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Changes in smoking behavior during pregnancy: prevalence and effect on selected adverse pregnancy and birth outcomes. The Murmansk County Birth Registry study

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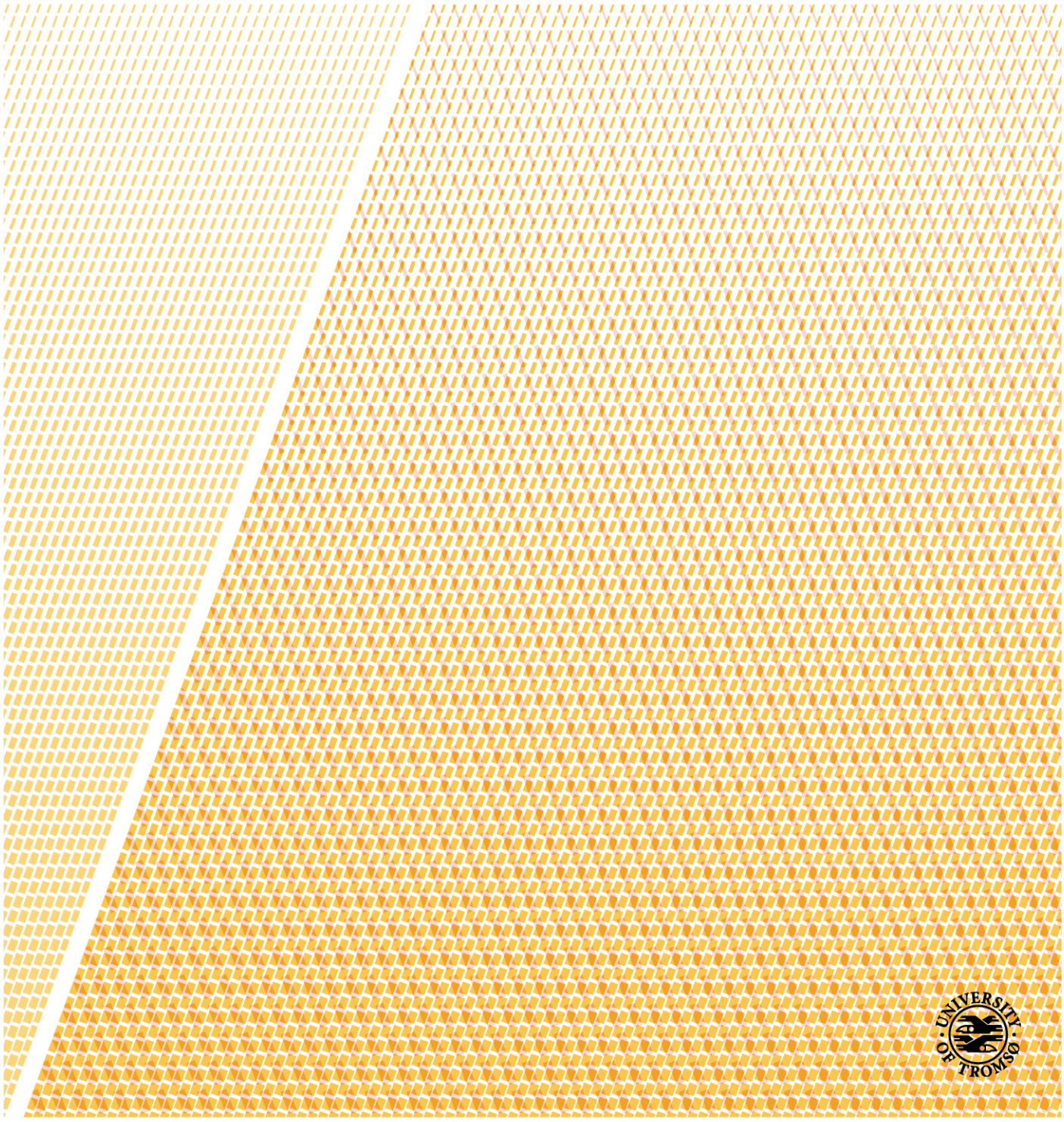

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Department of Community Medicine

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Preface

The idea to study smoking during pregnancy in Northwest Russia came to me long before my PhD studies. In 2005, Professor Andrej G. Soloviev of the Northern State Medical University (NSMU), Arkhangelsk, Russia, encouraged my involvement in the project Pregnancy and Tobacco Smoking. In 2006, I enrolled in the Arkhangelsk International School of Public Health which was a collaboration between UiT - The Arctic University of Norway (Tromsø, Norway), NSMU and other Nordic institutions. In 2009, I defended my Public Health Master thesis on "Smoking in Pregnancy and its Effect on Breastfeeding Duration in Northwest Russia".

I defended my candidate thesis in 2011 at Russian Center for Emergency and Radiation Medicine named after A.M. Nikiforov, Saint-Petersburg, Russia. It focused on clinical, psychological and social peculiarities of smoking pregnant women, and I received the Russian scientific degree Candidate of Psychological Sciences. During the preparation of this thesis, I began to understand the importance of using Russian data to illustrate the negative impacts of smoking on birth outcomes and on the pregnancy itself. Moreover, most Russian doctors did not recommend smoking cessation during pregnancy, and some even advised its continuation. When a new PhD position became available at UiT, I decided to apply for the project entitled "Effect of Maternal Smoking on Pregnancy and Birth Outcomes Using the Murmansk County Birth Registry". However, during the data analysis and preparation of Paper I my scientific interest shifted to smoking cessation and its reduction during pregnancy. This was done to demonstrate to health providers the importance of giving up smoking immediately after pregnancy recognition.

Acknowledgements

This thesis was carried out at the Department of Community Medicine, Faculty of Health Sciences, UiT – The Arctic University of Norway (Tromsø, Norway) and at the Central Research Laboratory, NSMU - Northern State Medical University (Arkhangelsk, Russia). I wish to express my gratitude to the Rector of UiT, Anne Husebekk and the NSMU Rector, Lubov N. Gorbativa for making available the facilities of both Universities to enable me to complete my thesis.

I wish to express my sincere thanks to my main supervisor Professor Jon Ø. Odland. Without his confidence in me at the stage of project approval and subsequently, there would be no thesis. He allowed and encouraged me to be as an independent researcher. In addition, I wish to acknowledge the contributions of provided by my co-supervisor Professor Andrej M. Grjibovski.

I also wish to thank my co-authors – Alexandra Krettek and Evert Nieboer - who kindly participated in the design of the study and the drafting of the manuscripts. Evert Nieboer served manuscript as a scientific/linguistic editor and with Jon Ø. Odland and other investigators participated in the setting up of the MCBR. I would especially like to thank my friend Ekaterina E. Sharashova MD, PhD for her valuable assistance with the statistical analysis.

I wish to express warm thanks to my fellow students – Elena Roik, Anton Kovalenko, Anna Usynina, Vitaly Postoev, Sergey Drachev, Yriy Sumarokov, among others – all of whom not only participated with me in the various PhD activities including courses and conferences, but also became my friends.

I am also grateful for the support of my Parents, especially their care for my children.

Finally, I would like to thank my Husband and Sons for their patience and psychological support throughout my life ☺

Abstract (in English)

Background.

Smoking during pregnancy is one of the most avoidable causes of adverse maternal and birth outcomes. In order to develop successful maternal cessation smoking public health programs in Russia, knowledge about the socio-demographic characteristics of prospective mothers who quit or reduce smoking during pregnancy and effect of the latter on pregnancy and birth outcomes should be considered.

Aims.

The specific objectives of this thesis were to i) determine the prevalence of smoking before and during pregnancy and to assess socio-demographic factors associated with discontinuing smoking or smoking reduction once pregnant; ii) investigate the effect of first-trimester smoking cessation while pregnant on Preeclampsia/eclampsia; and iii) explore the effect of changes in smoking behavior during pregnancy on selected adverse birth outcomes.

Methods.

This study was registry-based with data from Murmansk County Birth Registry (MCBR). Initially, the study population consisted of all women who were registered in the MCBR from 2006 to 2011 (N = 52,806). Sample size for the realization of different specific aims varied due to exclusion criteria. Information about smoking before and during pregnancy was self-reported and assessed during the first antenatal visit.

Results.

Almost 25 % of women smoked before pregnancy, and 18.9 % of these continued smoking during pregnancy. One fourth of smoking women stopped to do it after pregnancy recognition and on third reduced the quantity of cigarettes smoked during pregnancy. Parity, level of education and marital status or maternal age and number of children were associated with giving up smoking or its reduction, respectively, during pregnancy.

Maternal smoking was inversely associated with Preeclampsia/eclampsia. However, the women who quitted smoking during first-trimester of pregnancy had the same risk of this affliction as those who smoked while pregnant. Moreover, the pregnant women who stopped smoking during the first-trimester of gestation were at no greater risk of having a baby with adverse birth outcomes, namely, low values of birth weight, birth length, head circumference, ponderal index

or Apgar score at 5 min. Interestingly, smoking reduction during pregnancy was not associated with a decrease in the adverse birth outcomes examined.

Conclusions.

While maternal smoking decrease the risk of Preeclampsia/eclampsia, but giving up smoking during first-trimester of gestation does not influence this pregnancy outcome. Moreover, compared to non-smokers, the women who quit smoking during the first-trimester are at no higher risk of having a newborn with adverse birth outcomes. Thus, health provider should recommend smoking cessation during pregnancy as soon as possible after pregnancy recognition.

Abstract (in Norwegian)

Bakgrunn.

Røyking i svangerskapet er en av de mest unødvendige årsaker til svangerskapskomplikasjoner og dårlig svangerskapsutfall. For å utvikle folkehelsestrategier i Russland som kan redusere mors røyking i svangerskapet er kunnskap om sosio-økonomiske forhold for mødrene som reduserer eller klarer å slutte å røyke viktige å registrere, både med tanke på svangerskapsutfall og framtidige svangerskap.

Formål.

De viktigste formål med denne studien var å i) registrere forekomst av røyking før og under svangerskapet og å analysere sosio-demografiske faktorer i tilknytning til reduksjon eller stopp i røyking umiddelbart etter påvist graviditet; ii) å undersøke effekten av røykestopp i første trimester på utvikling av svangerskapsforgiftning; og iii) undersøke effekten av endring i røykevaner gjennom svangerskapet på utvalgte svangerskapskomplikasjoner og svangerskapsutfall.

Metode.

Vi gjennomførte en registerbasert studie med materiale fra Murmansk County Birth Registry (MCBR). Opprinnelig var studiepopulasjonen alle kvinner som ble registrert i MCBR fra 2006 til 2011 (N = 52,806). Størrelsen på utvalget for de forskjellige formål varierte ut fra definerte eksklusjonskriterier. Informasjon om røyking før og under svangerskapet var selv-rapportert og ble gjennomgått ved den første svangerskapskontrollen.

Resultater.

Nesten 25 % av kvinnene røykte før svangerskapet og 18.9 % av disse fortsatte å røyke gjennom svangerskapet. En fjerdedel av de røykende kvinnene sluttet å røyke etter at svangerskapet var påvist og en tredjedel reduserte røykingen gjennom svangerskapet. Antall barn, utdanningsnivå, ekteskapsstatus og alder var forbundet med røykestopp eller reduksjon av røyking gjennom svangerskapet.

Kvinnenes røykevaner var negativt assosierte med svangerskapsforgiftning. Imidlertid hadde de som sluttet å røyke i første trimester samme risiko som de som røykte gjennom svangerskapet. Likeså hadde de kvinner som sluttet å røyke i første trimester ingen øket risiko for de vanligste komplikasjoner, slik som lav fødselsvekt, fødselslengde, hodeomkrets, ponderal indeks (forhold

mellom vekt og lengde) eller Apgar score etter 5 minutter. Vi fant heller ikke at reduksjon i røykefrekvens hadde sammenheng med reduksjon i de registrerte svangerskapskomplikasjoner.

Konklusjoner.

