during pregnancy (Shipton et al. 2009), although there are studies which show high levels of agreement between self-reported smoking data and cotinine measurements among pregnant women (George et al. 2006, McDonald et al. 2005). In our clinical study, there were no samples collected for cotinine measurements to assess smoking exposure. However, the prevalence of smoking (18%) was at the same level as smoking rates in pregnancy (15%) in the whole of Finland generally (Jaakkola et

al. 2001a). Moreover, smoking habits were assessed on two different occasions in this study: during maternal antenatal care, and in a separate questionnaire before the discharge of the child. Repeated assessment of smoking during pregnancy is known to give more reliable data (Bakker et al. 2011, George et al. 2006).

The use of cotinine measurement is difficult in large epidemiological studies that collect vast material, as with our two current studies using data from Finnish registers that were based on maternal self-reporting. The proportion of women underreporting smoking during the study years is unclear. It is likely that the women who underreported might have been light smokers, because it is more unlikely that heavy smokers or women continuously smoking would succeed in hiding their smoking habits. In addition, the data on smoking during pregnancy in the Finnish Medical Birth Register has been in excellent agreement with the questionnaire information and the data from medical records (Jaakkola et al. 2001a). Furthermore, information on women who have stopped smoking during pregnancy (studies II–IV) is lacking. However, the cohort in the epidemiological studies was born during the end of the 1980s, when only 1 out of 10 women stopped smoking during pregnancy (Gissler et al. 2009).

The households of smoking and non-smoking pregnant women may differ in substantial ways. No information on fathers could be collected due to strict confidentiality legislation, and therefore we do not have any information on the fathers, including their smoking habits and background factors. The father's smoking habits would be important information because environmental smoke exposure for pregnant non-smoking women has been shown to associate with several adverse prenatal outcomes (Crane et al. 2011). In addition, smoking during pregnancy is more prevalent in women with a partner who smokes (Villalbí et al. 2007). Our studies also lack information on the children's exposure to environmental second-hand smoking during the first years of life, which has been suggested to have adverse effects, for example on the child's behavior in later life (Kollins et al. 2009, Twardella et al. 2010). There may be other environmental factors correlating to smoking exposure that are potentially harmful for brain development, which were not available in our studies.

The Finnish Medical Birth Register does not contain information on maternal alcohol or illicit drug use, although smoking women might have increased substance use. However, our clinical study (II) did include this information, which was one of its strengths. Moreover, our studies lacked information on the use of other tobacco products like snuff, but the use of snuff is generally very unusual for women in Finland, as only 0.4% of women use snuff occasionally or

daily (Health Behaviour and Health among the Finnish Adult Population, Spring 2010). In Sweden, a total of 0.5% of women use snuff throughout pregnancy (Smoking habits in pregnant women 2008).

6.4 Specific strengths and limitations of the original publications

6.4.1 Nordic birth register study (I)

The smoking data was collected similarly in all the Nordic countries, and therefore it is unlikely that there was a bias between the countries. However, the true prevalence of smoking may be lower in Norway, where an informed consent by the mothers is needed for collecting smoking data, compared to other countries in which it is not. In Norway, 12% to 19% of women did not give this permission. Changes in the background of women giving their informed consent may explain seemingly the recent increase in smoking during pregnancy in Norway. Data quality studies have shown that the register data has been collected properly in all the countries (Cnattingius et al. 1990, Gissler et al. 1995, Irgens 2000, Knudsen and Olsen 1998, Teperi 1993), although information on Danish teenagers was unreliable. One of the strengths of this Nordic birth register study was that we had information on smoking in both early and the end of pregnancy, and we could observe the proportions of women who stopped smoking during pregnancy, as an increasing number of women do.

6.4.2 Clinical study (II)

The specific strengths of our clinical study also included a regional cohort of preterm VLBW/VLGA infants born from 2001 to 2006. The recruitment and follow-up percentage was high in the study. A detailed MRI analysis was performed, and the reproducibility of the brain volume measurements was high. Limitations included the use of two different MRI equipments during the study, which might interfere with the results. However, the volume measurements were shown to be reliable between the MRI equipments. Our statistical analyses were confounded by a wide range of confounding factors including, for example, neonatal inflammatory diseases and maternal alcohol consumption during pregnancy.

