Risk factors of adverse pregnancy outcomes: opportunities and perspectives of a birth registry-based study - Anna Usynina

178

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"As a father and grandfather, I have witnessed firsthand the joy of new life entering the world. I know the pain and apprehension that goes along with premature births and birth defects".

Solomon Porfirio Ortiz, American Politician

CONTENT

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PREFACE

This thesis is based on work done with birth-registry data at the Department of Community Medicine, Faculty of Health Sciences at UiT The Arctic University of Norway.

In fact, my first contact with a birth registry happened already ten years ago. More precisely, at that time it was the Medical Birth Registry of Norway. In 2006, my colleagues and I, all neonatologists of the largest delivery hospital in Arkhangelsk (Russia), saw the printed annual report from 2003 and 2004 of the Birth Registry of Norway for the first time. We were impressed by the detailed information provided in the report. Fortunately, the English translation was also given. At that time in Russia, only descriptive statistics of perinatal events from national official statistical institutions was available. Information was not individualized as no personal identification number was implemented in Russia. Later, my colleague from the neighboring Murmansk County said one day that delivery hospitals and units in her county participated in an international project which collected information about all still- and liveborn infants by filling out registration forms.

In 2011, I started to work with the Murmansk County Birth Registry as a master student of Arkhangelsk International School of Public Health at the Northern State Medical University. A few years later, this regional registry became much more familiar to me as my PhD-studies at UiT The Arctic University of Norway started that were focused on data from the Murmansk County Birth Registry. As neonatologist, I understand how important it is for practical doctors and nurses as well as for health care providers to get precise detailed information about pregnant women and infant health, pregnancy outcome, and pregnancy or birth complications in time. To be sure our actions in prevention, treatment, and organization of maternal and babies care are correct and the efforts are effective, it is exceptionally essential to have access to

information and to analyze data regularly.

Implementation of the Murmansk County Birth Registry and further work with this registry database was made possible through a cooperation between the UiT The Arctic University of Norway and the Ministry of Health of Murmansk County, Russia.

Arkhangelsk, Russia, October 2016
Anna Usynina

ABSTRACT (in English)

Background: Preterm birth, perinatal death, and birth of babies small for gestational age are amongst common adverse pregnancy outcomes. Maternal lifestyle, mothers' health status before and during pregnancy, previous adverse pregnancy outcomes as well as socio-demographic factors all influence perinatal mortality, prematurity, and small for gestational age birth. To date, despite many studies of multiple risk factors, data on factors contributing to adverse pregnancy outcomes in Northwest Russia are insufficient. The implementation of a regional birth registry in Murmansk County located in the Northwest Russia provided an opportunity to study different pregnancy outcomes in relation to selected risk factors.

Aims: The specific aims of this thesis were to 1) explore associations between selected maternal and fetal characteristics and perinatal mortality based on data from the Murmansk County Birth Registry in Russia; 2) estimate the prevalence of preterm birth in Murmansk County and to investigate associations between selected maternal factors and preterm birth; 3) examine maternal social risk factors for term small for gestational age births.

Methods: The study population included all 52 806 live- and stillbirths recorded in the Murmansk County Birth Registry during 2006-2011. Exclusion criteria different for studied pregnancy outcomes were used in prevalence analyses. Chi-squared tests were applied to evaluate differences in distribution of selected risk factors between groups with studied adverse pregnancy outcomes and groups without corresponding perinatal event. Logistic regression was used to estimate the effect of risk factors on studied pregnancy outcomes.

Results: Maternal low education, unmarried status, overweight or obesity, alcohol abuse, as well as preterm deliveries and abortions in mother's medical history and antepartum hemorrhage and fetal growth retardation in current pregnancy associated with increased risk of perinatal mortality. Babies of underweight women were at lower risk of perinatal death. The prevalence of preterm birth ranged from 6.0% at 22-27 weeks gestation to 0.3% at 32-36 completed weeks, reaching 6.9% in total. Unmarried women, those with prior preterm birth, spontaneous or induced abortions had increased risk of preterm birth in current pregnancy. Additional risk factors varied throughout pregnancy. Maternal smoking and alcohol abuse increased the risk of term small for gestational age birth. Similar effect was observed in low educated, unemployed, and underweight women.

Conclusion: The Murmansk County Birth Registry served as an important tool to study risk factors for adverse pregnancy outcomes. This thesis demonstrated that both socio-demographic, lifestyle and medical factors contribute to perinatal death, preterm birth, and small for gestational age birth in Northwest Russia. Public health efforts should therefore focus on reducing smoking, alcohol consumption, and underweight and good nutrition in women planning pregnancy.

ABSTRACT (in Norwegian)

Bakgrunn: For tidlig fødsel, perinatal dødelighet, og veksthemming hos det ufødte barn er blant de mest vanlige svangerskaps- og fødselskomplikasjoner. Mors livsstil, mors helsestatus før og gjennom svangerskapet, tidligere svangerskapskomplikasjoner samt sosio-økonomiske faktorer kan alle påvirke spebarnsdødelighet og sykelighet, for tidlig fødsel og veksthemming hos det ufødte barnet. Til tross for mange studier av risikofaktorer er data knyttet til svangerskaps- og fødselskomplikasjoner i Nord-Vest Russland svært mangelfulle. Opprettelsen av et regionalt fødselsregister i Murmansk fylke har gitt oss muligheter til å studere en rekke svangerskapsutfall knyttet til spesifikke risikofaktorer.

Formål med oppgaven: De spesifikke temaer for denne oppgaven var 1) å undersøke sammenhenger mellom utvalgte egenskaper og karakteristika hos de gravide, barns fødselsvekt og barns sykelighet og dødelighet i svangerskap og fødsel basert på data fra Murmansk Fylkes Fødselsregister; 2) å undersøke forekomst av for tidlig fødsel i Murmansk fylke og undersøke sammenhenger mellom utvalgte helsefaktorer hos mor og for tidlig fødsel; 3) å undersøke mors sosiale risikofaktorer knyttet til veksthemming hos det ufødte og nyfødte barn.

Metode: Studigruppen bestod av alle 52 806 levende- og dødfødte registrert i Murmansk Fylkes Fødselsregister i perioden 2006-2011. Definerte eksklusjonskriterier uten betydning for de undersøkte variabler ble brukt i prevalens analysene. Chi-kvadrat tester ble brukt for å undersøke forskjeller i forekomst av utvalgte risikofaktorer mellom grupper med påviste komplikasjoner og grupper med samme bakgrunn, men uten tilsvarende komplikasjoner. Logistisk regresjon ble brukt for å estimere effekten av risikofaktorene på svangerskapsutfallet.

Resultater: Lav utdanning hos mor, status uten partner, overvekt, alkoholbruk i svangerskap, tidligere premature fødsel eller indusert abort samt blødning i svangerskapet er alle assosiert med øket risiko for perinatal dødelighet. For tidlig fødte barn hadde påvist høyere risiko for spebarnsdød. Forekomst av for tidlig fødsel varierte fra 6.0% mellom 22-27 uker til 0.3% ved 32-36 fullgåtte uker, totalt 6.9%. Ugifte fødende, de som hadde tidligere for tidlig fødsel, tidligere spontane eller induserte aborter hadde øket risiko for tidlig fødsel i det registrerte svangerskapet. Andre risikofaktorer varierte gjennom svangerskapet. Mødrenes røykevaner og alkoholbruk var knyttet til øket risiko for veksthemming hos barnet. En tilsvarende effekt ble påvist knyttet til lav utdannelse, arbeidsledighet og dårlig ernærte mødre.

Konklusjoner: Murmansk Fylkes Fødselsregister er et viktig instrument for å studere risikofaktorer for svangerskaps- og fødselskomplikasjoner. Denne studien viser at sosio-økonomiske, livsstils-, og medisinske faktorer bidrar til spebarnsdødelighet, for tidlig fødsel og veksthemming for det ufødte barn i Nord-Vest Russland. Folkehelsestrategier bør legge vekt på å redusere røyking og alkoholbruk, samt å arbeide for en god ernæringsstatus for kvinner før og under svangerskapet.

ABSTRACT (in Russian)

Введение: Преждевременные роды, перинатальные потери и рождение ребенка малого к сроку гестации находятся в ряду наиболее частых нежелательных исходов беременности. Стиль жизни матери, состояние ее здоровья до и во время беременности, неблагоприятные исходы предыдущих беременностей, а также социально-демографические факторы оказывают влияние на перинатальную смертность, преждевременные роды и рождение ребенка, малого к сроку гестации. Несмотря на многочисленные исследования различных факторов риска, данные о них на Северо-Западе России на сегодняшний день недостаточны. Внедрение регионального регистра родов в Мурманской области, расположенной в Арктической зоне Российской Федерации предоставило возможность изучения отдельных факторов риска неблагоприятных исходов беременности.