Røyking i svangerskapet ser ut til å redusere risiko for svangerskapsforgiftning, men røykestopp i første trimester påvirker ikke dette utfallet. Likeså, sammenliknet med ikke-røykere, har kvinner som sluttet å røyke i første trimester ingen høyere risiko for svangerskapskomplikasjoner. I folkehelseprogrammer skal vi anbefale røykestopp før eller under svangerskapet. Den som røyker skal vi anbefale å slutte med en gang graviditeten er påvist.

Abstract (in Russian)

Введение.

Курение во время беременности является одной из важных причин неблагоприятных исходов беременности и родов. Для того, чтобы разработать успешные программы по отказу от табакокурения во время беременности в России, необходимы собственные данные о социально-демографических характеристиках женщин, которые смогли самостоятельно отказаться от курения во время беременности либо снизили количество выкуриваемых сигарет, а также данные о влиянии последнего на исходы беременности и новорожденных.

Цели исследования.

а) изучить распространенность табакокурения до и во время беременности и оценить социо-демографические факторы, связанные с отказом от курения или снижением количества выкуриваемых сигарет во время беременности; б) изучить эффект отказа от табакокурения во время первого триместра беременности на развитие Преэклампсии/Эклампсии; и в) изучить эффект в изменении курительного поведения во время беременности на некоторые негативные исходы новорожденных.

Методы исследования.

Настоящее регистровое исследование использовало данные Мурманского Регистра Родов (МРР). Изначально, все беременные женщины, зарегистрированные в МРР с 2006 по 2011 гг (N = 52,806) были включены в анализ. Однако объем выборок для реализации разных целей варьировал в связи с разными критериями исключения. Информация о табакокурении женщин до и во время беременности собиралась с помощью опросника и оценивалась во время первого антенатального визита.

Результаты исследования.

Около 25 % женщин курили до беременности, а 18,9 % - продолжили табакокурение во время гестации. Каждая четвертая курящая беременная смогла отказаться от употребления табака, а каждая третья – снизила количество выкуриваемых сигарет во время беременности. Паритет, уровень образования и семейное положение, а также возраст матери и количество предыдущих детей были связаны с отказом от курения, а также со снижением выкуриваемых сигарет за сутки, соответственно.

Материнское табакокурение было связано обратно пропорционально с Преэклампсией/эклампсией. Однако женщины, которые отказались от табакокурения во время первого триместра беременности имели такой же риск возникновения Преэклампсии/эклампсии, как и женщины, курящие на протяжении всей беременности. Более того, женщины, отказавшиеся от табакокурения во время беременности, имели такой же шанс родить ребенка с низким значением веса, роста, окружности головы, пондерального индекса и по шкале Апгар на 5 минуте, как и женщины, которые не курили до и во время беременности. Однако, снижение количества выкуриваемых сигарет во время беременности не показало такого же позитивного результата.

Заключение.

Несмотря на то, что табакокурение во время беременности снижает вероятность развития Преэклампсии/эклампсии, однако отказ от курения во время первого триместра беременности статистически значимо не изменило риск ее возникновения. Более того, по сравнению с некурящими беременными, женщины, отказавшиеся от табакокурения, имеют такой же риск рождения детей с низкими значениями массы тела, роста, окружности головы, пондерального индекса и по Апгар шкале на 5 минуте. Таким образом, работники сферы здравоохранения должны сразу же рекомендовать отказ от курения при постановке на учет по беременности.

List of papers

This thesis is based on the research papers listed below:

Paper 1

Kharkova OA, Krettek A, Grjibovski AM, Nieboer E, Odland JØ: **Prevalence of smoking before and during pregnancy and changes in this habit during pregnancy in Northwest Russia: a Murmansk county birth registry study**. *Reprod Health* 2016, 13:18. doi: 10.1186/s12978-016-0144-x.

Paper 2

Kharkova OA, Grjibovski AM, Krettek A, Nieboer E, Odland JØ: **First-trimester smoking cessation in pregnancy did not increase the risk of preeclampsia/eclampsia: A Murmansk County Birth Registry study**. *PLoS One* 2017, 12(8):e0179354. doi: 10.1371/journal.pone.0179354. eCollection 2017.

Paper 3

Kharkova OA, Grjibovski AM, Krettek A, Nieboer E, Odland JØ: **Effect of Smoking Behavior before and during Pregnancy on Selected Birth Outcomes among Singleton Full-Term Pregnancy: A Murmansk County Birth Registry Study**. *Int J Environ Res Public Health* 2017, 14(8). pii: E867. doi: 10.3390/ijerph14080867.

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Abbreviations

BMI	Body mass index
CO	Carbon monoxide
WHO	World Health Organization
IGR	Intrauterine growth retardation
SGA	Small-for-gestational age
NRT	Nicotine replacement therapy
ICD-10	International Classification of Diseases, 10^{th} edition
M-2SD	Mean values minus 2 standard deviations
MCBR	Murmansk County Birth Registry
OR	Odds ratio
RR	Relative risk
95 % CI	95 % Confidence interval

1. Introduction

Tobacco smoking remains a public health problem. Even though this habit is less common among women than men in Russia, it appears to be on the increase among females aged ≥15 years [1]. Consequently, this trend will lead to an increased prevalence of smoking during pregnancy. At the end of the 20th century, the maternal smoking rates in Northwest and East Russia were: 16.3% [2], 17.4% [3], and 24.8% [4], and thereby is lower than in some European countries [5].

Pregnancy represents a unique public health opportunity to stop or reduce smoking, as it constitutes a primary health risk factor for the unborn baby. This thesis focuses on the prevalence of smoking cessation and its reduction during pregnancy in the context of potential adverse pregnancy and birth outcomes.

1.1 Prevalence of quitting smoking and of smoking reduction during pregnancy

The prevalence of giving up smoking during pregnancy varies by country and has cultural, economic and political components. For example, the cessation rate during pregnancy was 23-43 % in the USA, 27-47 % in Europe, 62-70 % in Japan and 4-47 % in other nations [6-30]. Data on smoking reduction during pregnancy are limited (Table 1). Moreover, studies conducted in Russia mostly report only maternal smoking rates [2-4].

As indicated in Table 1, wide ranges of factors have been associated with changes in smoking status during pregnancy. Smoking cessation rates and reduction during pregnancy are associated with socio-demographical and behavioral characteristics of women. Of these, age, education, parity, marital status are more prominent than ethnicity, residence, alcohol intake, partner smoking status, working status, income, etc.

Table 1. Reported socio-demographic characteristics of pregnant women in the context of cessation or reduction smoking during pregnancy

Reference	Sample size, country, year of the study	Quit rate during pregnancy	Smoking reduction rate during pregnancy	Indicators
Colman G.J. [7]	N = 115,000 U.S. 1993-1999	42.5%	-	Age, race, parity, education, planned pregnancy, marital status, number of cigarettes smoked before pregnancy
Kaneita Y. et al. [8]	N = 16,414 Japan 2002	61.9%	-	Age, education, parity, working status, current drinking behavior, number of cigarettes smoked before pregnancy
Mohsin M et al. [9]	N = 426,344 Australia 1999-2003	4.0%	-	Age, aboriginal status, parity, Country of birth, socio-economical status
Janevic T et al. [10]	N = 410 Serbia, Macedonia 2012-2013	39.4% in Serbia and 39.5% in Macedonia	-	Age, marital status, education, wealth index
Blaga O.M. et al. [11]	N = 2370 Romania 2012-2015	50.0%	50.0%	Age, ethnicity, education, marital status, residence, occupation, family income, parity, depressive symptoms
Curtin S.C. et al. [12]	U.S. 2003	24.2%	-	Age, education, race, ethnicity
Moore E. et al. [13]	N = 979,198 U.S. 2006-2012	24.7%	-	Age, education, race, prenatal care, parity, marital status
Balwicki L. et al. [14]	N = 4512 Poland 2007-2008	33.0%	-	Parity, education, marital status, working status, socio-economical status
Dias-Dame J.L. et al. [15]	N = 7572 Brazil 2007, 2010, 2013	18.0% in 2007, 21.1% in 2010, and 17.6% in 2013	-	Family income, education, age, skin color
Passmore E et al. [16]	N = 1,065,740 Australia 2000-2011	4% in 2000, and 25.2% in 2011	-	Age, number of previous pregnancies, country of birth, duration of pregnancy at first antenatal visit
Gilbert N.L. et al. [17]	$N_{smokers}$ = 1586 Canada 2006	53.0%	-	Age, education, attending prenatal classes, social support stress, partner smoking status
Flemming K. et al. [18]	N_{papers} = 42 A qualitative study, 2012	-	-	Psychological well-being, and relationship with partner

Table 1 (continued)

Reference	Sample size, Country, Year of the study	Quit rate during pregnancy	Smoking reduction rate during pregnancy	Indicators
Alves E. et al. [19]	N = 5420 Portugal 2005-2006	47.4%	41.7%	Age, marital status, education, working status, family income, had at least one subsequent pregnancy
Koshy P. et al. [20]	N = 12 A qualitative study	-	-	Influence of partner, family and friends
Kale P.L. et al. [21]	N = 1744 Brazil 2011	26.7%	21.6%	-
Fasting M.H. et al. [22]	N = 711 Norway 2000	66.7%	-	Age, education
Robinson M. et al. [23]	N = 2900 Australia 1989-1991	54.2%	-	Age, education, marital status, family income, stress, alcohol intake
Rattan D. et al. [24]	N = 6703 Australia 1981-1983	16.0%	14.0%	Age, education, race, family income, alcohol, depression, physical activity, planned pregnancy, parity
Smedberg J. et al. [25]	N = 1481 Europe 2011-2012	73.6%	-	Age, marital status, education, working status, planned pregnancy, alcohol consumption
Jaddoe V.W. et al. [26]	N = 7098 Netherlands 2002-2006	32.7%	-	Age, parity, education, ethnicity
Roza S.J. et al. [27]	N = 7042 Netherlands 2002-2006	31.2%	-	Age, education, ethnicity, parity, alcohol use during pregnancy, depression score
Andersen M.R. et al. (38) [28]	N = 266 Denmark 2003-2004	48.8%	-	Age, parity, working status, caffeine intake, alcohol intake
Suzuki K. et al. [29]	N = 9369 Japan 2011	31.9%	-	Age, income, primigravida, partners smoking status
Luo Z-Ch et al. [30]	N = 605 Canada 2004-2006	47.2%	-	Age, ethnicity, parity, education, working status

In accordance with the data summarized in Table 1, the mentioned indicators are grouped into the following determinants of smoking cessation during pregnancy: demographic, socio-economical, determinant relating with family issues, relating to drinking behavior during pregnancy and psychological determinant.

Demographic determinant.

Nine studies [9, 13, 16, 19, 23, 25-27, 29] show that the prevalence of women who stop smoking during pregnancy increases with age. By contrast, studies assessing age as a continuous variable demonstrate that younger age is more common in quitters than among smokers while pregnant [7, 15, 22]. The rest studies do not show an influence of age on the cessation rate.

Ethnicity or race as an indicator of demographic determinant appears to be a less consistent findings in relation to smoking cessation during pregnancy. Fifty per cent of studies show an association between ethnicity/race and rate of quitting smoking during pregnancy [12, 13, 16, 24, 26], while others do not [7, 11, 15, 28, 30]. Only one study explored residence as an indicator of smoking cessation during pregnancy [11]. Moreover, Blaga et al. [11] demonstrated that women living in an urban setting were more likely to stop smoking during pregnancy compared to those living in rural areas.

Socio-economical determinant.

It is considered that pregnant women with a higher social status including level of education, working status or income indicators seem to quit smoking at a higher rate [6]. Three studies that included all the mentioned indicators of social status show that richer women, those attaining a university degree or having a non-manual job are more likely to quit smoking during pregnancy [11, 14, 19]. Another 11 studies which focused on education level illustrated a positive association, namely that the prevalence of smoking discontinuance during pregnancy is higher among educated women [7, 8, 13, 15, 22-27, 30]. Only four studies explore the association between working status and rate of smoking cessation during pregnancy [8, 25, 28, 30], with three of them reporting a positive result [25, 28, 30]. Studies that feature a positive relationship between income and smoking cessation during pregnancy involved Australian cohorts [9, 23, 24], while a study conducted in Japan showed no such association [30].