6.4.3 Epidemiological studies on psychiatric morbidity (III–IV)

Various register data was used in the current epidemiological studies. The Finnish Medical Birth Register includes a large set of data, including data on smoking during pregnancy for practically all deliveries in Finland. Previously, the register data has been shown to be reliable (Gissler et al. 1995, Teperi 1993).

All diagnoses given during specialized health care or during inpatient care in private hospitals are recorded in the National Hospital Discharge Register. A total of 99% of the diagnoses related to mental disorders were registered under the correct ICD chapter, according to a data quality study (Keskimäki and Aro 1991). Limitations of using hospital-based psychiatric morbidity include a concern about the accuracy of the diagnoses. The data was analyzed according to main diagnostic categories, which lowers the possibility of systematic bias in the categorization with the exception of schizophrenia (Isohanni et al. 1997).

The true prevalence of the population with psychiatric problems might have been underestimated, because we lacked information on those seeking help from private health care, or those not seeking help at all. It is probable that only a limited number of children used private health care exclusively, due to the comprehensiveness of the public health care system, and the low availability of private psychiatric services for children in Finland (Statistical Yearbook of the Social Insurance Institution 2007). In addition, the more severe psychiatric problems are only treated within specialized health care, and this hospital-based data, used in the third study, lacked information on milder psychiatric problems that are treated within primary health care. To reach this population, with psychotropic drug use but no visits to specialized health care, we linked data on children's psychotropic drug use from the Drug Prescription Register to our data.

The Drug Prescription Register contains information on all reimbursed prescription drugs in Finland. As all psychotropic drugs are reimbursable, self-medication with "over-the-counter" drugs is unlikely to have interfered with the results. This approach of using pharmacy data make it possible to observe psychiatric morbidity from a different, and a broader, point of view than only using data on psychiatric diagnoses. A total of between 29% and 44% of children using hypnotics/anxiolytics and antidepressants were not included in the hospital registers. The limitations of using pharmacy data included the lack of information on the doses, or an indication of which drugs were prescribed. The other potential limitation is a lack of information about the actual use of the purchased drug. However, self-reporting of medication use and data on purchases have been shown to be in sufficient agreement for research purposes (Haapea et al. 2010).

The Cause-of-Death Register contains information on all deaths of Finnish citizens in Finland and abroad. After the data linkage of the registers, we had a complete follow-up of the children until the end of 2007 or the death of the child, including all inpatient care episodes with a psychiatric diagnosis from the birth of the child, outpatient visits from 1998, and a 13-year cumulative use of

psychotropic drugs. A long follow-up is necessary because most psychiatric problems emerge in adolescence, or later. Unfortunately, information was missing for children who migrated out of Finland.

Contrary to previous epidemiological studies investigating the effects of smoking exposure to later psychiatric problems, we were able to adjust the analyses with various background factors including a mother's severe psychiatric illnesses, treated in hospital. These severe psychiatric problems show a greater genetic predisposition for psychiatric illnesses such as psychoses and severe mood disorders (Bienvenu et al. 2011, Lichtenstein et al. 2009, Wray and Gottesman 2012) than for milder psychiatric problems (Bienvenu et al. 2011, Kendler et al. 1992), for which we lacked information. Personality characteristics or strong maternal nicotine addiction can lead to the continuation of smoking during pregnancy. These characteristics may also be signs of a genetic risk for psychiatric problems, which can lead directly, or through poor parenting skills, to an increased risk for psychiatric problems in the offspring (Fagot et al. 1998, Hill 2002). Our results showed a strong association between prenatal smoking exposure and an increased risk for psychiatric morbidity, despite the adjustment for severe maternal psychiatric illnesses. However, it is unlikely that these adjustments accounted for the whole genetic predisposition for psychiatric morbidities in the children.

Separate analyses with pharmacy data were done to assess the association between prenatal smoking exposure and psychotropic drug use in the low-risk populations (analyses separately excluding young mothers, children born premature, and those with a low birth weight) for controlling environmental factors. The results remained strong for the low-risk populations, although the analyses could not take into account all environmental factors such as secondhand smoke exposure. Exposure to secondhand smoke has been reported to have direct health effects for exposed children including, for example, an increased risk for lower respiratory diseases or upper respiratory infections, and it may even affect the predisposition for psychiatric morbidities (Best 2009).