Цели: 1) Используя данные Регистра родов Мурманской области (Россия), изучить связь между отдельными характеристиками матери и плода и перинатальной смертностью 2) оценить распространенность преждевременных родов в Мурманской области и определить связь между отдельными материнскими факторами и преждевременными родами 3) изучить материнские социальные факторы риска рождения ребенка, малого к сроку гестации.

Методы: Исследуемая популяция включала 52 806 случаев родов (как живорожденных, так и мертворожденных), зарегистрированных в Регистре родов Мурманской области в 2006-2011 гг. При анализе распространенности использованы критерии исключения, различные в зависимости от изучаемого исхода беременности.

Критерий хи-квадрат применялся для изучения различий в распространенности отдельных факторов риска в группах, имеющих неблагоприятный исход и без таковых. Для оценки эффекта факторов риска на изучаемые исходы беременности использовался метод логистической регрессии.

Результаты: Женщины с низким уровнем образования, одинокие или живущие в нерегистрированном браке, имеющие ожирение или избыточную массу тела, алкогольную зависимость, преждевременные роды и аборты в анамнезе, а также дородовое кровотечение или задержку роста плода при настоящей беременности имели повышенный риск перинатальной смертности. Дети и плоды матерей с дефицитом массы тела имели повышенный риск смерти в перинатальный период. Частота преждевременных родов изменялась от 6.0% в 22-27 недель до 0.3% в 32-36 полных недель, составляя в целом 6.9%. Незамужние женщины, а также имевшие преждевременные роды, спонтанные или индуцированные аборты в анамнезе, составляли группу повышенного риска преждевременных родов при настоящей беременности. Дополнительные факторы риска варьировали для изучаемых неблагоприятных исходов беременности. Курение и алкогольная зависимость матери являлись факторами риска рождения доношенного ребенка, малого к сроку гестации. Подобный эффект отмечался в случае дефицита массы тела матери, ее низкого уровня образования или безработицы.

Заключение: Регистр родов Мурманской области явился важным иструментом, позволившим изучить факторы риска неблагоприятных исходов беременности. Настоящее исследование продемонстрировало значимость стиля жизни, социально-демографических факторов, а также факторов медицинского характера для перинатальной смертности,

преждевременных родов и рождения ребенка, малого к сроку гестации в Северо-Западной России. Общественному здравоохранению следует сфокусировать свои усилия на уменьшении распространенности курения, потребления алкоголя и дефицита массы у женщин, планирующих беременность.

LIST OF PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

Paper I

Usynina AA, Grjibovski AM, Krettek A, Odland JØ, Kudryavtsev AV, Anda EE.
Risk factors for perinatal mortality in Murmansk County, Russia: a registry-based study.
Global Health Action 2016; resubmitted and accepted

Paper II

Usynina AA, Postoev VA, Grjibovski AM, Krettek A, Nieboer E, Odland JØ, Anda EE.
Maternal risk factors for preterm birth in Murmansk County, Russia: a registry-based study**.**
Pediatric and Perinatal Epidemiology 2016, 30(5):462-72

Paper III

Usynina AA, Grjibovski AM, Odland JØ, Krettek A.
Social correlates of term small for gestational age babies in a Russian Arctic setting.
International Journal of Circumpolar Health. 2016;75.

LIST OF TABLES

LIST OF FIGURES

DEFINITIONS

Early neonatal death   Death of liveborn baby during the first 7 days of life [1]

Extremely preterm birth   birth at gestational age <28 weeks [2]

Moderate-to-late preterm birth birth at gestational age from 32 to 37 weeks [2]

Neonatal death   death of liveborn infant during the first 28 completed days after delivery [1]

Perinatal mortality   number of deaths per 1 000 births of fetuses weighing ≥500 g or born at 22 completed weeks of gestation with unknown birth weight, and newborns up to 7 completed days after delivery [1]

Preterm birth   birth before 37 completed weeks or 259 days of gestation [2]

Small for gestational age   birth with infant birth weight and birth length below the 10th percentile for gestational age [1]

Very preterm birth   birth at gestational age from 28 to 32 weeks [2]

ABBREVIATIONS

BL	Birth length
BMI	Body mass index
BW	Birth weight
CI	Confidence interval
GA	Gestational age
ICD-10	International Classification of Diseases, 10th revision
LMP	Last menstrual period
MCBR	Murmansk County Birth Registry
ORs	Odds ratios
PTB	Preterm birth
P10	The 10th percentile
SD	Standard deviation
SGA	Small for gestational age births
SGA$_W$	Small for gestational age births with infant's birth weight <10th percentile
SGA$_{WL}$	Small for gestational age births with infant's both birth weight and birth length <10th percentile
WHO	World Health Organization

1 INTRODUCTION

National birth registries are a valuable data source for perinatal epidemiology [3-10]. They can be used to provide epidemiological surveillance of different perinatal health problems [4, 11] as well as long-term outcome related to the perinatal period [4]. Based on regular recording of pregnancy outcomes at gestational age (GA) more than 12 or 22 weeks, such registries enable us to investigate causes, risk factors and outcomes of different health conditions in mothers, fetuses, and newborns. The quality of antenatal and delivery care service can also be monitored through birth registries [4, 5]. Many birth registries are increasingly being used in research [6, 11]. To date, important findings based on data from birth registries include the association between insufficient periconceptional folate and folic acid intake and birth defects [12]. Increasingly used linkage between birth registries and other regular registries provides a future perspective for birth registry-based epidemiological research and surveillance.

1.1 The history of birth registries

Most birth registries were established decades ago [3-5, 11]. The existence of a well-organized system of birth registration in a country is a prerequisite for the introduction of a birth registry. In the Nordic countries, regular birth registrations are used and a unique personal identification number is given to all citizens which predestined the establishment of birth registries primarily in those countries. Norway, Denmark, Sweden, Finland, and Iceland all have a long history of collecting birth records [3, 4, 8, 11, 13]. In these countries, reporting data on births is mandatory on the national level. Size, completeness, accuracy, long follow-up period, and the quality of the registries were concluded good for research purposes [3, 11, 13-17].

The content of the birth registries in the Nordic countries varies, but all

databases contain information on maternal socio-demographic status, maternal medical history of previous pregnancies and deliveries, complications of current pregnancy and delivery, information on mothers' and newborns' diseases, as well as care and interventions during the time of pregnancy and delivery [18].

The Medical Birth Registry of Norway and the Norwegian Mother and Child Cohort Study

The Medical Birth Registry of Norway was established in 1967. Its particular mission was to detect possible predisposing risk factors of birth defects [11, 15]. In the late 1960s, birth defects increased in rate which determined the need of epidemiological studies. The negative role of Thalidomide for fetus development, more precisely the association between its intake and limb reduction deformities in fetuses, contributed to the implementation of the Medical Birth Registry of Norway [11]. Regular recorded registry-based data were also urgently needed for the health care system to prevent further increase in the rates of birth defects and other adverse perinatal outcomes [11, 15].

Research based on data from the Medical Birth Registry of Norway also established that side sleep position could not be considered safe for babies as it increased the risk of sudden infant death syndrome [19]. Perinatal outcomes in pregnant women suffering from diabetes mellitus [20], asthma [21], inflammatory joint diseases [22, 23], neuroses [24], epilepsy [25], tuberculosis [26] and other diseases are in focus of recent epidemiological and clinical studies based on the Medical Birth Registry of Norway.

The Norwegian Mother and Child Cohort Study (MoBa) studies causes of a child's health for further improvement of prevention of diseases. Maternal health, stress at work, lifestyle, nutritional factors, exposure to different toxins as well as genetic factors and paternal health are under investigation as potential components of the causal chain [27]. Since 1999, MoBa has collected information about more than 114 000 pregnancies and serves as a base for 221 research projects [28].

In 2007-2009, the Northern Norway mother-and-child contaminant cohort study entitled MISA recruited 515 pregnant women in Northern Norway. A set of laboratory and clinical examinations were done to explore the effect of prenatal exposure to environmental pollutants on children's health [29].

The Danish Medical Birth Registry and the Danish National Birth Cohort

The Danish Medical Birth Registry started in 1968. Its electronic database was established in 1973 [5]. Similar to other birth registries it is widely used either as a single data source, or linked with other national registries. Data from interviews and self-completed questionnaires are also used in a linkage with the Danish Medical Birth Registry [5].

In Denmark, one more database has appeared in the 1990s to explore multiple associations between different exposure factors and complications of pregnancy as well as fetal and infant pathology. The Danish National Birth Cohort repeatedly collected prospective data on 100 418 primarily first trimester pregnant women between 1995 and 2002 [30, 31]. The linkage of the Danish National Birth Cohort to the Danish National Patient Register provides a unique opportunity to investigate how early life exposures influence human health long-term [30]. Studies based on the Danish National Birth Cohort demonstrate association between acetaminophen intake in pregnancy and increased risk of asthma in the offspring [32] and an increased risk of stillbirth and infant mortality in binge drinking pregnant women [33, 34]. In contrast, an intake of oral contraceptives during pregnancy does not associate with increased risk of miscarriage or stillbirth [35].