Determinant relating to family issues.

Marital status, parity, intentional pregnancy and husband/partner smoking status are considered family issues. In most studies marital status classified as married or unmarried was associated with quitting smoking during pregnancy [7, 13, 19, 23, 25]. Balwichi et al. [14] used another combination of this variable. Specifically, women cohabiting or unmarried, divorced or not

living with a partner and those single or not living with a partner were less likely to stop smoking while pregnant compared to those married. Ten studies from thirteen assessing an association between parity and rate of quitting smoking during pregnancy show that nulliparous women are more likely to do so during pregnancy than those who have one or more babies [7-9, 11, 14, 16, 24, 26, 27, 29]. The remaining studies cited in Table 1 did not support these findings [13, 20, 28, 30].

There is no consistent evidence to determine if giving up smoking during pregnancy is associated with the intention of having a pregnancy. Two studies demonstrate no statistical association [7, 24], whereas Smedberg et al. [25] showed that unplanned pregnancies were less prevalent among quitters compared to smokers.

Living with a non- or ex-smoking partner/husband was associated with a higher prevalence of maternal smoking cessation during pregnancy [17, 29]. In a qualitative study Flemming et al. [18] report that some women noted how their partners facilitated quitting and describe them as supportive. Smoking partners appear to constitute a negative effect on pregnant spouse who smoke [20]. They provide temptation and reminders about pleasures of smoking and tend not to encourage pregnant women to stop smoking.

Determinant relating to drinking behavior during pregnancy.

Alcohol consumption appears to have the greatest negative influence on smoking termination [23, 27]. However, not all studies have demonstrated this [24, 25, 28].

Psychological determinant (stress or depression during pregnancy).

Smoking is protective of wellbeing for individuals suffering psychosocial stress or who are chronically disadvantaged [18]. In this context, smoking diminishes stress by providing brief moments of relaxation. Nevertheless, anxiety and depression scores have been observed to be higher in mothers who smoked during pregnancy than those who stopped do so [23, 24, 27].

The summary provided in Table 2 of the literature review outlined above constitutes a portrait of women who stopped smoking during pregnancy and those who did not.

Table 2. Social portrait of women who stopped smoking during pregnancy and of those who smoked while pregnant

Determinants	Quitters	Smokers
Demographic	older	younger
	urban	rural
Socio-economical	higher educated	less educated
	high income	low income
	being employed/non-manual job	unemployed/manual job
Family issues	married	unmarried
	nulliparous	multiparous
	non-smoking partner	smoking partner
Psychological	less anxious	more anxious

1.2 Adverse pregnancy outcomes in relation to quitting smoking or smoking reduction during pregnancy

The adverse effects of maternal smoking on pregnancy outcomes are demonstrated in a meta-analyses by Castles [31], Shobeiri et al. [32], Ananth et al. [33], in a reviews by Salihu et al. [34], Cnattingius [35], Conde-Agudelo [36], in a registry-based study by Baba et al. [37], and in a cross-sectional study by Hyland et al. [38]—among others. Generally speaking, women who smoke during pregnancy have higher rates of preterm birth, stillbirth, perinatal mortality, ectopic pregnancy and placental complications (including placenta previa, placental abruption, or placenta accrete), as well as low rates of preeclampsia/eclampsia.

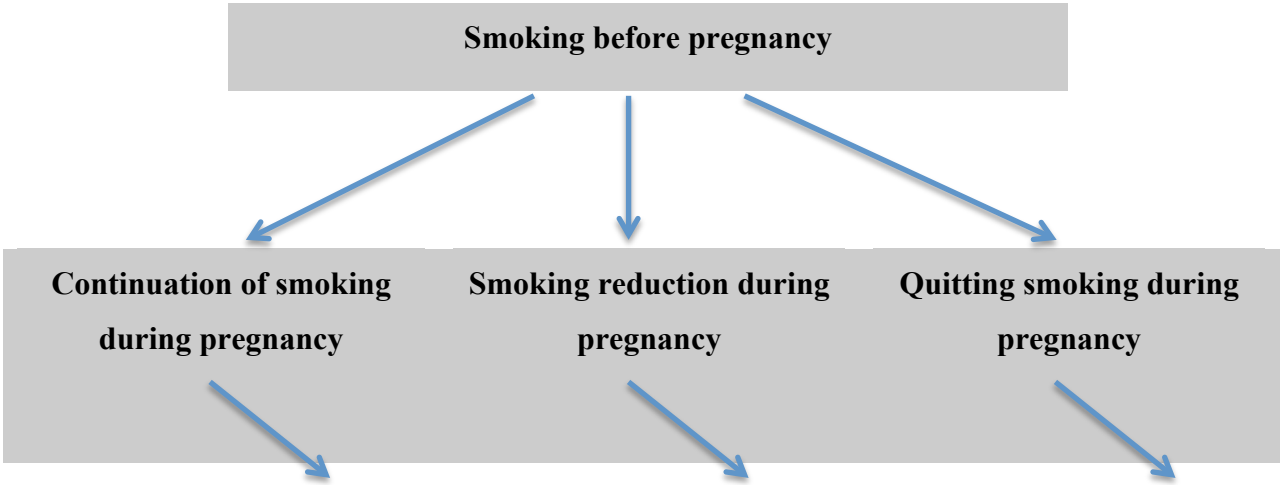
However, studies assessing possible association between pregnancy outcomes and quitting smoking or its reduction during pregnancy are limited; they primarily concern placental complications, preeclampsia, gestational hypertension or preterm births. Interestingly, one study completed more than 30 years ago showed that mothers who stopped smoking had a 23 % lower frequency of placental abruption and a 33 % of placenta previa compared to those who continued to smoke [39].

A retrospective cohort study conducted in Australia during the period 1997 to 2006 found that there were no statistically significant differences in placenta previa, placental abruption and preterm delivery among women who stopped smoking during pregnancy and non-smokers or smokers [40]. Luo et al. [30] carried out a study estimating maternal smoking status at 24-26 weeks' gestation by measurement of plasma cotinine concentration: > 3.0 ng/mL (current smokers), 0.2-3.0 ng/mL (previous or passive smokers) and < 0.2 ng/mL (non-smokers). They could not distinguish between ex-smokers and passive smokers because of the absent of known cutoff levels. As a result, they found increased risk of preeclampsia among "previous and passive smokers" when compared to non-smokers. However, there was no significant difference in the risk of preeclampsia among "current smokers" and "non-smokers". They explained these findings by the relatively low statistical power of their study, although Lain et al. [41] have reported a protective effect of active smoking on the development of preeclampsia. However, Xiong et al. [42] showed that early smoking cessation, namely quitting smoking before week 20 of gestation was not associated with a reduced risk of preeclampsia compared with never having smoked. Close results have been demonstrated by England et al. [43, 44]. Moreover, England et al. [44] did not find an association between quitting after their last menstrual period and the development of gestational hypertension (adjusted RR = 0.9 with 95 % CI: 0.7-1.1).

A retrospective population-based cohort study using a large database spanning 20 years [45] indicated that giving up smoking during the first trimester of pregnancy reduced the prevalence of stillbirths and preterm births. Moreover, Polakowski et al. [46] showed that the discontinuance of smoking in the first trimester during pregnancy lowered the odds of delivering a preterm small-for-gestational age (SGA) infant by 31 % and a preterm non-SGA infant by 53 % when compared to its continuance. Srybold et al. [47] demonstrated that not only cessation of smoking led to a lower number of preterm deliveries, as well as its reduction during pregnancy.

1.3 Impact of quitting smoking or its reduction during pregnancy on anthropometric indices and Apgar Score of the newborn

It is essential to know how different women's smoking status during pregnancy influences birth outcomes in order to develop preventive measures. Most studies have dealt with the continuation of women's smoking during pregnancy (Figure 1). Changes in smoking behavior during pregnancy ant its effect on birth outcomes are less studied (Figure 1).



	reference	reference	reference
Birth weight	[48-63]	[60, 64-66]	[57-61, 64, 65]
Birth length	[48, 52, 53, 55, 58, 59, 61]	no data	[58, 59, 61]
Birth head circumference	[48, 52, 54, 55, 58, 59, 61, 67, 68]	no data	[58, 59, 61]
Ponderal index	[52, 53, 58, 59, 68]	no data	[58, 59]
Apgar score at 5 min	[54, 55, 69-71]	no data	no data

Figure 1. Published studies that focused on associations between maternal smoking status during pregnancy and anthropometric indices and/or Apgar score at 5 min

Birth weight, length and head circumference at birth are major indices of fetal growth that maternal smoking appears to suppress [48, 50-56, 58-62]. Compared to the number of studies on low birth weight [57-61, 64-66], the influences of quitting smoking or its reduction during

pregnancy on birth length [58, 59, 61] and head circumference [58, 59, 61] are not as well documented.

The ponderal index is a measure of birth weight in relation to crown-heel length [52]. It is used as a proxy for body composition to assess growth abnormalities of infants. Asymmetric infants are either thinner and have less birth weight per centimeter of length (i.e., low ponderal index), or are shorter and have high birth weight per centimeter of length (high ponderal index) than symmetrical newborns. However, there is no consistent evidence to determine if smoking or giving it up during pregnancy influences this variable. One study in relation to smoking cessation during pregnancy demonstrated no statistical association [59], whereas another indicated that infants of smokers who stopped smoking had a statistically significant increase in ponderal index of 0.027 (95 % CI: 0.009-0.045) compared with the infants of non-smokers [58].

The Apgar score is widely used as a standardized index of the newborn health status in the immediate neonatal period [72]. A low Apgar score (i.e., <7) is strongly associated with a risk of neonatal and infant death [73]. Walfisch et al. [54] reported that babies of smoking mothers had lower Apgar scores at 5 min compared to those of non-smokers, although smoking during pregnancy was not an independent predictor of the Apgar score. Moreover, it is unclear whether giving up smoking or smoking reduction during pregnancy affects the Apgar score because of the absence of such studies.

1.4 Smoking cessation interventions during pregnancy

As summarized above (Section 1.2 and 1.3), literature reviews have shown that smoking during pregnancy negatively effects on pregnant women and infants. However, changes in smoking habits during pregnancy, namely quitting smoking and its reduction can potentially lower the negative influences of tobacco smoking on the pregnancy and birth outcomes. Unfortunately, not every pregnant woman can quit smoking without special support.

Strategies for reducing the number of smokers during pregnancy are reviewed in this subsection using the grouping proposed by Wagijo et al. [74], namely psychosocial interventions, incentive-based, pharmacological, and harm reduction interventions (among others).

Psychosocial interventions.

The Cochrane review "Psychosocial interventions for supporting women to stop smoking in pregnancy" [75] provided high quality evidence that counseling increased smoking cessation in late pregnancy compared to usual care (average RR for 30 studies was 1.44 with 95 % CI: 1.19-1.73), as did less intensive intervention approaches (average RR for 18 studies was 1.25 with 95 % CI: 1.07-1.47). Moreover, it was demonstrated that if women received psychosocial interventions they had a 17 % reduction in infants born with low birth weight and a 22 % reduction in neonatal intensive care admissions. In relation to preterm births and stillbirths the differences were unclear.

Incentive-based interventions.

Ierfino et al. [76] estimated prolonged cessation in an unselected population of English pregnant smokers who were "offered financial incentives for quitting, and 'gaming', i.e. false reporting of smoking status in order to go in the scheme or gain an incentive". They found that 39 % of smokers were enrolled into the project, of whom 60 % attempted smoking cessation. Of those recruited, 20 % were quit at delivery and 10 % at six months postpartum. There was evidence that 4 % of gamers enrolled on one or more occasions to receive vouchers.

Tappin et al. [77] assessed the efficacy of a financial incentives added to pregnancy stop-smoking services by specialists administering routine care to help pregnant smokers to quit. Almost 23 % in the incentive group and 8.6 % in the control group stopped smoking. Moreover, the RR of not smoking at the end of the pregnancy period was 2.63 with 95 % CI: 1.73-4.01. It was concluded that incentives for smoking cessation during pregnancy work. A positive effect of incentive intervention on smoking cessation was also demonstrated in the mentioned Cochran review [75].