The Medical Birth Register does not collect information on maternal psychotropic drug use during pregnancy, which has been connected with adverse pregnancy outcomes like preterm birth (Hayes et al. 2012) and even an increased risk for problems in an infant's psychological and cognitive development (Gentile 2010). However, the common understanding is that psychotropic drug use during pregnancy is relatively safe, and it is thus advisable to use psychotropic medication if the mother requires treatment (Einarson 2009, Lorenzo et al. 2011).

7. SUMMARY AND CONCLUSIONS

7.1 Main findings

The objectives of our study were to increase the knowledge of the long-term consequences of prenatal smoking exposure on brain development and psychiatric problems in children. In addition, one of the objectives was to identify the target groups for interventions to reduce prenatal smoking exposure, because such adverse effects of smoking exposure to the fetus are preventable.

In study I, we demonstrated that the women who are single, young, who have not had a previous delivery, or who have low socioeconomic positions were more likely to smoke during pregnancy than others. In addition, there were significant differences in smoking rates during pregnancy between the Nordic countries, for example in Sweden smoking rates during pregnancy have decreased significantly during the last decades which is contrary to Finland where the prevalence of smoking during early pregnancy has remained stable. Most worryingly, smoking rates among pregnant teenagers have increased in Finland and in Norway. This study contains information on smoking in early pregnancy as well as in the end of pregnancy, which is important because the prevalence of smoking throughout pregnancy has decreased in all countries.

In study II, we investigated the adverse effects of prenatal smoking exposure on fetal brain development by using volumetric brain MRI in preterm infants at term equivalent age. Our study showed a significant association between prenatal smoking exposure and reduced volumes of both the frontal lobe and cerebellum. These regions are important for normal psychological development, and these findings may partly explain the association between prenatal smoking exposure and an increased risk for later behavioral problems.

Study III and IV showed that prenatal smoking exposure was associated with an increased risk for a wide range of psychiatric problems in the offspring, even when controlling for severe maternal psychiatric morbidities. The risk was further increased if the child had been exposure to higher amounts of prenatal smoking. By using both hospital and pharmacy-based data we showed that prenatal smoking exposure is linked to both mild and severe psychiatric problems.

Our studies, based on different kinds of approaches, all showed significant associations between prenatal smoking exposure and adverse effects for the offspring, suggest a causal effect of prenatal smoking exposure on the health of

the offspring. We also discovered specific populations with high smoking rates during pregnancy, and pointed out significant differences in national health policies that might explain in part the differences in smoking rates during pregnancy between the Nordic countries. Therefore, this thesis emphasizes the importance of developing new national strategies to reduce the prevalence of smoking during pregnancy.

7.2 Clinical implications

We can speculate, based on the findings from study I, that one effective way to reduce smoking during pregnancy may be to increase the availability of pregnancy planning and prevention services, especially for teenagers. Our studies suggest that the burden of psychiatric problems might be nationally decreased if the prevalence of prenatal smoking exposure could be reduced.

These results are helpful in clinical practice. It is reasonable to suggest that prenatal smoking exposure should be considered as an important factor when evaluating the need for support or interventions for a child, to prevent later behavioral and other psychiatric problems. The risk of attention problems, and medication for attention problems, was particularly affected. Thereby, prenatal smoking exposure as a strong risk factor could support the providing of measures to help cope with attention problems.

7.3 Implications for future research

In the future, more research is needed into the factors affecting smoking during pregnancy. It would be important to better understand which groups of women underreport smoking during pregnancy, and therefore miss smoking cessation interventions. The possible effects of prenatal smoking exposure on brain development in full-term infants remain unclear, and should be further studied. In addition, more specific studies with functional MRI should be conducted, to study the associations between smoking exposure and executive functions of the brain. Cotinine measurements verifying prenatal smoking exposure would be important to add in these kinds of studies, to obtain objective data on smoking exposure during pregnancy. It would also make it possible to assess the dose-response of smoking exposure. Moreover, it would be interesting to study gene-environment interactions between prenatal smoking exposure and different genomic alleles on brain development and psychiatric morbidity, to gain a better understanding of the possible pathways of the effect of smoking on psychiatric problems. More studies are needed to understand in more depth the factors in the social environment that affect both smoking and child outcomes.

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Mikael Ekblad

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