Studies based on the Danish National Birth Cohort address different issues such as maternal socio-demographic and life-style factors and their influence on perinatal outcome. In 2008, an increased risk of stillbirth in smokers was confirmed [36]. Furthermore, women who use multiple nicotine replacement products have higher risk of delivering babies with lower birth weight (BW) [37]. Additionally, fixed night shifts are unsafe for pregnancy as they increase the risk

of late fetal loss [38]. Women who are physically active are at lower risk of having a preterm birth (PTB) [39]. In contrast, excessive exercise early in pregnancy increases the risk of miscarriage [40].

The Swedish Medical Birth Register

The Swedish Medical Birth Register was founded in 1973 [41] and has been modified several times since its introduction to improve its reliability and quality [3]. It has cross-links to the Swedish Registry of Congenital Malformations and the Hospital Discharge Register [3]. Stillbirth risk factors [42], multiple pregnancies and assisted reproductive technologies [43], as well as causes of increased rate of cesarean sections [42] are currently the main research focus.

The Swedish Medical Birth Register is linked to the records of the National Board of Health and Welfare which makes it possible to investigate the causes of increased risk of neurological pathologies in children. A high prevalence of multiple pregnancies, as well as PTB and low BW are risk factors of cerebral palsy in infants born after in vitro fertilization [43]. Epidemiological findings based on the Swedish Medical Birth Register continue to be an important tool for clinical practice. They help to understand the effects of current changes in health care service. Thus, implementation of new recommendations for obstetricians for term breech delivery contributes to an increased rate of planned cesarean sections [44].

In 2003, a two-fold reduction in maternal cigarette smoking was reported by a study based on the Swedish Medical Birth Register [45]. The same study also confirmed an increase of mean BW over time and a decrease of early neonatal mortality in both term and preterm babies, but did not reveal a reduction of stillbirth [45].

The Finnish Medical Birth Register

The Finnish Medical Birth Register was implemented in 1987. Now it is one of the most widely used health registries in Finland [46]. Over the years, the quality

has been improved through several reforms. The basis for these reforms was a quality control study in 1987 that demonstrated insufficient quality of records related to diagnoses and medical procedures [17]. Later, the introduction of a check-box question format in the registration form improved the quality of collected data as well as the validity of the registry [16, 47]. As there are more than twenty national social welfare and health registries in Finland and the country uses a personal identification number since 1964 [4], there are good perspectives for Finnish epidemiological studies both today and in the future.

The association between maternal smoking during pregnancy and increased risk of schizophrenia in offspring are among recently published results based on the Finnish Medical Birth Register [48]. Study of socioeconomic differences in pregnancy outcomes demonstrate a higher risk of PTB, perinatal mortality (PM), and having a small for GA (SGA) baby or a low BW infant in white color workers in Finland compared to women from the lowest socioeconomic group [49].

A comparison of two care models, i.e., the maternity health clinic and an integrated care model with a combined maternity and child health clinic, were done recently on the basis of the Finnish Medical Birth Register [50]. Both models showed equally good results concerning perinatal health outcomes. That study demonstrates the capacity of any birth registry of high quality to be used for organizational aims to improve existing practice on the basis of a scientific approach.

The Icelandic Medical Birth Register

Similar to other birth registries in the Nordic Countries, the Icelandic Medical Birth Register is a population-based registry. Established in 1972, it covers all births in Iceland since 1972 and onwards [51]. It is widely used in linkage with birth registries in the other Nordic countries [52].

In a study of pregnancy-induced hypertensive disorders in 2005–2012, no changes in prevalence were observed for preeclampsia. Statistically significant

increase in prevalence of gestational hypertension has been demonstrated in the first year following the 2008 economic collapse in Iceland [51]. In contrast, favorable years of national economy (2005-2006) were accompanied by the highest prevalence of maternal obesity and smoking. In subsequent years, cigarette smoking decreased during pregnancy, whereas the prevalence of obesity remained unchanged [8].

Birth registries in other European countries

Many European countries have their national birth registries. Austria, Cyprus, Czech Republic, Estonia, Italy, Germany, Malta, the Netherlands, Luxembourg, Latvia, Lithuania, Slovak Republic, and Slovenia have medical birth registries for perinatal health monitoring [53]. Despite some differences in content (the set of variables), these databases are similar. The EURO-PERISTAT project combined data on perinatal health from 26 European countries to monitor perinatal health in Europe. It concluded that the coverage of the European birth registries is good and that there is a possibility to link data from birth registries to death certificates to obtain information about children's deaths that occur after they have been discharged from hospital [53].

1.2 The linkage between birth registries and other registries in the Nordic countries

The Nordic countries with their total population of 25 million [52] have a set of other population-based registries besides their national medical birth registries. In Denmark, for example, the Danish Cancer Registry was founded in 1942 [54], the Danish Pathology Register started in 1997 and covered all pathological specimen data in Denmark [55]. Additionally, the Danish National Patient Register was implemented in 1977 and records data on all people hospitalized in Danish hospitals [56].

One additional registry, the Danish National Birth Cohort, contains nationwide data during 1996-2002 on pregnancies and long-term follow-up of their outcomes

[31]. Its primary aim was to investigate the early life origin of cardiovascular diseases, asthma, cancer, allergy, and mental disorders [31]. The Danish National Birth Cohort is considered valuable for reproductive epidemiology as it includes information on different exposures in pregnant women [30]. This database does not substitute the existing national birth registry but provides additional information. The Danish National Birth Cohort linked to data obtained from a food-frequency questionnaire shows an association between artificially sweetened soft drinks and increased risk of PTB [57].

In 1997, there were more than twenty different registries in the Nordic countries that could be linked to the national birth registries [4]. These registries are linkable at the individual level because of the unique identification number given to all residents. This identification number ensures identification of the person, makes it possible to gather information on the same person in different registries [58], and facilitates statistical use of the data. Nowadays, possible linkage between national birth registries and other registries provides possibilities for further investigations in perinatal epidemiology. Common or compatible format of data records facilitate research collaboration and exchange of data within and between the Nordic countries.

Combined data on births, hospital records, causes of death, cancer diagnoses, and prescribed drugs are recorded in different national registries in the Nordic countries. Recently combination of such data was used to investigate the risks of congenital birth defects and other complications in relation to maternal medication [52]. Collecting biological samples together with birth registry data also provides new perspectives in registry-based studies. Cooperation between Denmark and Norway in research using registry-based records, questionnaires and interview data as well as samples from biobanks can be useful to obtain information on existing and suggested health challenges in children and their parents [6].

The comparison of data from the Finnish Medical Birth Register and in vitro fertilization data in Finland in 1996–1998 provided better accuracy in recording

major congenital anomalies in the Finnish Medical Birth Register [59]. At the same time, information on in vitro fertilization was missing in almost one-fourth of such babies in the national birth registry [59]. So far, the linkage of the birth registry to other data sources can be used to assess the quality of registries. In Finland, the Medical Birth Register is closely linked to the Register on Congenital Anomalies and Birth Defects that is widely used in scientific research [18].

Birth registration practices as well as data collection and recording must be of good quality to provide an opportunity to compare data within and between countries without concerns. International comparisons of infant mortality in the United States, Canada, and the Nordic countries demonstrate differences in birth registration practices. Post-neonatal mortality is higher in Canada and the United States compared to Finland. The latter could partly be explained by differences in the birth registration systems as well as GA assessments. High prevalence of PTB and its risk factors in Canada and the United States was also suggested as contributing factor to post-neonatal mortality [60].

1.3 Birth registration system and birth registries in the Russian Federation

Birth registration system and hospital records

Birth registration is a system of recording an infant's birth. It is the responsibility of the administrative institution, whose activity is coordinated by a government [61]. The birth record confirms a child's existence. According to the Russian legislation (Federal law N 317-F3, 25.11.13), all live born babies must be included in the official birth registration system up to one month of their life. No personal identification numbers are used in the Russian Federation. Furthermore, the birth registration system carries limited information about the infant and does not contain any medical information. Data on the date and place of birth as well as information about parents are presented in the birth certificate. It cannot be used in research without linkage to other valuable sources of information.

Hospital records can be used as the only source of information or combined with other databases. Not only medical records ("medical histories") of

hospitalized infants and pregnant women but also hospital discharge records can be used. Studies based on these records are usually limited to one delivery hospital.

In the city Severodvinsk located in Arkhangelsk County which neighbors Murmansk County, maternal low education [62], smoking, alcohol abuse, living in poor conditions, and perceiving stress [62, 63] associate with lower infant BW.