Pharmacological interventions.

Pharmacological interventions, such as nicotine replacement therapy (NRT) and antidepressant drugs (e.g., bupropion), have been proven effective and safe in the general population [78]. Other forms of NRT including patch, nasal spray, or chewing gum are also part of an effective strategy to help giving up smoking. All forms of NRT are as category D drugs in according to the USA Food and Drug Administration [79]. These drugs should only be used during pregnancy

if the benefit to the fetus outweighs the risk. Nevertheless, studies show either positive or neutral effects of NRT on both smoking cessation rate and adverse pregnancy and birth outcomes. Berard et al. [80] report that bupropion and nicotine patch replacement therapy during pregnancy were associated with high rates of smoking termination (81 % and 79 %, respectively). Moreover, 60 % of bupropion and 68 % of nicotine replacement therapy users did not smoke after discontinuing smoking cessation medications. In relations to adverse pregnancy and birth outcomes, bupropion was associated with a lower risk of prematurity for smokers, whereas nicotine patch replacement therapy use was associated with lower risks of prematurity and small-for-gestational-age [80].

Coleman et al. [81] report that the rate of abstinence from the quit date was higher at one month in the nicotine replacement group compared to the placebo cohort. However, these authors did not find a significant difference between these study groups in the abstinence rate up to delivery (9.4 % and 7.6 %, respectively).

Harm reduction interventions.

Wagijo et al. [74] have reviewed the evidence that vitamin C may reverse the negative effect of nicotine on fetal lung development. They refer to an article with the conclusion that "vitamin C may be an inexpensive and simple approach (with continued smoking cessation counseling) to decrease some of the effects of smoking in pregnancy on newborn pulmonary function" [82].

Other interventions.

According to the Cochran review [75] mentioned earlier, the effect of social support interventions provided by peers is unclear (average RR of six studies was 1.42 with 95 % CI: 0.98-2.07).

Bittoun and Femia [83] in their extensive review concluded that because smoking during pregnancy is harmful to pregnant women and their fetus, every pregnant woman who smokes should at a minimum be offered psychosocial smoking cessation counseling throughout pregnancy. Furthermore, they recommend that low-dose NRT might be provided for women who find it difficult to quit smoking.

2. Aims of the Thesis

The overall aim of this thesis was to explore changes in smoking behavior during pregnancy using Murmansk county birth registry from 2006 to 2011 and to assess the effect of quitting smoking or smoking reduction while pregnant on selected adverse pregnancy and birth outcomes.

The specific objectives were:

1) To determine the prevalence of smoking before and during pregnancy and to assess socio-demographic factors associated with discontinuing smoking or smoking reduction once pregnant (Paper 1).

2) To investigate the effect of first-trimester smoking cessation while pregnant on Preeclampsia/eclampsia (Paper 2).

3) To explore the effect of changes in smoking behavior during pregnancy on selected adverse birth outcomes (Paper 3).

3. Material and Methods

3.1 Data source and study design

Our study focuses on Murmansk County, which was founded on May 28th, 1938. The County is located in the northwestern part of the Russian Federation. It covers an area of 144,902 square km, which corresponds to 0.85 % of the area of Russia [84], and has borders with the Republic of Karelia (Russia), Lapland Region (Finland) and Finnmark County (Norway) as shown in Figure 2. Murmansk County is surrounded in part by the Barents Sea and the White Sea. The population of the County was 766,281 on January 1st 2015 [85].

According to the 2010 Census, the ethnic make-up of the County was as follows [86]: Russians (89 %), Ukrainians (4.8 %), Belarusians (1.7 %), Tatars (0.8 %), Azeris (0.5 %), Mordvins (0.2 %), Karelians (0.2 %), Komi (0.2 %), Saami (0.2 %), and others (2.4 %).

The Murmansk County is very rich in natural resources and has deposits of over 700 minerals. The largest industries are mining, refining, apatite concentrate production (for fertilizers), electric power-production, marine transportation, and food-industry, including fishing [87].

Fig. 2. Map of Murmansk County (the area demarcated by the red line)

We conducted registry-based studies with data from the Murmansk County Birth Registry (MCBR). The MCBR is a joint effort of the University of Tromsø (Norway) and Murmansk County Health Department (Russia). It was established in 2005, with the Norwegian Medical birth Registry as the model [88]. Quality controls demonstrated that the proportion of errors was less than 1 %. The implementation of the MCBR has been described previously [88-91].

Based on medical records and personal interviews with pregnant women, the MCBR contains data on maternal characteristics including maternal age, ethnicity, residence, education, marital status, parity, alcohol abuse as diagnosed by a doctor, self-reported smoking with numbers of cigarettes smoked per day before and during pregnancy, and maternal weight and height measured at the first antenatal visit. Data in the MCBR on gestational diabetes, excessive weight gain during pregnancy, gestational age, name of the delivery department and year of delivery were derived from individual obstetric journals. Based on newborn delivery records, the MCBR also contains information about infant birth weight, birth length, head circumference and Apgar score at 5 min (see Appendix).

3.2 Study population

Initially the study population consisted of all women who were registered in the MCBR from 2006 to 2011. In all three thesis publications, we excluded those who had missing data on socio-demographic characteristics (Figure 3), namely: maternal age (N = 90), marital status (N = 92), maternal education (N = 228), ethnicity (N = 64), residence (N = 114), parity (N = 39), alcohol abuse (N = 243), year of delivery (N = 64), and smoking status before and/or during pregnancy (N = 741).

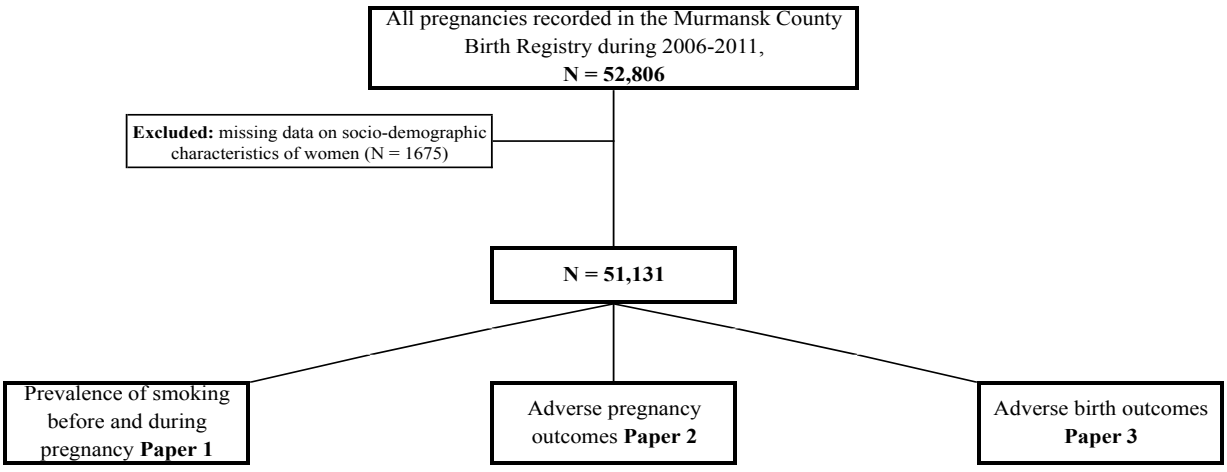


Fig. 3. Chart illustrating the selection of study participants

Paper 1 focused on the socio-demographic characteristics of pregnant women in relation to smoking status during pregnancy and associations between them and giving-up smoking during the first-trimester of the pregnancy. Consequently, participants who did not smoke either before or during pregnancy were excluded from the analyses (N = 38,260). Thus the subsample of this component comprised 12,871 participants. To examine the number of cigarettes smoked per day during pregnancy in relation to socio-demographic characteristics and to assess possible associations between smoking reduction during pregnancy and selected maternal characteristics, we excluded participants who smoked before but not during pregnancy (N = 3219) and those with missing data on the number of smoked cigarettes per day before or during pregnancy (N = 4878). Consequently, the subsample employed in the second part of Paper 1 involved 4774 participants.

Multiple pregnancies (N = 433), first antenatal visit after 12 weeks (N = 9523) or unknown (N = 978) and chronic hypertension (N = 631) were not included in the analyses of Paper 2. Thus, 39,566 were included in the analysis of possible associations between smoking status during pregnancy and development of preeclampsia/eclampsia. Furthermre, 3240 records with missing data on the number of smoked cigarettes per day before or during pregnancy had to be excluded in an assessment of the association between the number of smoked cigarettes per day during pregnancy and the development of preeclampsia/eclampsia. Consequently, the subsample for this component of Paper 2 comprised 36,376 participants.

In Paper 3, missing or appropriate exclusion criteria data including gestational age < 37 weeks (N = 6158), multiple pregnancy (N = 230), infant's birth weight (N = 101), birth length (N = 11), head circumference (N = 60), infant's sex (N = 28) and Apgar score at 5 min (N = 57) were excluded. A subsample of N = 44,486 was used to assess possible association between smoking, giving up smoking and selected adverse birth outcomes. Furthermore, 3784 records with missing data on the number of cigarettes smoked per day during pregnancy were excluded when exploring possible association between daily numbers of cigarettes smoked during pregnancy and selected adverse birth outcomes. This subsample included 40,702 participants. Finally, from the total subsample (N = 44,486) non-smokers (N = 33,767), quitters (N = 2877), and missing data on number of smoked cigarettes per day before or during pregnancy were excluded to assess possible associations between smoking reduction during pregnancy relative to its pre-gestational level and selected adverse birth outcomes. For this purpose, subsample comprised 3968 participants.

3.3 Smoking behavior information

In terms of smoking status during pregnancy, women were grouped as smokers (did so before and during pregnancy), quitters (smoked before but not during pregnancy), or non-smokers (did not smoke before nor during pregnancy). Smoking status was assessed during the first antenatal visit. Number of smoked cigarettes per day during pregnancy was taken as a categorical variable, specifically as 0, 1–5, 6–10, and ≥ 11. Smoking reduction during pregnancy relative to its pre-gestation level was dichotomized as "Yes" and "No". The latter included women who increased the number of cigarettes smoked per day during pregnancy, as well as those who did not change their smoking pattern.

3.4 Outcome variables

In Paper 2 Preeclampsia and eclampsia were classified according to the International Classification of Diseases, tenth revision (ICD-10) [92]. Preeclampsia (ICD-10 codes O14.0 "mild to moderate preeclampsia"; O14.1 "severe preeclampsia") is a pregnancy-induced hypertensive state that occurs after 20 weeks of gestation. It is characterized by hypertension (blood pressure of 140/ 90 or higher), along with oedema and proteinuria (300 mg of protein in a 24-hour urine sample) [93, 94]. Eclampsia (ICD-10 code O15.0) involves convulsions and coma in pregnant or puerperal women along with hypertension, oedema, and proteinuria. We analyzed preeclampsia (N = 3276) and eclampsia (N = 5) cases together because of the limited number of cases of eclampsia. The variable "preeclamsia/eclampsia" (N = 3281) was treated as binary.

In Paper 3 low birth weight, length and head circumference were defined according to the World Health Organization as the mean values minus 2 standard deviations (M-2SD) for girls and boys separately [95]. Respectively for girls and boys, low birth weight was <2400 g and <2500 g; low birth length <45.4 cm and <46.1 cm; and low birth head circumference <31.5 cm and <31.9 cm.

We used the ponderal index in newborns to assess asymmetrical intrauterine growth retardation (IGR). This was defined as 100 × birth weight (g)/length^3 (cm), and a low score below the 10th (<2.14) was taken as an estimate of disproportionate IGR. The Apgar score at 5 min is a combined score of five readily identifiable neonatal characteristics that includes skin color, heart rate, respiratory effort, muscle tone, and reflexes [72]. Scores of six or lower are considered low.

3.5 Independent variables and potential confounders

Socio-demographic characteristics of women were treated as independent variables and potential confounders in Papers 1, 2 and 3. Maternal age was classified as: ≤ 19 years, 20–24 years, 25–29 years, 30–34 years and ≥ 35 years. Residence was defined as urban or rural. In terms of ethnic background, women were registered as either Russian or other. Education was categorized either incomplete secondary (0–9 years of schooling), secondary (10–11 years), vocational, university and unknown in Paper 1; or less than university that included primary (0–9 years of schooling), secondary (10–11 years of schooling) and vocational training, university and unknown in Paper 2 and 3. Marital status was characterized as married, cohabitation or single (includes divorced or widowed). Parity was classified as 0, 1, and ≥ 2 deliveries. Alcohol abuse (based on documented evidence provided by physicians) was dichotomized into yes and no. Year of delivery was presented by the exact year. Fifteen delivery departments were comprised only in Paper 1.

The set of clinical potential confounders varied in Paper 2 and 3. For example, body mass index at the first antenatal visit of women and excessive weight gain during pregnancy were considered in Papers 2 and 3. Body mass index (BMI) was calculated for the women's weight at the first antenatal visit (kg) divided by height (m^2). By BMI, women were classified into five groups: underweight (18.4 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2), obese (30.0 kg/m2), and unknown. Excessive weigh gain in pregnancy was defined as weight gain during pregnancy of >18 kg in underweight women, >16 kg in normal weight women, >11.5 kg in overweight women, and 6 kg in obese women. Excessive weight gain in pregnancy (ICD-10 code O26.0) was dichotomized as yes and no. Gestational diabetes (yes/no) and gestational age (in weeks) were added as potential confounders in Paper 3.

3.6 Data analyses

Analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL) and STATA 13 statistical software. In Papers 1-3 Pearson's Chi-square tests were used to assess differences in prevalence of smoking behavior before and during pregnancy in accordance to socio-demographic characteristics of the pregnant women (Paper 1), and in relation to adverse pregnancy (Paper 2) and birth (Paper 3) outcomes.

In Paper 1 we examined the relationships between socio-demographic characteristics of women and smoking cessation during pregnancy, as well as the reduction in smoking while

pregnant. To correct for any deviation from uniform risk within specific delivery departments, clustered robust standard errors were used.

In Paper 2 logistic regression was used to explore the effect of smoking cessation during pregnancy on the risk of preeclampsia/eclampsia, and its association with the daily numbers of cigarettes smoked while pregnant.

In Paper 3 we employed logistic regression to investigate the associations between selected adverse birth outcomes and smoking status during pregnancy, the number of cigarettes smoked per day during pregnancy, as well as the impact of a reduction in smoking while pregnant.

In all three Papers, we tested for trends by entering ordinal variables as continuous in he regression analyses (Papers 1-3).

3.7 Ethical aspects

This study was approved by the Ethical Committees of the Northern State Medical University, Arkhangelsk (Russia) (identification code: No. 08/12-14 from 10.12.2014) and the Norwegian Regional Committee for Medical and Health Research Ethics (REC-North), Tromsø (Norway) (identification code: No. 2014/1660).

4. Main Results

4.1 Paper 1: Prevalence of Smoking before and during Pregnancy and Changes in this Habit During Pregnancy in Northwest Russia: a Murmansk County Birth Registry study

Of the all study participants, 25.2 % (95 % CI: 24.8– 25.5 %) smoked before pregnancy of whom 18.9 % (95 % CI: 18.5–19.2 %) continued smoking during pregnancy. The overall proportion of women who smoked before pregnancy but stopped doing so once pregnant was 25.0 % (95 % CI: 24.3–25.8 %). Smoking pregnant women were younger, had lower education, and were more likely to reside in rural areas. We found that smoking before and during pregnancy was more common in single women and those who were cohabiting. Furthermore, smoking before and during pregnancy was associated with alcohol abuse and multigravida.

In the crude analysis, we found that smoking cessation during pregnancy was associated with maternal age, residence, education, marital status and parity but not ethnicity. After adjustment for confounders, the associations between maternal age, residence, ethnicity and quitting smoking were not significant. We found that pregnant women with incomplete secondary, secondary, or vocational education had decreased odds of giving up smoking during pregnancy compared to those with university education (adjusted $OR_{incomplete\ secondary}$ = 0.19 with 95 % CI: 0.15-0.24; for $OR_{secondary}$ = 0.39 with 95 % CI: 0.27-0.55; and for $OR_{vocational}$ = 0.57 with 95 % CI: 0.41-0.78). Single pregnant women and those co-habiting were almost two-fold less likely to quit smoking during pregnancy than married women. Furthermore, nulliparae and pregnant women who had one previous delivery were more likely to stop smoking during pregnancy than multiparae (adjusted OR = 2.21 with 95 % CI: 1.78-2.75; and for OR = 1.69 with 95 % CI: 1.46-1.95, respectively).

Crude analysis demonstrated a significant association between a reduction in number of cigarettes smoked during pregnancy and maternal age and parity. In both crude and adjusted logistic regression analyses, neither residence, ethnicity, education, nor marital status were significantly associated with the dependent variable. After adjustment for covariates, younger pregnant women (aged ≤ 19–24 years) decreased the numbers of cigarettes smoked per day during pregnancy more frequently than women aged ≥ 25–29 years (adjusted $OR_{aged\leq19}$ = 1.14 with 95% CI: 1.01-1.28; and for $OR_{aged\ 20\text{-}24}$ = 1.14 with 95% CI: 1.02-1.26). Moreover, we

found that smoking nulliparae and pregnant women who had one child were more likely to reduce the absolute numbers of cigarettes smoked per day compared to those having ≥ 2 children (adjusted $OR_{nulliparae}$ = 1.62 with 95% CI: 1.36-1.93; for $OR_{one\ child}$ = 1.40 with 95% CI: 1.08-1.83 with $p_{for\ linear\ trend}$ <0.001).

4.2 Paper 2: First-trimester Smoking Cessation in Pregnancy did not Increase the Risk of Preeclampsia/eclampsia: a Murmansk County Birth Registry study

Of the all participants in our study, 8.3 % (95 % CI: 8.0–8.6 %) had preeclampsia/eclampsia during their current pregnancy. The prevalence of preeclampsia/eclampsia was 6.7 % (95 % CI: 6.1-7.4 %) among women who smoked in pregnancy and 8.7 % (95 % CI: 8.4-9.0 %) among those who did not (p<0.001). The proportion of women with preeclampsia/eclampsia decreased with the number of cigarettes smoked per day while pregnant (p<0.001).

Non-smokers both before and during pregnancy had a greater risk of preeclampsia/eclampsia compared to smokers. A dose-response relationship was evident between the daily number of cigarettes smoked during pregnancy and the risk of preeclampsia/eclampsia ($p_{for\ linear\ trend}$ < 0.001). We found that pregnant women who smoked 1–5, 6–10 or ≥ 11 cigarettes per day during pregnancy had decreased odds of having preeclampsia/eclampsia compared to non-smokers. Adjustment for potential confounders, such as maternal age, residence, ethnicity, marital status, parity, alcohol abuse, year of delivery, body mass index and excessive weight gain, did not change the association (adjusted $OR_{1\text{-}5cig.}$ = 0.69 with 95 % CI: 0.56–0.87; for $OR_{6\text{-}10cig.}$ = 0.65 with 95 % CI: 0.51–0.82; and for $OR_{11cig.}$ = 0.49 with 95 % CI: 0.30–0.81, respectively).

Women who smoked before but not during pregnancy had lower risk of having preeclampsia/ eclampsia compared to those who did not smoke before and during pregnancy (adjusted OR = 0.80 with 95 % CI: 0.68–0.94). However, there was no significant difference in the occurrence of preeclampsia/eclampsia among women smoking before but not during pregnancy and those who smoked both before and during pregnancy—either before or after adjustment for other maternal characteristics (adjusted $OR_{smoked\ before\ but\ not\ during\ pregnancy}$ = 1.09 with 95 % CI: 0.91-1.30).

4.3 Paper 3: Effect of Smoking Behavior before and during Pregnancy on Selected Birth Outcomes among Singleton Full-Term Pregnancy: a Murmansk County Birth Registry study

The overall prevalence of low birth weight, low birth length, low head circumference, low ponderal index, and low Apgar score at 5 min were, respectively: 1.1 % (95 % CI: 1.0-1.2 %), 0.6 % (95 % CI: 0.5-0.6 %), 2.4 % (95 % CI: 2.3-2.6 %), 11.0 % (95 % CI: 10.7-11.3 %), and 1.0 % (95 % CI: 0.9-1.1 %), respectively. These adverse birth outcomes were more prevalent in women who smoked during pregnancy and their proportions increased with the number of cigarettes smoked per day during pregnancy ($p_{\text{for linear trend}} < 0.001$), with ponderal index the exception. For the latter, the highest proportion of newborns with a low value was most common among women who smoked 1–5 cigarettes per day during pregnancy, while the lowest proportion occurred among those who smoked ≥ 11 cigarettes daily.

A dose-response relationship is evident between the number of cigarettes smoked per day during pregnancy and the odds of low birth weight, low birth length, low head circumference, low ponderal index and low Apgar score at 5 min. Adjustment for potential confounders did not change these associations. Respectively, mothers who smoked ≥ 11 cigarettes per day while pregnant were 2.1, 5.4, 5.2 and 2.1 times more likely to deliver an infant with low values of birth weight, birth length, head circumference and Apgar score at 5 min compared to non-smokers. Women who smoked 1–5 cigarettes per day during pregnancy had a higher odds of having a low ponderal-index infant compared to non-smokers (before and after adjustment for confounders; adjusted $OR_{1–5\ \text{cig.}} = 1.57$ with 95 % CI: 1.38–1.80), while those who smoked ≥ 11 cigarettes per day during pregnancy were almost two-fold less likely to have such infant (before and after adjustment; adjusted $OR_{\geq 11\ \text{cig.}} = 0.56$ with 95 % CI: 0.40–0.80).

Low birth weight and low birth length were almost three times more likely among smokers (both before and during pregnancy) compared to non-smokers in the crude analysis (crude OR = 2.92 with 95 % CI = 2.44-3.52 and OR = 3.00 with 95 % CI = 2.31-3.88, respectively). Similarly, their babies had higher odds of having a low head circumference, low ponderal index or low Apgar score at 5 min, respectively: crude OR = 2.21 with 95 % CI: 1.94-2.53, OR = 1.15 with 95 % CI: 1.06-1.24 and OR = 1.32 with 95 % CI: 1.04-1.66. After adjustment for confounders, the statistical significance for the Apgar score was lost. In addition and relative to non-smokers, interruption of smoking during pregnancy had no significant impact on the adverse birth outcomes considered (prior and subsequent to adjustments for potential confounders). Moreover, smoking reduction during pregnancy did not alter the odds of the selected adverse birth

outcomes: adjusted $OR_{\text{low birth weight}} = 0.87$ with 95 % CI: 0.54-1.39, $OR_{\text{low birth length}} = 0.83$ with 95 % CI: 0.47-1.46, $OR_{\text{low head circumference}} = 0.83$ with 95 % CI: 0.62-1.12, $OR_{\text{low ponderal index}} = 0.86$ with 95 % CI: 0.50-1.46 and $OR_{\text{low Apgar score at 5 min}} = 1.10$ with 95 % CI: 0.91-1.34.

5. Discussion

5.1 Methodological considerations

Patient registries have been defined as being "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s)" [96]. Clearly registry studies play a key role in the development of knowledge, particularly when a researcher evaluates changes that occur during extended time periods or assesses important outcomes as these require large sample sizes [97, 98]. In this context, our registry-based studies had the potential of answering the research questions stated in the Study Aims.

5.1.1 Internal validity

Study of validity refers to an absence of bias and is closely related to its absence in the measured variables [97]. Exposures and outcomes as well as other co-variables and confounding factors are considered main variables in clinical and epidemiological studies. Having a study free of bias is referred to as internal validity [97, 99]. Major weaknesses in epidemiological studies can result from random and systematic errors [100].