Tula birth and perinatal death records

In 2000, data on all births and perinatal deaths in Tula County in Middle Russia were included in a database for further analyses of the association between selected risk factors and adverse perinatal outcomes. Altogether, data on 11 172 births were included between January 1 and December 31, 2000 [64]. PM rate was 16.8 per 1 000 births. Maternal low education level as well as being single increased the risk of low BW in infants. Mean BW was also lower in non-ethnic Russians compared to ethnic Russians [64]. The same database was used to demonstrate a considerable variation in the prevalence of cesarean section (3.3-37%), amniocentesis, and episiotomy between hospitals. Discrepancy in equipment availability could contribute to such differences [65].

The Kola Birth Registry

The Kola Birth Registry contains data on 96% of all births with GA ≥28 weeks during 1973-1997 in the city Monchegorsk in Murmansk County, Northwest Russia. A total of 21 214 births were recorded in the registry and data were collected retrospectively [66, 67]. During this time, PM in Monchegorsk decreased two-fold and was lower compared to the overall PM in Russia [66]. Another study based on the Kola Birth Registry found that unmarried mothers were at higher risk of delivering preterm and lighter infants compared to married women. Mother's occupation influenced her infant's BW [68]; unemployed or housekeeping women were at higher risk of SGA birth [69].

In a study of the prevalence of risk factors for selected adverse pregnancy

outcomes, high proportion of pelvic inflammatory disease, as well as spontaneous and induced abortions was detected in Monchegorsk. There was lower prevalence of heavy smoking, obesity, and diabetes compared to Norway [70].

Monchegorsk is an industrial city and a nickel refinery is located nearby. There is a concern regarding possible toxic effect of nickel on offspring of those women who are exposed to nickel during work. In 2007, a study based on data from the Kola Birth Registry did not show any contribution to SGA birth of nickel exposure during the first half of pregnancy [69]. However, the effect of water-soluble nickel exposure on the fetus later in pregnancy could not be excluded. Maternal exposure to nickel during pregnancy did not increase the risk of genital malformations in fetuses irrespective of gender [67].

The Murmansk County Birth Registry

In contrast to the well-established medical birth registries in the Nordic countries, the Murmansk County Birth Registry (MCBR) has a short history [71]. The MCBR is the first population-based prospective medical birth registry in the Russian North. Its description is presented more in Section 3.1 of this thesis. To date, several MCBR-based studies have been conducted. The prevalence of PTB was higher in Murmansk County compared to Northern Norway (8.7% versus 6.6%). In Murmansk County, term infants were at higher risk of PM compared to the reference group of corresponding GA from Northern Norway. Overall PM determined by data from the MCBR was almost 1.5-fold higher compared to data from Norway [72].

A recently published study of smoking among pregnant women demonstrates that one-fourth of these women quit smoking and one-third reduce the number of daily cigarettes during pregnancy [73]. Underweight and obese women are at increased risk of spontaneous PTB. Overweight and obesity in early pregnancy associate with increased risk of very PTB [74].

Linking the MCBR and the Kola Birth Registry provides an opportunity to investigate changes in health care in Northwest Russia. A five-fold decrease in

PM during 1973-2011 in infants with any birth defect was explained by improved prenatal detection of severe malformations during ultrasound examination which resulted in pregnancy termination [75]. In Monchegorsk, an increase from 0.2 to 19.1 per 1 000 births in the prevalence of urinary tract defects was found [76]. There was an association between infections, use of medications during pregnancy, pre-pregnancy diabetes mellitus, gestational diabetes and congenital malformations of the urinary tract [77].

1.4 The role of birth registries in studies of risk factors of adverse pregnancy outcomes

Birth registries are widely used worldwide to investigate risk factors of adverse pregnancy outcomes [78, 79]. A summary of data on registry-based studies that have investigated risk factors of PM, PTB, and SGA births are presented below.

Studies on risk factors for perinatal mortality

Women with a reproductive history of repeated PTB exhibit increased risk of PM [78]. In Scotland, mothers who delivered a preterm SGA infant during their first pregnancy were at five-fold risk of unexplained stillbirth during subsequent pregnancies [80]. Similar results have been described in a nationwide Swedish study [81].

   A study that combined the births in 955 804 women in Norway and Sweden during a 20-year period shows that women aged >30 years and/or who were overweight or obese are at higher risk of fetal death [82]. In Norway, post-term SGA infants have increased risk to die during the perinatal period [83].

   In Tanzania, long interpregnancy interval (>3 years) was associated with increased risk of PM [84]. These data correspond to results of a Swedish study that confirms the association between long interpregnancy interval (≥72 months) and increased risk of stillbirth, whereas the association between long interpregnancy interval and early neonatal mortality was not significant [85].

   In a study based on the England Multiple Pregnancy Register, monochorionic

twins have increased risk of perinatal death compared to dichorionic twins. The observed phenomena can be explained by a high rate of stillbirth in monochorionic twins [86].

The Estonian Medical Birth Registry was also used to investigate PM risk factors. Aged women (≥35 years), smokers and single mothers had increased risk of PM. Multiple births were associated with higher PM [87].

Studies of preterm birth

In Tanzania, a birth registry-based study demonstrates that previous PTB increases the risk of PTB by 17% during the current pregnancy [78]. Furthermore, there is an association between an interpregnancy interval less than 2 years or over 3 years and increased risk of PTB and delivery of low BW babies [84].

A Finnish Medical Birth Register-based study demonstrated that the contribution of smoking to socioeconomic disparities in extremely, very and moderate PTB was higher compared to the impact of selected medical (reproductive) risk factors [88].

Recently, a study based on the Medical Birth Registry of Norway demonstrated an association between maternal low education, single marital status and PTB. Asia-born women are at higher risk of PTB compared to ethnic Norwegians [89]. These data are consistent with a previous study that demonstrated increased risk of PTB in women from the lowest socio-economic group. The observed association remained unchanged during an 18-year period [90]. Combined registry-based data during 1981-2000 from Norway, Denmark, Finland, and Sweden show socio-economic inequalities in PTB; maternal lower education associates with increased risk of very and moderate PTB in all four countries [91]. National birth registries were also used in a study of maternal low education as a risk factor of stillbirth. Educational inequalities in stillbirth were found in all four Nordic countries [92].

A study based on data of the Swedish Medical Birth Register demonstrated an association between maternal overweight and obesity and increased risks of PTB.

Compared to normal-weight women, mothers with body mass index (BMI) of >40 have three-fold higher risk of extremely PTB [79]. Another study from Finland confirms higher proportion of preterm babies among overweight and obese mothers. Further during infancy, these babies are at a higher risk of mortality [93]. In a population-based retrospective cohort study in the USA, underweight women with poor weight gain during pregnancy and short interpregnancy interval had increased risk of PTB [94].

In Australia, a population-based study of 393 450 women showed 1.5-fold higher PTB rate among mothers giving birth after assisted reproductive technology compared to women with singleton pregnancies without such technology [95].

In the USA, the Missouri Department of Health's birth registry was used to study the contribution of paternal and maternal race to PTB. Infants of nonwhite parents have highest risk to be delivered preterm [96]. The American cohort of 2 845 686 singleton births was used in another study that addressed the impact of paternal race on PTB. In that study, paternal black race increased the risk of PTB irrespective of maternal race [97].

Studies of small for gestational age birth

In Sweden, aged mothers, women with low height, smokers, those who have had pre-eclampsia and essential hypertension as well as low pre-pregnancy BMI are at higher risk of term SGA birth [98]. The same risk factors, except low BMI, associate with increased risk of moderate preterm SGA birth. Low maternal education contributes to preterm SGA birth [98]. Another study in Sweden, based on registry data, found that maternal smoking in early pregnancy associates with term SGA birth. Quitting smoking in early pregnancy contributes to greater reduction of risk compared to quitting smoking in late pregnancy [99]. In Finland, a registry-based study also found that quitting smoking during the first trimester of pregnancy results in decreased risk of SGA births to the level comparable with non-smokers [100]. Low family income as well as maternal occupation (electric,

wood, textile workers, mechanics, and iron and metalware workers) associated with increased risk of SGA [101].

In Denmark, data from the national birth registry demonstrate that chronic hypertension, maternal smoking, underweight, and time to planned pregnancy over 12 months all increase the risk of both term and preterm SGA birth. Young (<20 years) and older (>36 years) mothers as well as those who had multiple previous spontaneous abortions in early pregnancy are at higher risk of preterm SGA [102].

1.5 Background and motivation for the thesis

To date, limited information on risk factors for adverse pregnancy outcomes is available in Northwest Russia. Official general information is annually published by the Federal State Statistics Service of the Russian Federation via its website (http://www.gks.ru). Individual information is not provided and cumulative data on maternal and infant health are collected through an established form ("form N32"). Delivery hospitals are annually required to fill out this form and to send it to the regional Ministry of Health. The latter presents regional perinatal statistics in its regular reports. Most of the information is descriptive. Data on perinatal events including stillbirth and perinatal death are also available. Available selected indicators in Murmansk County and the Russian Federation in 2006, the year the MCBR was implemented, and in 2014, the year of the latest available MCBR data, are presented in Table 1. The population of Murmansk County decreased during 2006-2014, whereas the number of births during this period increased.