Random error is variability in the data that cannot be readily explained [100]. It causes inaccurate measures of association [99]. Rothman [100] states that if a study is large, the estimation process would be comparatively precise and there would be little random error in the estimation. In our study, the large sample size minimized such error sources and thereby increased the accuracy. Moreover, we used the 95% confidence interval or p value to indicate the degree of random error. The p-value was calculated in relation to the null hypothesis, which states that there was no association between variables. So, $p \leq 0.05$ indicated that the data were not very consistent with the null hypothesis.

Systematic error occurs in epidemiology when results differ in a systematic manner from the true values. A study with a small systematic error is said to have high accuracy. There are two types of systematic errors: selection and information.

Selection bias. Selection bias occurs when there is a systematic difference between the characteristics of the people selected for a study and the characteristics of those who are not [99]. When such bias occurs, participants may not be representative of the population and findings of the study may not be applicable to the general population. MCBR is almost population-based registry. Despite of the registry data were collected in clinics, the number of births registered in the MCBR comprised 98.8% of the official number of births recorded by the Health Department in Murmansk County [88].

Main possible source of selection bias is non-responders. In Papers 1 and 3 we assessed a possible association between smoking reduction during pregnancy and socio-demographic characteristics of women and selected adverse birth outcomes, respectively. In our study, information about smoking reduction during pregnancy compared to that before gestation was missing for 49.4% of all smokers. This nonresponse may have led to bias. Furthermore, since smoking reduction was based on a dichotomous variable (yes/no), an attenuation effect may have occurred.

Information bias. A systematic error in a study can emerge because the information collected about or from study participants is inaccurate or erroneous [100]. This can lead to misclassification of subjects for either exposure or disease. In our study all data regarding smoking status was self-reported, which may have contributed to misclassification, and thus would constitute measurement bias. As a result, it may have led to an underestimation of smoking rates. Our information about smoking behavior was collected during the first antenatal visit. Raisanen et al. [101] consider that gathering smoking status information during the first antenatal visit is more reliable than obtaining it at the time of birth. Giglia et al. [102] illustrate that self-reported smoking status is a good measurement tool. Meta-analysis of studies comparing self-reported smoking with biochemical assessments have found that self-reports of smoking are precise in most studies and are sufficiently sensitive and specific [103]. Moreover, nicotine in blood or saliva, cotinine in urine, or carbon monoxide in exhaled breath allow the identity of active smokers during pregnancy. However, it is almost impossible to define those who stopped or reduced smoking after pregnancy recognition.

If exposure misclassification did occur in our study, it most likely was among smoking women who falsely reported that they stopped after pregnancy recognition, or among those who gave up smoking in the first trimester during pregnancy but subsequently resumed this practice. This type of misclassification would have decreased the risk of preeclampsia/eclampsia (Paper 2) or have increased the risk of adverse birth outcomes including low values of birth weight, birth length, head circumference, ponderal index and Apgar score at 5 min (Paper 3) among those who gave

up smoking while pregnant. However, we found that women who reported that they gave up smoking after pregnancy recognition had the same risk of preeclampsia/eclampsia as those who indicated they smoked before and during pregnancy (Paper 2). In addition and relative to non-smokers, interruption of smoking during pregnancy had no significant impact on the adverse birth outcomes considered (Paper 3).

Information on social characteristics of pregnant women was also self-reported. Study participants can intentionally or unintentionally misreport their educational level, marital status, parity, or number of smoked cigarettes per day before and during pregnancy (Paper 1).

In Paper 2, the observed preeclampsia/eclampsia prevalence in Murmansk County of 8.3% is higher than previous estimates [93, 104-108]. This could reflect different definitions and differing proportions of primiparae [109]. Regional data are often different from national figures, as the latter reflect the variation of preeclampsia/ eclampsia within one country. For example in St. Petersburg (located in the Northwest federal district of Russia), the prevalence of preeclampsia/eclampsia in 2005 was 7.1%, while it was 8.6% in Orenburg County (Volga federal district), 10.5% in Kurgan County (Ural federal district) and <0.1% in Vladimir County (Central federal district) and Vologda (Northwest federal district) [106]. Unfortunately, we have not possibility to diagnose preeclampsia and eclampsia directly and only used the codes from the forms. However, Russian doctors are guided by Federal clinical guidelines where preeclampsia is characterized by hypertension (blood pressure 140/90 or more), along with oedema and proteinuria (300 mg of protein in a 24-hour urine sample) [93]. Furthermore, preeclampsia is more common in primiparae than in multiparae, which is a potential reason for discrepancies in parity between countries.

Confounding. Confounding is another major issue in epidemiological studies. This definition implies that the effect of the exposure is mixed together with the effect of another variable, which lead to a bias [100]. Confounding is a systematic error that researcher aim either to prevent or to remove from a study [100].

In Paper 1, we examined socio-demographic factors associated with discontinuation smoking or its reduction during pregnancy. The MCBR database did not allow us to explore potential confounders such as household income, working status, partner/husband smoking status, maternal smoking during previous pregnancies and relevant psychological factors as such data had not compiled. The variable alcohol abuse was based on documented evidence provided by physicians. However, no detailed information was available in the MCBR on alcohol consumption before and during pregnancy, nor about the breakdown of alcohol types consumed

or drinking levels. However, the latter variables might have been more relevant to our study than only alcohol abuse.

Potentially, the association between preeclampsia/eclampsia and maternal smoking could have been confounded by both socio-demographic and clinical characteristics of the pregnant women. Consequently, the effect of maternal age, residence, ethnicity, marital status, parity, alcohol abuse, year of delivery, body mass index at the first antenatal visit and excessive weight gain during pregnancy were mutually adjusted in the logistic regressions (Paper 2). There were other characteristics that could have been potential confounders, including working status of the pregnant women, their socio-economical status etc., but these were either inapplicable or were not presented in the registry database.

The association between adverse birth outcomes, including low birth weight, low birth length, low head circumference, low ponderal index and low Apgar score at 5 min, and women's smoking during pregnancy also could be confounded by both socio-demographic and clinical characteristics. In our study we adjusted for maternal age, residence, ethnicity, marital status, parity, alcohol abuse, year of delivery and such clinical characteristics as body mass index at the first antenatal visit, pregnancy diabetes, gestational age and excessive weight gain during pregnancy (Paper 3). Unfortunately, we could not adjust for partner smoking status or total weight gain while pregnant as done in some previous studies [48, 49, 64].

One way to control confounding is to limit the study to subjects who have particular characteristics [99]. For example in our study on the effect of first-trimester smoking cessation on Preeclampsia/eclampsia (Paper 2), participation in the study was restricted to singleton pregnancy, absence of pre-pregnancy hypertension, or having the first antenatal visit before week 12 of gestation. In Paper 3, in assessing an association between adverse birth outcomes and maternal smoking, we excluded women who had delivered before 37 completed weeks of gestation or had a multiple pregnancy.

5.1.2 External validity

Internal validity is necessary for external validity, but does not guarantee the latter. External validity or generalizability is the extent to which the results of a study apply to people not in it [99]. External validity identifies the accuracy of the research findings, by exploring its applicability from one setting to another [110]. It requires external quality control of measurements and conclusions in order to extrapolate the findings. As mentioned earlier (see

Sections 3.1 and 5.1.1), quality controls established that the proportion of error in MCBR was less than 1 % [88]. Moreover, since our study only included women giving birth at the maternity clinics, the results may not be generalizable to women who gave birth out-side such facility. However, the number of births registered in the MCBR comprised 98.8% of the official number of births recorded by the Health Department in Murmansk County [88].

5.2 Discussion of the main results

5.2.1 Prevalence of smoking before and during pregnancy and socio-demographic factors associated with discontinuing smoking or smoking reduction once pregnant

This study found that every fourth pregnant woman attending the antenatal clinics at the 15 delivery departments in the Murmansk County during 2006–2011 reported smoking before pregnancy. Of these, one fourth stopped smoking during pregnancy. The overall rate of smoking before and during pregnancy in our study is close to available Russian figures [2, 3, 111], but lower than in some European countries [5]. Pregnant women may stop smoking during pregnancy because of concerns about fetal and infant health [35]. We determined the proportion of quitters during pregnancy to be 25.0 %, which is less than in Australia [112], Spain [113] and the United States [114], but higher than in Denmark [115] and Greece [116]. Such differences may be related to variations in study design and sample selection, or the consequence of policy and social issues.

We show that selected socio-demographic characteristics constitute an indicator of maternal smoking cessation during pregnancy in Murmansk County, which contrasts that done in other studies [5, 7]. We did not find an association between maternal age and the odds of quitting smoking during pregnancy. As was suggested by Smedberg et al. [5], this specific association becomes non-significant after adjustment for potential confounders [5]. However, Colman et al. [7] illustrate that younger women are more likely to stop smoking during pregnancy compared to older women.

Our finding that women were more likely to quit smoking during pregnancy if they had no previous deliveries agrees with earlier findings [102, 116]. Moreover, we show a positive linear

association between the number of previous deliveries and the odds of quitting smoking during pregnancy. This may be explained by a women's individual experience of giving birth to a healthy child despite smoking during pregnancy [5, 6].

Marital status has been extensively investigated as an indicator of smoking during pregnancy [5, 117, 118]. Our finding that single women and those with a cohabitor were twice less likely to quit smoking during pregnancy than married women. This has been interpreted to reflect a response to circumstances in women's lives such as unsupportive partners [18].

Although rural women in our study smoked 1–5 cigarettes per day more often compared to urban women, the latter did so more heavily. Rural women were less likely to quit smoking during pregnancy than their urban counterparts. A Greece study suggests that the rural living is generally associated with lower smoking rates, which did not change during pregnancy [116].

A systematic review has demonstrated that to lessen the negative effects of smoking on pregnancy and fetal development, some women attempt to reduce their smoking rather than quit entirely [18]. In a literature review of 19 studies, 17 clearly demonstrate that more than half of all smoking women do not quit smoking completely during pregnancy [6]. These findings are consistent with our data that only one third of the pregnant women who smoked during pregnancy reduced the absolute numbers of cigarettes smoked. Moreover, older pregnant women and women with ≥ 2 children were less likely to reduce the number of cigarettes smoked than younger women and primipara, or those having one child.

Although common in other countries, studies like the current one are still lacking in Russia. Our examination of the socio-demographic determinants associated with reduced smoking or its cessation fills a void in North-west Russia. We conclude that the socio-demographic characteristics identified in relation to altering smoking habits during pregnancy are similar between countries, despite cultural differences. Furthermore, we observed that for the marital status variables considered in the Russian tradition, namely married, cohabitation and being single, indicated that only married women quit smoking during pregnancy.

5.2.2 The effect of first-trimester quitting smoking in pregnancy on preeclampsia/eclampsia

This study found that the risk of preeclampsia/eclampsia increased in women who were ≥ 35 years old, have less education than university, were single, primiparae and overweight or obese at the first antenatal visit are consistent with earlier studies [109, 119, 120].

Our finding of a 2-fold protective effect for the development of preeclampsia/eclampsia in women who smoked more than 11 cigarettes per day relative to non-smokers supports previous reports [36, 119, 121]. According to Linqvist et al. [120], moderate smokers (1-9 cigarettes per day) have a lower incidence of preeclampsia compared to non-smokers. Similarly, Yang et al. [122] report an inverse exposure-response association as does Bainbridge et al. [123]. Venditti et al. [124] state that the use of carbon monoxide (CO) could prevent the development of hypertension and proteinuria in a rodent model of preeclampsia. Bainbridge et al. [123] suggest that CO, a product of combustion in cigarettes, may be the active agent. More recently Zhai et al. [125] also demonstrated an inverse correlation between increased environmental ambient CO and preeclampsia. However, any interpretations must consider that the pathogenesis of preeclampsia is complex and appears to involve genetic, immunological and environmental factors [126].

Tobacco smoking during pregnancy can potentially impact angiogenic factors, endothelial function and the immune system, which could lead to a lower risk of preeclampsia. However, this protective role is most likely explained by CO's biological role in heme-degradation processes including the promotion of anti-inflammatory and pro-angiogenic effects [127-129]. On the other hand, the mechanisms underlying the increased risk of preeclampsia among previous and passive smokers remain unclear. Luo et al. [30] suggest that this could be due to adverse chronic effects of low tobacco exposure in the absence of significant exposure to a transient protective factor such as CO in association with current smoking.