Table 1. Data on population size and pregnancy outcomes in the Russian Federation and Murmansk County in 2006 and 2014 [103-105].

Indicators	2006		2014	
	Russian Federation	Murmansk County	Russian Federation	Murmansk County
Population	142 862 700	864 000[1]	146 267 300	766 381[3]
Births	1 479 637	8 455	1 942 683	9 017
Preterm births	46 000		76 700	
Preterm live born infants	78 000		111 100	
Perinatal deaths	14 238	66	17 228	66
Perinatal mortality rate (per 1000 live births and stillbirths)	9.57	7.77	8.81	7.28
Stillbirths	7 934	38	11 769	43
Stillbirths (per 1000 live births and stillbirths)	5.33	4.47	6.02	4.75
Early neonatal deaths	6 304	28	5 459	23
Early neonatal deaths (per 1000 live births and stillbirths)	4.24	3.30	2.81	2.55

[1] Data on January 1, 2007 [104]

In the Russian Federation, increase in PTB, perinatal death, and stillbirth can be partly explained by a change of perinatal statistics in Russia. Since 2012, perinatal deaths cover late fetal deaths of 22 or more weeks and infant deaths within the first 7 days of life [106]. In both 2006 and 2014, the number of stillbirths was higher compared to early neonatal death both in the Russian Federation and in Murmansk County. Available data on female population size, pregnant women age, and

pregnancy and childbirth complications in the Russian Federation and Murmansk County are presented in Table 2.

Table 2. Female population size, pregnant women age, and pregnancy and childbirth complications in Murmansk County and the Russian Federation in 2006 and 2014 [103, 105].

Indicators	2006		2014	
	Russian Federation	**Murmansk County**	**Russian Federation**	**Murmansk County**
Female population	76 810 947		78 495 564	
Female aged 16-54 years	44 083 564		40 997 945	196 524[1]
Women with pregnancy and childbirth complications	2 519 000		2 801 300	814[2]
Live births to unmarried women, proportion in total number of births	29.2	29.9	22.2	21.8
Live births per 1000 females at age, years				
15-19	28.6	24.2	26.0	22.8
35-49	21.9	18.8	47.5	42.6
Live births to mothers aged at 17 and under	34 916	162	20 017	85
Average age of women with live births in the current year	26.6		28.1	

Table 2 continued

Number of diseases in pregnant women, per 1 000 births			
Anemia	260	235	21.2[3]
Edema, proteinuria, and arterial hypertension	20.8	14.6	14.7[3]
Diabetes mellitus	0.2	1.3	3.0[2]
Urinary and genital systems disorders	21.3	17	

[1] Females aged 15-49 years (from annual report of the regional Ministry of Health in 2013, unpublished data)

[2] Number per 1 000 births (from annual report of the regional Ministry of Health in 2013, unpublished data).

[3] Proportion of all pregnant women. Data on 2013. Annual report of the regional Ministry of Health in 2013 (unpublished data).

There is an increase of pregnant women with diabetes mellitus in Russia. In Murmansk County, the number of mothers who had this disease was twice as high compared to data from Russia. From 2006 to 2014, the proportion of aged mothers both in Russia and Murmansk County increased more than two-fold. Data on women with pregnancy and childbirth complications (814 person per 1 000 births) taken from the unpublished annual report of the regional Ministry of Health in 2013 require further analysis. Available data on live births and multiple births in the Russian Federation are presented in Table 3.

Table 3. Live births and multiple births in the Russian Federation in 2006 and 2014 [104, 107].

Indicators	Russian Federation	
	2006	**2014**
Live births	1 457 376	1 942 683
Twin births	11 156	21 926
Triplets	142	464

Since 2006, a two-fold increase in multiple births in the Russian Federation has occured. This fact also needs further analysis but a possible explanation is a true increase in both twins and triplets in Russia and a change of birth registration and perinatal statistics in the country. Increased use of artificial reproductive technologies in Russia should be taken into account [108].

The MCBR collects individual information on different socio-demographic, lifestyle and medical risk factors [71] and thereby provides sufficient information to conduct detailed risk factors analyses. Identification of risk factors may help to develop new as well as improve existing intervention strategies in perinatal medicine and public health in Northwest Russia.

Before planning health care system interventions and develop new standards and guidelines for maternal, perinatal, and neonatal care such a study has to be undertaken. This thesis therefore addresses the prevalence and selected risk factors of adverse pregnancy outcomes, i.e., PTB, PM, and SGA birth in Murmansk County.

2 AIMS OF THE THESIS

The overall aim of this thesis was to investigate associations between selected risk factors and adverse perinatal outcomes.

Specifically I wanted to:

- Explore associations between selected maternal and fetal characteristics and PM based on data from MCBR (Paper I).

- Estimate the prevalence of PTB in Murmansk County and to investigate associations between selected maternal factors and PTB (Paper II).

- Examine maternal social risk factors for term SGA births (Paper III).

3 MATERIAL AND METHODS

3.1 Data source

The Murmansk County Birth Registry

The MCBR was established in 2006 in Murmansk County, Northwest Russia (Fig. 1). Murmansk County is one of the largest counties in Northwest Russia; its territory is 144 900 km^2 [109]. In 2015, it had 766 281 inhabitants, 92.6% of them comprise the urban population with a mean age of 38.6 years [105]. Russians represent the major ethnic part (89%) of the population; Ukrainians and people of other nationalities comprise less than 5% [110]. Murmansk is the administrative center with a population of 336 137 inhabitants [109]. The County has 16 cities, 12 "urban type" villages and 112 rural settlements [111]. Metallurgy, marine transportation, fishing industry, and electric power-production are the leading industries in Murmansk County. Nickel, apatite concentrate, copper, and cobalt production contribute to export-oriented economy of this natural resource-rich County. Different minerals are concentrated in 60 big deposits on the Kola Peninsula [112].
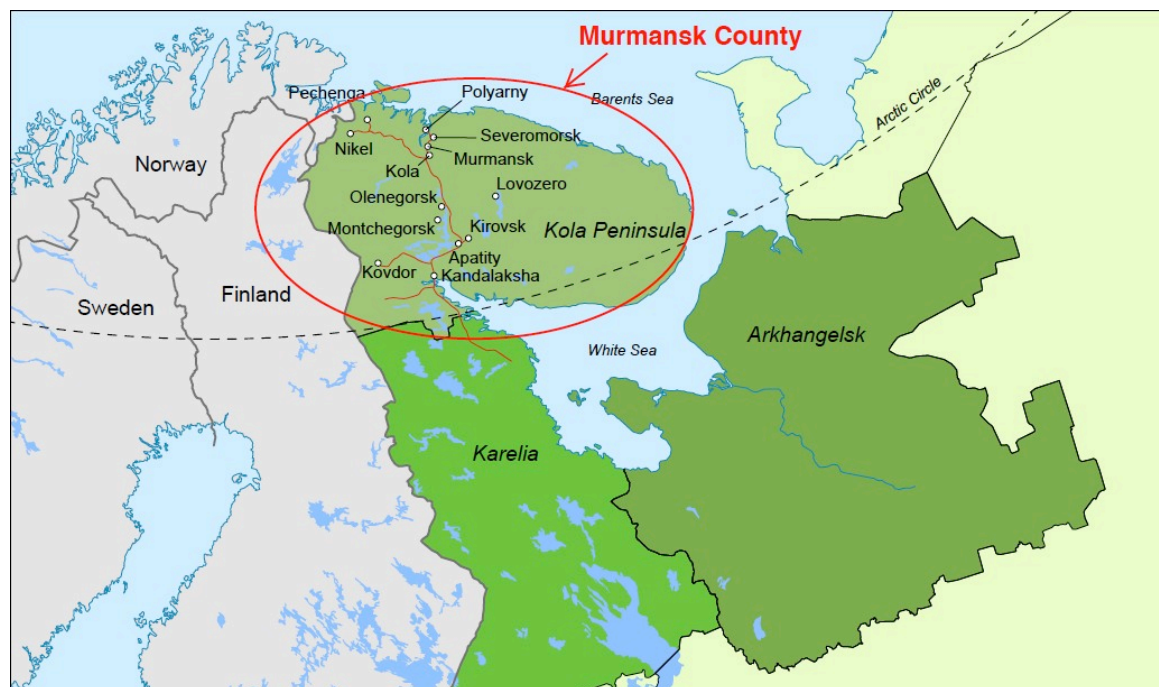

Figure 1. Barents Region map with Murmansk County.

In 2013, the birth rate and motrality rate in Murmansk County comprised 11.8 and 11.0 per 1000, respectively. Cardiovascular diseases and cancer continue to be the leading causes of mortality among the adult population [111].

About 8 500-9 000 births are registered each year in Murmansk County. The implementation of the MCBR described in detail in a set of previous publications [71, 72, 74-76]. The registration form of MCBR includes information from the medical history of pregnancy and delivery and history of the newborn. It also contains information on all births, including stillbirths, from 22 weeks of gestation. Individual socio- demographic characteristics of mothers, maternal health status before and during pregnancy, selected interventions during pregnancy and delivery are registered in a standardized registration form and merged in the registry [71]. The compatibility of the MCBR with birth registries in countries of the Barents region, for example the Medical Birth Registry of Norway, provides a unique opportunity for researchers to make comparisons between countries and to increase the power of studies that explore the nature of rare diseases.

3.2 Study population

The initial study population in this thesis included all live- and stillbirths registered in MCBR from January 1, 2006 to December 31, 2011 (n = 52 806). Different exclusion criteria were applied for Papers I-III. Structure of the thesis is presented in Figure 2.

For Paper I, multiple births (n=457), infants with congenital malformations (n=1 471), births with missing data on GA (n=536), and births prior to 22 and after 45 completed weeks (<154 and >315 days) of gestation (n=1 202) were excluded. Finally, 3 666 births were excluded from the initial population to estimate the prevalence of PM in 49 140 single births. Next, 2 356 records with missing data on studied independent variables or potential confounders were excluded to perform further risk factors analyses. The final study sample in Paper I included 46 784 births.
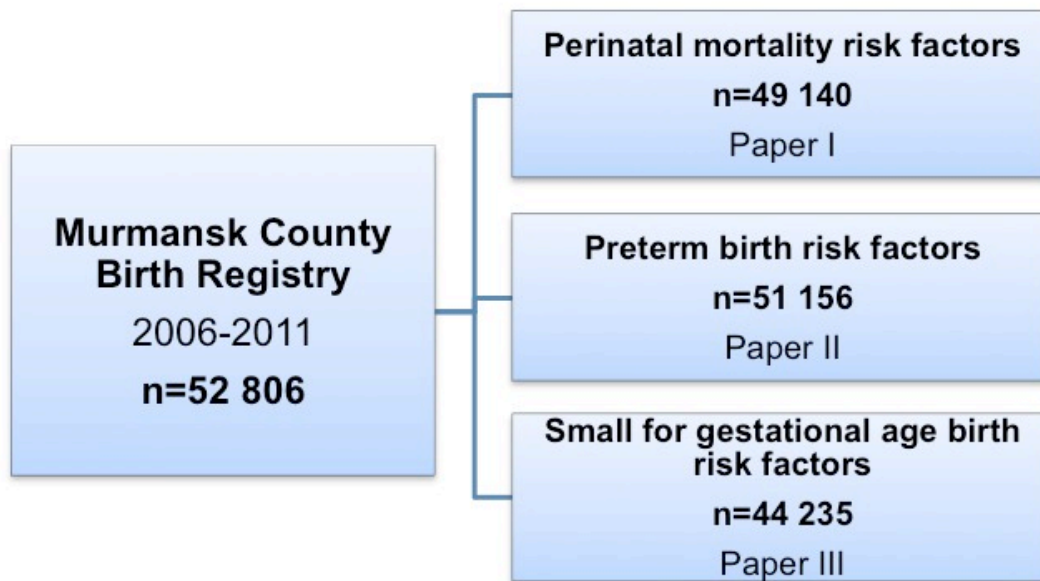
Figure 2. Structure of the thesis. Populations eligible for studies of PTB, PM and SGA births are described in Section 3.2.

In Paper II, multiple births, births with missing information on BW or GA, and births with GA <154 and >315 days (in total 1 564 births) were excluded. After this, both Tukey's methodology [113], a method used by Alexander et al. [114], growth charts for preterm infants [115] as well as clinical opinions were applied to exclude extreme outliers (104 births) at GA 22-32 weeks. In total, 51 156 births were included for prevalence analysis of PTB. Births with missing data on studied independent variables and potential confounders were further excluded from the study population for Chi-squared testing and logistic regression analyses.

In Paper III, 8 571 births with missing data on BW, birth length (BL), GA, and missing or unknown infant sex were excluded. A total of term 44 235 births were included in the prevalence analyses of SGA births with infant's BW<10th percentile (SGA$_W$) and SGA births with infant's both BW and BL <10th percentile (SGA$_{WL}$) births. The final study sample included 42 239 births as 1 996 births with missing data were also excluded in further logistic regression analyses.

Gestational age assessment

The MCBR started in 2006. For different reasons, including inaccessibility of ultrasound examination for pregnant women in Murmansk County, there were no records on ultrasound–estimated GA before January 1, 2009. Data on the last menstrual period (LMP) were recorded in the MCBR database. In Paper I, perinatal mortality risk factors were studied and GA was determined based on LMP. There were 1 251 women with missing LMP data. From those 1 251 women, 536 had no data on first trimester ultrasound and therefore, were excluded from the further analyses. Hoffman et al. showed a correspondence between first trimester reported LMP and first trimester ultrasound GA estimations [116].

In Papers II and III, ultrasound dating recommended as reliable accurate method [117] was used. In MCBR, data on ultrasound were not available in 4 001 births and for those births GA was therefore determined based on LMP.

In total number of 52 806 births in the MCBR, there are 25 206 available records on GA, at which first ultrasound examination was performed. In 1 982 pregnancies, the first ultrasound examination was done during the second and the third trimesters. More precisely, 1348 and 634 pregnancies were estimated at GA 22-27 completed and 28+ weeks, respectively. Ultrasound dating during second trimester is less accurate compared to that performed in the first trimester; its accuracy is ±10-14 days [118]. After 28 weeks of pregnancy, discrepancy between ultrasound dating and LMP dating can reach 21 days [117]. Recently, new approach with accuracy of ≤ 9 days was offered to estimate GA based on ultrasound fetal measurements between 14 and 22 weeks [119]. It makes ultrasound dating at these GA more accurate than it was before.

At the same time, ultrasound dating does not completely exclude errors in GA estimation. Ultrasound and LMP dating are not completely independent from each other, as LMP is usually used to define time of the first ultrasound examination [120]. Misclassification of GA estimated by LMP may be caused by postconceptual bleeding at the time of the next menstrual period [121].

3.3 Outcome variables

In Paper I, PM was used as dependent variable. PM was defined as number of deaths per 1 000 births of fetuses weighing ≥500 g or born at 22 completed weeks of gestation with unknown BW, and newborns up to 7 completed days after delivery [1].

In Paper II, PTB was defined as birth at GA ≥22 completed weeks of gestation and before 37 weeks. Respectively, extremely PTB, very PTB, and moderate-to-late PTB were considered as PTB during 22-27, 28-31, and 32-36 weeks of gestation.

In Paper III, SGA was used as a dichotomous outcome variable. For BW or both BW and BL for each week of GA between 37 and 41 tenth percentile was used to determine, SGA_W and SGA_{WL} births, respectively.

3.4 Independent variables and potential confounders

Maternal socio-demographic and lifestyle characteristics, pre-pregnancy, pregnancy and infant characteristics were treated as independent variables and potential confounders. The set of exposure variables varied in Papers I-III. Most of these were used as categorical variables; maternal age (<18, 18–34, ≥35 years); education (none or primary [grade 1-9], secondary [grade 10-11], vocational school, higher); cigarette smoking and evidence of alcohol abuse during pregnancy (yes/no). Civil status was categorized as single, married, and cohabiting. In Paper II, the first category included divorced and separated women. WHO classification was used to define four groups of maternal BMI: underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5-24.9 kg/m^2), overweight (BMI = 25-29.9 kg/m^2), and obese (BMI ≥ 30.0 kg/m^2). All women were categorized as primipara or multipara. Previous PTB, previous spontaneous and induced abortions, diabetes mellitus or gestational diabetes, fetal growth retardation, and birth defects were treated as dichotomous variables. In Paper III, maternal occupation and place of residence were categorized as urban/rural and

unemployed/employed, respectively. The last category included students and pupils.

3.5 Data analyses

In Papers I-III, Chi-squared tests were initially used to assess differences in distribution of selected risk factors in birth groups with and without the studied adverse pregnancy outcome (PM, PTB, and SGA in Paper I, II, and III, respectively). A set of maternal characteristics (socio-demographic, lifestyle, pre-pregnancy, and pregnancy) was different for Papers I-III and depended on the aim of each individual Paper. Paper II, aimed to investigate PTB risk factors, also included infant characteristics (birth defects).

In Paper III, the regression models with both outcomes, SGA_W and SGA_{WL} births, were checked for multicollinearity. The effect of multicollinearity was not found. Interactions between all variables in the regression models with both SGA_W and SGA_{WL} births taken as outcomes were also checked. Two interactions were found significant: an interaction between smoking and education in a model with SGA_W as an outcome dependent variable and interaction between maternal age and employment in the model with SGA_{WL} as a dependent variable. Therefore, categories smoker/non-smoker for each category of education in the final regresion models for SGA_W birth for boys and girls were utilised. Categories employed/unemployed women in each of three maternal age groups were applied in regression analyses for risk factors of SGA_{WL} births for both sexes.