Our statistical analyses suggest that discontinuing smoking after pregnancy awareness did not alter the risk of preeclampsia/eclampsia statistically speaking. By contrast, some studies demonstrate a lower incidence of preeclampsia among women who stop smoking at the beginning of pregnancy compared to those who never smoked [107, 130]. Neither do our findings align with those of England et al. [44] in their randomized clinical trial "Calcium for Preeclampsia Prevention" (N = 4,589). They observed that the incidence of preeclampsia among women who stopped smoking 13–21 weeks before pregnancy was similar to that among women who never smoked. This difference is likely related to whether cessation of smoking occurred after pregnancy recognition rather than well before pregnancy.

Studies based on the measurements of biomarkers of smoking such as plasma or salivary cotinine demonstrate diverse findings as well [30, 131]. A prospective pregnancy cohort study defined smoking status according to plasma cotinine, and found that previous and passive smokers compared to non-smokers were almost six-fold more likely to exhibit preeclampsia [30]. However, women who smoked during their current pregnancy had almost the same risk of

preeclampsia as non-smokers. Another study did not show significant differences in pre-eclampsia rates using lower cutoffs of cotinine exposure [131].

Mainstream smoke contains multiple toxic chemicals in addition to nicotine and CO that are volatile, e.g., acetaldehyde, hydrogen cyanide, nitric acid, acetone, ammonia, hydrogen sulfide, hydrocarbons, nitrosamines, and carbonyl compound [131]. The smoke particulate phase also contains multiple toxicants such as carboxylic acids, phenols, terpenoids, paraffin waxes, tobacco-specific nitrosamines, polyaromatic hydrocarbons. Clearly smoking during pregnancy is not recommended in the context of reported detrimental concerns that include increases in perinatal mortality, abruptio placenta, intrauterine growth retardation [132, 133] and birth defects (e.g., oral clefts) [134, 135].

5.2.3 The effect of changes in smoking behavior during pregnancy on selected adverse birth outcomes

Neonatal low weight at birth is either the result of preterm birth (before 37 weeks of gestation) or due to restricted fetal growth [135]. Consequently, we limited our study to births after the 37th week. Perhaps this explains the unexpectedly low prevalence of infants having low birth weight in our study in comparison with other studies that include preterm births and multiple pregnancies [29, 49-51]. Our observation that the risk of low birth weight was associated with maternal smoking agrees with earlier studies [29, 48, 50, 51, 136, 137].

Kato et al. [138] indicate that birth length is an important predictor of subsequent health. In our study, less than 1.0 % of term infants had low birth length that was associated with smoking during pregnancy. Nevertheless, low birth length was almost three times higher among smokers compared to non-smokers. Inoue et al. [48] observed the same outcome. Similarly, other studies have reported that children of mothers who continued smoking during pregnancy were shorter until the age of 4 years [28, 52, 136].

Several reports identify reduced head circumference and biparietal diameter as parameters of total growth restriction in fetuses of smoking mothers [26-28, 48]. We found an association between low head circumference at birth and maternal smoking. It has been suggested that this association is not only due to premature birth and smoking during pregnancy, but also by a negative effect of maternal smoking on intrauterine head growth [67]. Fattal-Valevski et al. [139] indicate that head size is an index of abnormal brain condition or neurodevelopmental delay in cognitive functions, and therefore reflects a child's long-term cognitive outcome [139].

Our adjusted odds for asymmetrical infants was 15% higher among women who smoked both before and during pregnancy compared to non-smokers. Previous studies with the ponderal index as a continuous variable have demonstrated decreases in its mean with maternal smoking [53, 140], although Ingvarsson et al. [52] reported no such relationship.

The absence of an association between maternal smoking and the odds of having infants with low Apgar score at 5 min might have been influenced by the fact that we focused on term births only. Walfisch et al. [54] also observed a non-significant association. Furthermore, a study of tobacco biomarkers in meconium did not observe an association between low Apgar score at 5 min and maternal smoking [55].

The dose-response relationship we demonstrated between daily number of cigarettes smoked during pregnancy and adverse birth outcomes is supported by earlier reports. Our finding is comparable to that indicated by Ko et al. [49], namely adjusted OR = 2.48 with 95% CI = 1.76–3.49). Ward et al. [51] have investigated the dependence of birth weight on cigarette smoking and observed a linear trend for reduced birth weight with increasing level of exposure involving either environmental tobacco smoke exposure (only partner smoked during the pregnancy) and for maternal smoking. Comparable findings have been reported by Durmus et al. [136] and Wang et al. [56]. Even though the study by Lindley et al. [53] comprised singleton births with gestational ages of more than 24 weeks, they also demonstrated that moderate maternal smoking was associated with a decrease in mean crown-heel length of 0.63 cm, while for heavy smokers the decline was 0.84 cm.

The number of studies examining dose-response relationships between daily cigarettes smoked during pregnancy and other anthropometric parameters of the newborn is limited. Jaddoe et al. [26] investigated associations of maternal smoking during pregnancy with longitudinally measured fetal growth characteristics, in particular head circumference for mid- and late gestations. The largest impact was observed in late gestation for the highest smoking category, namely ≥9 cigarettes per day [26]. Also in a large Swedish birth cohort of 1,362,169 infants, significant dose-response effects were observed for the effect of maternal smoking on head circumference <32 cm and less than the mean-2SD of its expected value [67].

Lindley et al. [53] also demonstrated that compared to non-smokers, heavy maternal smoking was associated with an increase in the ponderal index of 0.04. Thus infants of heavy smokers are more symmetrical in their growth retardation than those of light smokers. It is considered that the neonatal morbidity rate for symmetrical IGR is higher than that for asymmetrical IGR, and that term symmetric infants with IGR tend to have a lower mean birth weight implying a higher

incidence of small placentas than for term infants with asymmetrical IGR [69]. It may be concluded that heavy smoking during pregnancy relative to light smoking leads to a reduction in a newborn's health.

We did not find an association between low Apgar scores at 5 min and maternal smoking. However, a dose-response relationship between these variables was evident. Most of the studies estimating dose-responses were done more than 20 years ago and showed differential results. For example one study suggested a negative influence of maternal smoking on Apgar score at 5 min [69], while others showed no effect [70, 71].

Like Vardavas et al. [61], we observed that women who stop smoking after pregnancy recognition are at no greater risk of having a term baby with all selected adverse birth outcomes compared to non-smokers. Nijiati et al. [57] also showed that mean birth weight is not significantly different when comparing participants who stop smoking during pregnancy to non-smoking participants, and therefore conclude that smoking cessation in pregnancy is beneficial. By contrast, others have reported that maternal smoking in the first trimester is not associated with growth differences in head circumferences, lengths, and weight when compared to non-smokers [116, 136].

The lack of an effect of reduced smoking we observed may have been limited by a number of factors, including the accuracy/completeness of our data on smoking, heterogeneity of mitigating factors and the relatively low number of cigarettes smoked daily by the Russian women. However, in some studies a statistical association between a reduction in the number of cigarettes smoked per day during pregnancy and birth weight was not been observed [60, 64-66].

5.3 Implications for public health practice and research

In accordance with our findings each fourth woman who smoked in the pre-gestational period was able to change her smoking behavior and quit smoking after pregnancy recognition. Of the smokers who changed the number of cigarettes smoked per day during pregnancy, 1.1 % increased the number cigarettes per day, 62.1 % made no adjustment, and 36.8 % reduced their smoking frequency. Thus, the women included our study reported relatively high smoking rates before and during pregnancy (25.2 % and 18.9 %, respectively), and a small number quit smoking during pregnancy. One implication of this is a lack of smoking cessation programs in Northwest Russia, especially for pregnant women or for those who plan a pregnancy.

For the period July 10, 2001 to June 1, 2013 Russian federal law #87 addressed tobacco smoking restrictions [141]. This law was thus in force for our study period of 1 January 2006 to 31 December 2011. Generally speaking, this federal law focused on regulating activities for the production of tobacco products (item 1); the wholesale and retail sale of tobacco products (item 3); the prohibition of the retail sale of tobacco products to persons under the age of 18 (item 4); and knowledge about the dangers of tobacco smoking (item 7) etc. Unfortunately, this law did not provide specific services such as programs for treatment of nicotine dependence such as during pregnancy. In this context, pregnant women who were willing to stop smoking and could not do it themselves need special professional support. However, this support was not available in the antenatal clinic, although for a fee there were private drug treatment clinics.

In our sample, women were more likely to continue smoking during pregnancy if they were younger, had low education, resided in rural areas, and were single. This suggests that the smokers in our study had low socio-economic status, which prevented them from using the services of private clinics. Clearly, the development and availability of free smoking cessation programs targeting pregnant women would most likely encourage more women to quit smoking, at least during pregnancy. Such activities would lead to a decrease in adverse pregnancy and birth outcomes.

Future activities should focus on the development of smoking cessation programs that take into account the socio-demographic characteristics of women in order to decrease adverse pregnancy and birth outcomes.

6. Concluding Remarks

The Murmansk County Birth Registry included data for the period January 1, 2006 to December 31, 2011. It included both socio-demographic and clinical characteristics of the women and their infants for most of the 52,806 births. This large sample size and the ability to control for the influence of possible confounding factors enabled us to assess the effect of smoking cessation and smoking reduction while pregnant on selected adverse pregnancy and birth outcomes. Based on our studies, we make the conclusions itemized below.

1) Of the 51,131 mothers in the study, 25.2 % (95 % CI: 24.8– 25.5 %) smoked before pregnancy, and 18.9 % (95 % CI: 18.5–19.2 %) of these continued smoking during pregnancy. About 25.0 % of smoking women in Murmansk County, Russia, stopped smoking during pregnancy and one third reduced the quantity of cigarettes smoked during pregnancy. Our study demonstrates that primiparous women with higher education or those having a husband are more likely to stop smoking during pregnancy. Maternal age and the number of children were additional indicators that influenced smoking reduction during pregnancy.

2) Maternal smoking was inversely associated with preeclampsia/eclampsia. Increasing the number cigarettes smoked daily during pregnancy decreased the odds of preeclampsia/eclampsia. Interestingly, the women quit smoking during pregnancy had the same risk of preeclampsia/eclampsia as those who smoked while pregnant.

3) Compared to non-smokers, the women who stopped smoking during the first trimester were at no higher risk of having a baby with adverse birth outcomes, including low birth weight, low birth length, low head circumference, low ponderal index, or low Apgar score at 5 min. Of special interest is that smoking reduction during pregnancy was not associated with a reduction in the adverse birth outcomes examined. Although our study was of limited statistical power, these outcomes cannot be dismissed.

7. Future Perspectives

The first future perspective is a continuation of the MCBR. Unfortunately, the MCBR contains data only from 2006 to 2011. It was happen because the project aimed to develop a birth registry was completed in 2012. Nowadays the MCBR has no financial support and has suspended data collection. However, in 2012, the Arkhangelsk County Birth Registry was implemented based on the MCBR. Almost 45 000 records were collected during 2012-2014. This is important, as it will facilitate new studies including on tobacco smoking.

The second future perspective is a conducting of the study aimed to examine the accuracy between self-reported smoking and cotinine levels among Russian pregnant women. It is necessary to understand whether it is possible to evaluate smoking status by questionnaire or should use biomarkers.

The third future perspective is a development of smoking cessation programs for pregnant women or those who plan a pregnancy. During our study we defined a target group who could not stop smoking during pregnancy themselves. Clearly the research described in this thesis, and in the 3 publications on which it is based, demonstrate that the importance of an awareness of the socio-demographic characteristics of pregnant women who smoke is essential in the design of pertinent intervention strategies.

Finally, the fourth future perspective is an assessment of the established smoking cessation programs.