Binary logistic regression was used to estimate the effect of variables selected for analysis on definite pregnancy outcomes. Possible associations between selected characteristics and studied outcomes were investigated further by multivariable logistic regression. Crude and adjusted odds ratios (ORs) with 95% confidence intervals were calculated for the studied risk factors. ORs, determined by logistic regression, were considered as proxy estimates of relative risks as the prevalence of all studied outcomes was low. All statistical analyses were

performed using SPSS Statistics for Macintosh, Version 23.0 (IBM Corporation, Armonk, NY, USA, 2015).

3.6 Ethical approval

The studies presented in this thesis were approved by the Ethical Committee of Northern State Medical University, Arkhangelsk, Russia (Protocol 04/5-13) and the Regional Committee for Medical and Health Research Ethics in Northern Norway (2013/2300 REK nord). The MCBR registration forms do not contain personal identifiers such as names, surnames, addresses, and phone numbers. Health information in the MCBR is confidential and therefore no personal consent was required.

4 MAIN RESULTS

This section presents the key results of the thesis based on the three individual papers. For a more detailed description, please refer to the individual papers at the end of this thesis.

4.1 Paper I: Risk factors for perinatal mortality in Murmansk County, Russia: a registry-based study.

From January 1, 2006 to December 31, 2011, MCBR registered 466 perinatal deaths in Murmansk County, which resulted in overall PM 8.8 per 1 000 births. After the exclusion criteria application, there were 338 perinatal deaths among the 49 140 births, yielding a PM of 6.9 per 1 000 births.

Low education level, unmarried status, prior PTB, prior spontaneous and induced abortions, antepartum hemorrhage, antenatally detected or suspected fetal growth retardation, overweight or obesity, and alcohol abuse remained statistically significant factors for PM after controlling for other variables in the model. Low maternal BMI was associated with reduced risk of PM.

The largest proportion of perinatal deaths (42.9%) was among infants with a BW of <1 500 g. In bivariate analysis, the risk of PM among babies with a BW of 1 500-2 499 g was 17-fold higher compared to infants with a BW of 2 500-4 000 g. Heavy fetuses and newborns were not at increased risk of PM.

As congenital malformations and multiple births are well known health conditions predisposing to perinatal death [122], PM in 1 471 singleton infants with congenital malformations and in the 457 multiple births that were initially excluded from the analysis was also estimated. Thirty-one infants with congenital malformations died in the perinatal period which accounted for PM of 21.1 per 1 000 births. This was almost three-fold higher compared to PM in the original study sample in Paper I. Among 918 babies born in 457 multiple births, 47 perinatal deaths occurred; PM therefore was 51.2 per 1 000 multiple

births. Perinatal deaths of babies from multiple pregnancies contributed 10.1% of all PM. Twenty-five infants (53.2% of PM in multiple births) were stillborn, 27 deaths occurred among second infants.

4.2. Paper II: Maternal risk factors for preterm birth in Murmansk County, Russia: a registry-based study.

The overall prevalence of PTB was 6.9% during 2006-2011. There was a statistically significant downward trend in PTB rate; for these years it was 7.6, 6.9, 6.9, 7.1, 6.7, and 6.4%, respectively. The proportions of extremely, very and moderate-to-late PTB were 0.3, 0.6 and 6.0%, respectively.

Compared with term births, all three PTB groups demonstrated higher proportions of unmarried mothers, women with low educational level, smokers, overweight and obese women, and mothers with alcohol abuse as well as women suffering from diabetes mellitus and gestational diabetes. Compared with term births women who delivered preterm infants demonstrated higher proportions of such previous adverse pregnancy's outcomes as PTBs and spontaneous or induced abortions. Almost every ninth woman from the extremely PTB group had one or more multiple PTBs in her medical history. Diabetes mellitus and gestational diabetes were also higher in all PTB groups when compared with term births.

Young (<18 years) and aged (≥35 years) women were at increased risk of moderate-to-late PTB compared with women aged 18-34 years. Lower education, alcohol abuse, smoking, single status, underweight or overweight and obesity as well as diabetes mellitus and gestational diabetes all contributed to increased risk of moderate-to-late PTB. Women with prior PTBs, prior spontaneous and induced abortions in their reproductive history were also at higher risk of moderate-to-late PTB.

Women with secondary education had higher risk of very PTB compared with university-educated mothers. Single mothers as well as women with alcohol abuse and diabetes mellitus and gestational diabetes demonstrated an increased risk of

very PTB. Prior pregnancy adverse outcomes (prior PTBs, prior spontaneous and induced abortions) also increased the risk of very PTB. None or primary education increased the risk of extremely PTB. Single mothers as well as cohabitant were at higher risk of PTB. Prior PTBs and prior abortions (both spontaneous and induced) were also significantly associated with extremely PTB in the study.

4.3 Paper III: Social correlates of term small for gestational age babies in a Russian Arctic setting.

Different criteria of SGA births were applied; accordingly, 4.1% and 9.7% of all births were classified as SGA_{WL} and SGA_W, respectively. Boys were heavier than girls at each studied GA. At 38-39 weeks of gestation the 10th percentile for BL in boys was higher compared with girls. More SGA_{WL} girls were born compared with SGA_{WL} boys at GA of 37, 40, and 41 weeks.

Compared with non-SGA births, both the SGA_{WL} and SGA_W birth groups had higher proportion of young, single mothers, women with low educational level, smoking, unemployed and underweight women, as well as mothers with evidence of alcohol abuse. Proportions of overweight and obese women were less in both SGA_{WL} and SGA_W babies compared with non-SGA_{WL} and non-SGA_W infants. Maternal rural residence was higher in SGA_{WL} compared with non-SGA_{WL} births.

After adjustment for studied variables and potential confounders, low educated, unmarried, underweight, or smoking women had an increased risk of SGA_{WL} births compared with the corresponding non-SGA_{WL} group. Unemployment was associated with increased risk of both SGA_W and SGA_{WL} births. Those with evidence of alcohol abuse were at increased risk of birth of SGA_{WL} and SGA_W boys. Low educated smoking women with lower education were at high risk to deliver SGA_W boys and girls. Maternal overweight and obesity were associated with lower risk of both SGA_{WL} and SGA_W births compared with normal weight mothers.

5 DISCUSSION

5.1 Discussion of main results concerning risk factors of adverse pregnancy outcomes

5.1.1 Perinatal mortality

This thesis applied the WHO definition of PM, i.e., perinatal death is considered as death of a fetus at 22 weeks of gestation and more or death of a newborn during the first seven days of life [1]. Hereby risk factors for PM were investigated in this thesis without separating them specifically into risk factors for stillbirth and early neonatal mortality. A similar approach has previously been applied in other studies [78, 83, 84, 123]. To date, it is known that some factors contribute to higher risk of stillbirth or fetal death [33, 80, 81, 85, 92, 124, 125], whereas others are risk factors of early neonatal death [85, 126]. For instance, a long interpregnancy interval associates with stillbirth but does not increase the risk of a babies' death up to the 7th day of life [85]. Studies that specifically investigated risk factors of early neonatal death show that inadequate antenatal care, the presence of thick meconium staining in the amniotic fluid, male sex, BW <1500 g [127] as well as low GA at birth [127, 128] increase the risk of a babies' death during the first week of its life. Studies investigating stillbirth risk factors underline contribution of fetal growth retardation to stillbirth [125, 129]; fetal growth retardation two-folds increases the overall rate of stillbirth [125].

Socio-demographic and lifestyle factors
The findings in this thesis correspond to the results of a recently published birth registry-based study conducted in Sweden and Norway that confirms high risk of fetal death in overweight and obese mothers [82]. In England, a large cohort study with 92 218 singletons showed 1.6-fold increased risk of stillbirth in obese women [125]. This thesis showed that overweight and obese women had 1.4-fold higher risk of PM compared to women with normal weight.

Low education is a known risk factor of poor perinatal outcome including perinatal death [64, 130]. This thesis demonstrates a two-fold higher risk of PM among women who had either none or primary education. Furthermore, unmarried women exhibited increased risk of PM which corresponds to findings from other studies [131, 132]. Both low maternal education [62, 64] and unmarried status [64] contribute to increased risk of lower BW. In this thesis, mean BW in PM group was lower compared to group without PM. One could speculate that low education and unmarried status could be associated with PM via a babies' weight. Indeed in Finland, a birth registry-based study showed that certain maternal risk factors such as single marital status, low socioeconomic status, smoking during pregnancy, nulliparity, in-vitro fertilization, prior stillbirth, advanced maternal age, and maternal insulin-dependent diabetes mellitus contributed to low BW in babies, thereby influencing increased PM [132].