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Paper 1

Paper 2

Paper 3

APPENDIX. Data contained in the MCBR (in Russian)

А – Персональные данные матери и отца

1. Название роддома	**2. Роды вне роддома** ☐ Дома ☐ Другое место ☐ Во время перевозки	**3. Год (0000) и номер медицинского файла** _____
4. Год рождения последнего живого ребенка (0000) ☐☐☐☐ Если дата не введена → клетка 4.1	**4.1 Нет даты, так как:** ☐ Ранее не было живого ребенка ☐ Нет информации	**4.2 Год последнего аборта** (0000) ☐☐☐☐ Если дата не введена → клетка 4.3
4.3 Нет даты, так как: ☐ Ранее не было абортов ☐ Нет информации		
5. Дата рождения матери (день/месяц/год, 00.00.00) ☐☐☐☐☐☐	**6. Этническая принадлежность** ☐ Саами ☐ Русская ☐ Азербайджанка ☐ Другая (уточните) _____	**7. Место жительства (Район)**
7.1 Город/поселок/село		
8. Менялся ли официальный адрес матери во время беременности? ☐ Нет ☐ Да (если «Да», то откуда ->)	**8.1 Область/Район**	**8.2 Город/поселок/село**
9. Семейное положение **Замужем:** ☐ Да ☐ Гражданский брак ☐ Нет ☐ Другое		
10.Образование, закончен. ☐ Никакого ☐ Начальное (1-9 класс) ☐ Среднее (10-11 класс) ☐ Среднее специальное ☐ Высшее	**11. Профессия матери**	**11.1 Место работы матери**
11.2 Цех, где она работает		
Информация об отце **12. Возраст отца** ☐☐	**13. Профессия отца**	**13.1 1 Место работы отца**
13.2 Цех, где он работает	**14. Этнич. принадлежность** ☐ Саами ☐ Русский ☐ Азербайджанец ☐ Другая (уточните) _____	

B – О беременности и здоровье матери

15. Срок бер-ти при первой явке в связи с этими родами (неделя, 00)
_____

16. Рост (в см)

17. Вес (при первой явке) (в кг)
_____

18. Последняя менструация, первый день кровотечения (д/м/г)
☐☐☐☐☐☐
☐ уверена ☐ не уверена

19. Когда проведено первое ультразвуковое обследование
☐☐☐☐☐☐
☐ ни разу не проводилось

B1. МКБ-10 код(ы)

B2. МКБ-10 код(ы)

19.1 Срок родов, прогнозир. ультразвуком
д. м. г.
☐☐☐☐☐☐

19.2 Патология, обнаруженная УЗИ у матери или ребенка
☐ Нет
☐ Да (уточните в клетке B1)

20. Патология, выявленная у ребенка, с помощью амниоцентеза, кордоцентеза, хорионбиопсии
☐ Нет
☐ Да (уточните в клетке B2)

Возраст ребенка в неделях. при первом УЗИ _____

На какой неделе беременности произошло родоразрешение? _____

21. Предыдущие беременности матери (исключая этого ребенка) Только целые недели

21.1
Рождение живого ребенка _____
Мертворождения >= 22 недель

Рожден живым, умер в течение 7 дней

21.2
Преждевременные роды (22-29 недель)
Преждевременные роды (30-36 недель)____
Кесарево сечение во время предыдущих родов

21.3 Спонтанные аборты
13-22 недель
=< 12 недель ____

B3.Уточните МКБ-10 коды по мед. показаниям:
1.
2.

21.4 Медицинские аборты (по собственному желанию)
=< 12 недель ____
была ли это мед причина?
☐ нет ☐ да

21.5 Медицинские аборты с
(заполните 21.6)
13 недель _____

21.6
Социальные причины
_____
Медицинские причины
____ (уточнить код в B3)

22 Витамины/алкоголь/ наркотики
☐ Рубец на матке по другим причинам

24. Признаки злоупотребления алкоголем
☐ Нет
☐ Да

25. Признаки употребления наркотиков
☐ Нет
☐ Да

22. 1 Прием витаминов перед беременностью
Поливитамины
☐ нет ☐ да
Таблетки фолиевой к-ты
☐ нет ☐ да

22.2 Во время беременности
Поливитамины
☐ нет ☐ да
Таблетки фолиевой к-ты
☐ нет ☐ да

23. Курение до беременности
☐ Нет
☐ Да, сколько сигарет
_____ в день

23.1 Курение во время беременности
☐ Нет
☐ Да, сколько сигарет
_____ в день

B6. Фармацевтическое название препарата
1.Название
С даты (д/м)
☐☐☐☐

2. Название
С даты (д/м)
☐☐☐☐

3. Название
С даты (д/м)
☐☐☐☐

26. Болезни до беремен-ности
☐ **Ничего особенного**
☐ Хронич. инфекция полового тракта
☐ Хронич. инфекция мочевого тракта и почек
☐ Астма
☐ Варикозная болезнь н/к
☐ Хроническая гипертония
☐ Ревматоидный артрит
☐ Сердеч. забол.
☐ Эпилепсия
☐ Диабет, тип 1
☐ Диабет, тип 2
☐ Гепатит B
☐ Гепатит C
☐ другое (уточните в B4)

B4. Уточните МКБ-10 код (ы)

27. Болезни во время беремен-сти (включая несчастные случаи)
☐ Ничего особенного
☐ Кровотечение< 13 нед.
☐ Кровотечение13-28нед.
☐ Кровотечение> 28 нед.
☐ Диабет беременной
☐ Тромбоз
☐ Легкая преэклампсия
☐ Средняя преэклампсия
☐ Тяжелая преэклампсия
☐ Эклампсия беременной
☐ HELLP- синдром (гемолитич. ….)
☐ Легкая анемия
☐ Умеренная анемия
☐ Тяжелая анемия
☐ ОРВИ
☐ Варикозная болезнь н/к
☐ Hb > 135 г/л
☐ Угр. прерывания (O20.0)
☐ Отеки берем. (012.0)
☐ Инфек почек (023.0)
☐ Инфек пол путей (023.5)
☐ Чрезмерное увеличение массы беременной (026.0)
☐ инфекции (B5)
☐ другое (B5)
☐ лекарства (B6)

B5. Уточните МКБ-10 код (ы)

C – О родах

28. ☐ Использовалось эластическое бинтование (компрессия) ног в родах

29. Предлежание плода
☐ затылочное/ нормальное
☐ Ягодичное
☐ Поперечное
☐ Головное аномальное
☐ Другое

30. Тип родов
☐ Спонтанные
☐ Провоцир.
☐ Кесарево сечение

31. Кесарево сечение Было ли оно запланировано до родов?
☐ Нет
☐ Да

32. Показания для хирургического вмешательства и/или провоцирования
☐ Осложнения, описанные ниже
☐ ВПР плода
☐ Переношенная беременность
☐ Другое, уточните в C1

33. Осложнения во время родов
☐ Никаких
☐ Отхож. вод за 12-24 часов
☐ Отхож. вод за >24 часов
☐ Клиническое несоответст.
☐ Дистоция плечиков
☐ Предлежание плаценты
☐ Отслойка плаценты
☐ Разрыв промеж-ности (1-2 ст.)
☐ Разрыв сфинктера (3-4 ст.)
☐ Кровотечение 500-1000 мл
☐ Кровотечение 1000-1500 мл
☐ Кровотечение > 1500 мл
☐ Эклампсия в родах
☐ Угроза внутриутробной асфиксии
☐ Разрыв шейки матки
☐ Выпадение пуповины
☐ 1-я слаб-ть род.деят.
☐ 2-я слаб-ть род.деят.
☐ Маточная гипотон.
☐ Дискоорд.род.деят
☐ Другое, уточните в C2

C1. МКБ-10 код (ы)

C2. МКБ-10 код (ы)

34. Анестезия
☐ Никакой
☐ Закись азота
☐ Эпидуральн.
☐ Спинномозг.
☐ Промедол
☐ Наркоз
☐ Не наркотический анальгетик
☐ Другое, запишите в C3

35. Плацента
☐ Нормальная
Вес 1 (граммы)
_____
Вес 2 (граммы)
_____
☐ Инфаркт плаценты
☐ Ретроплац.гематома
☐ Инфекция
☐ Фетоплац. недостаточ.
☐ Другое, запишите в C4

C3. Препарат

36. Пуповина
☐ Нормальная
☐ Вуалеобразное прикрепление
☐ Периферическое прикр.
☐ Сосудистые аномалии
☐ Пуповина вокруг шеи
☐ Другие петли
☐ Истинный пуповинный узел
36.1 Длина пуповины 1 (в см)
36.2 Длина пуповины 2 (в см)

C4. МКБ-10 код (ы)

37. Околоплодные воды
☐ Нормальные
☐ Полигидрамнион
☐ Олигогидрамнион
☐ Грязные воды
☐ Наличие крови
☐ Инфекционные

38. Осложнения у матери после родов
☐ Ничего особенного
☐ Температура > 38.5°C
☐ Сепсис
☐ Тромбоз
☐ Эклампсия послеродовая
☐ Интенсивная терапия
☐ Другое, запишите в C5
☐ Переведена

Мать переведена в (название больницы)
_____

C5. МКБ-10 код (ы)

ГОРОД _____ Название ЖК _____ Номер индивидуальной карты беременной и родильницы из ЖК _____

D- О новорожденном

39. Дата родов (д/м/г) ☐☐☐☐☐☐ **40. Время родов** (час, мин.) ☐☐☐☐	**41. Многоплодные роды** Если многоплодные: No. ___ ребенка из ___ (общее количество) детей	**42. Пол** ☐ Мужской ☐ Женский ☐ Неизвестно	**43. Вес ребенка (в граммах)** ☐☐☐☐ **44. Рост (в см)** ☐☐	**45. Окружность головы** **(в см)** ☐☐	**46. По шкале Апгар** **1 мин.** ☐☐ **5 мин.** ☐☐	
47. Ребенок родился: ☐ живым ☐ мертвым (47.1) ☐ Выкидыш Подтвердите причину смерти в D1	**47.1 Для мертворожденного:** ☐ Смерть до начала родов ☐ Смерть во время родов ☐ Время смерти неизвестно	**48. Родился живым, но умер в течение 24 часов** Время смерти (Час, мин.): _____ _____	**49. Ребенок умер позднее:** Число (день/мес.) ____ ____ Время(час, мин.) ____ ____	**50. Ребенок умер в больнице?** ☐ Да ☐ Нет	**D1. МКБ-10 код (ы)**	
51. Диагноз новорожденного ☐ Ничего особенного	☐ Гипогликемия <50 мг/дл) ☐ Аспирационный синдром ☐ Неонат. судороги ☐ Врожд. анемия(hb<13.5) ☐ Интракраниальное кровотеч.☐ Инфекция пупка/кожи ☐ Дисплазия тазобед.сустава ☐ Церебральное раздражение ☐ Перинат.инфекции, уточ- ☐ Транзиторн.частое дыхание ☐ Церебральная депрессия нite в D3 ☐ Дыхат. дистресс-синдром ☐ Абстиненция ☐ Другие инфекции (D2) ☐ Конъюнктивиты ☐ Другое, уточните в (D3)				**D2. МКБ-10 код (ы)**	
☐ Перелом ключицы ☐ Перелом конечностей ☐ Лицевой парез ☐ Повреждение сплетения ☐ Другое, включая травмы (D4)	**52. Виды лечений:** ☐ Сист.антибиотики ☐ ИВЛ ☐ Глазные капли	**Леченная желтуха:** ☐ УФ светолечение ☐ Переливание крови	**Причина:** ☐ Несовместимость по системе АВО ☐ Резус-иммунизация ☐ Физиологическая		**D3. МКБ-10 код (ы)**	
53. **Врожденные дефекты** ☐ Да ☐ Нет	Описание повреждений, неонатального диагноза и врожденных дефектов МКБ-10 код ☐☐☐☐ Другое: МКБ-10 код ☐☐☐☐				**D4. МКБ-10 код (ы)**	
54. Даты выписки	Мать выписана ☐☐☐☐☐☐	Ребенок выписан / переведен ☐☐☐☐☐☐ Переведен в _____			**Номер истории болезни**	