In this thesis, the results of bivariate analyses demonstrated 1.6- and 4.4-fold increased risk of PM in smokers and women with alcohol abuse, respectively. Both smoking [133] and alcohol consumption [134] associate with PM or stillbirth and the contribution of smoking [133] and alcohol [135] to low BW is known. Therefore, the lack of statistical significance in association between smoking and PM in multivariable logistic regression (Table 4 in Paper I) may be explained by influence of smoking on PM through reducing infant BW. Underreported prevalence of smoking may also contribute to the lack of statistical significance in this thesis. In 1971, Yerushalmy found lower PM in low BW infants born by smokers compared to PM in non-smoking mothers. He suggested that not maternal smoking but other characteristics of pregnant women increased the risk of perinatal mortality [136]. His suggestions were widely criticized later [137]. Wisborg et al. showed increased risk of stillbirth in smoking women after adjustment for potential confounders [138]. Recently published results of meta-analysis confirmed the association between active maternal smoking and both stillbirth and perinatal death [139]. Ananth and Platt

concluded that the the effect of smoking on neonatal mortality was mediated through reduction of fetal growth and shortened duration of gestation [140]. In this thesis, strong association between antenatally detected/suspected fetal growth retardation and PM was found. The effect of interaction between maternal smoking and fetal growth retardation showed by others [125] was not confirmed in this thesis. No significant interactions were also found between smoking and alcohol consumption as well as between alcohol abuse and antenatally detected or suspected fetal growth retardation. Association between alcohol abuse and PM remained significant after adjusting for other variables in the model.

Maternal reproductive history

In this thesis, prior PTBs were associated with higher risk of PM; those women who had prior PTB in their reproductive history exhibited two-fold increased risk of PM during their current pregnancy. Mahande et al. [78] demonstrate similar results; term infants delivered by mothers who had prior PTB have PM of 10%.

Antepartum hemorrhage: does it deserve more attention?

In Little and Weinberg's study [124], antepartum haemorrhage during current pregnancy contributes to a 3.4-fold increased risk of stillbirth [125] . In rural Bangladesh, bleeding during pregnancy strongly associates both with stillbirth (adjusted ORs=22.4) and the newborn's death (adjusted ORs=19.6) [141]. In a recently published study conducted in Kenya, PM risk is 2.4-fold higher for women who have antepartum haemorrhage during their current pregnancy [123]. This thesis also demonstrates an association between antepartum haemorrhage and PM; PM risk is almost twice as high in women who had antepartum haemorrhage during their current pregnancy. Taken together, these data suggest that an increased clinical focus on prevention of antepartum hemorrhage has beneficial effect on PM.

Diseases in newborns and inappropriate care as contributors to perinatal mortality

Neonatal morbidity can also contribute to the risk of early neonatal mortality. Respiratory distress syndrom and hypothermia in preterm infants are independent risk factors of their early death [128]. In Uganda, respiratory disorders due to premature babies' lungs increase the risk of early neonatal death more than 30 times [142].

Lack of proper interventions can also contribute to increased risk of a newborn's death. Inappropriate fetal heart monitoring during labor associates with high risk of early neonatal mortality [142]. Antenatal steroids are routinely used to decrease the risk of respiratory insufficiency in preterm infants and, therefore, to reduce neonatal mortality in this the most vulnarable category of newborns [143, 144]. A lack of antenatal steroids increases the risk 1.5-fold of early neonatal death among very low BW infants [128]. However, this thesis did not include antenatal steroids as well as other interventions and characteristics of antenatal care in a set of indepedent veriables.

Birth weight and gestational age-specific risk factors and perinatal mortality

Risk factors of early neonatal death can be different depending on GA and BW. The absence of antenatal steroids use, multiple births, male sex, low 5th minute Apgar score, BW<1000 g, GA<28 weeks, use of surfactant, and the lack of a pain scale application associate with increased risk of early neonatal death among infants with weight <1500 g [128]. In a case-control study in Papua New Guinea, the exclusion of extremely low BW babies from the study population made the lack of proper antenatal care and male sex non-significant for early neonatal death [127].

Babies of lower GA or BW have increased risk of both PM [72, 145], early neonatal [127, 128, 146] or neonatal mortality [147], and infant mortality [148]. In this thesis, mean BW and standard deviation in PM group comprised 1958

(1164) g compared to 3383 (513) g in a group without PM; in bivariate analysis, risk to die during the perinatal period was highest among babies weighing <1500 g. A study in Brazil applied hierarchical assessment of early neonatal death and related low BW and PTB to health conditions of newborns which contributed to early neonatal mortality [146]. The heaviest infants demonstrate increased risk of PM [149]. Contrary to other studies [72, 149] this thesis did not reveal such an association.

Labour complications as a cause of perinatal mortality

This thesis did not address intranatal/labour risk factors that could contribute to PM. Placenta abruption [131, 150], maternal infection [131], acute asphyxia [151], and malpresentations [150, 152] contribute to stillbirth or early neonatal death. To date, the impact of these factors on PM in high-income countries with high level of antenatal and intrapartum care becomes less meaningful compared to women's diseases and pregnancy complications [153].

Congenital anomalies as predisposing factors for perinatal mortality

In this thesis, babies with congenital anomalies were excluded from the study population to investigate the contribution of other risk factors. This strategy has been previously applied in other studies [83, 154-156]. Birth defects or congenital anomalies are strongly associated with increased PM [106, 145] and neonatal mortality [147, 157]. In China, infants with congenital anomalies have 74-fold higher PM compared to babies without similar health conditions [145].

5.1.2 Preterm birth

Prior abortions in maternal reproductive history

In this thesis, all PTB groups had higher proportion of prior PTB and spontaneous or induced abortions compared with term births. Multivariable logistic regression analyses showed that these pregnancy outcomes increased the risk of both moderate-to-late, very, and extremely PTB births.

Data in this thesis on abortions as contributing risk factor to consequent PTB correspond to other studies [158, 159]. In Russia, the number of abortions, despite a decline in recent years, remains high among primigravida women. In 2014, there were 78 000 abortions compared to 161 500 in 2005 [107]. In women aged 15-49 years, 25.9 and 42.7 abortions per 1 000 women were performed in 2014 and 2005, respectively.

In 2014, every second pregnancy in Murmansk County was terminated by abortion [105] and there were 24 abortions per 1 000 women aged 15-49 years which corresponded to data from the Russian Federation. The registration form of the MCBR does not contain information about the method of abortion during prior pregnancy if such has occurred. Recently published results of a systematic review and metaanalysis show that prior surgical abortion increases the risk of PTB [159]. To make future registry-based studies more informative, it is therefore important to include information on method of prior abortions (surgical or medical) into registry records. Regarding the procedure in practice, medical methods and the least harmful surgical techniques should be used for abortions [159].

Marital status as a contributor to preterm birth
This thesis demonstrated increased risk of moderate-to-late and very PTB among single mothers. In 2014 in Murmansk County, 21.8% liveborn babies were born by unmarried women [105]. These data correspond to data in the Russian Federation; 23.0% and 22.2% infants were born by unmarried mothers in 2013 and 2014, respectively [105]. Other studies confirm higher risk of PTB among unmarried women [68, 160]. Social disadvantage and other risk factors, such as smoking, unemployment, and prior abortions are factors that could predispose to an increased risk of PTB in single mothers [160].

Reduction of preterm birth: potential preventive strategies
Since smoking, alcohol abuse, obesity, underweight as well as diabetes mellitus

and gestational diabetes were associated with high risk of PTB, one could speculate that strategies aimed to reduce prevalence of abovementioned risk factors in pregnant women might be beneficial in PTB reduction.

Reduction of alcohol consumption and smoking during pregnancy require strategies applied at both individual and population levels. Assessment and intervention at individual level play preferential role being a principal prevention strategy for reducing alcohol consumption prevalence in pregnant women [161]. Behavioral therapy and incentives were shown as promising in abstaining from smoking during pregnancy. Nicotine replacement therapy could serve as alternative for those who continue to smoke despite individual counseling [162].

In Russia, Health Ministry legislation act №572n, officially published in April, 2013 defined an order of care on pregnant women suffering from diabetes mellitus or gestational diabetes. Strict clinical guidelines aim to detect and manage indicated pathology during pregnancy properly. The same document obliged health care professionals to assess BMI in early pregnancy and record the data in woman's medical history. Before that, no mandatory recommendations existed and prevalence of overweight and underweight pregnant women in official reports therefore could be underreported.

5.1.3 Small for gestational age birth

Cigarette smoking and alcohol abuse increase the risk of SGA birth
In this thesis, higher risk of SGA_{WL} was associated with maternal smoking. Smoking women with lower education were at high risk to deliver SGA_W boys and girls (Table V). Recently published study showed that maternal smoking overrode the contribution of other factors including maternal education to SGA birth. Smoking cessation among women with low education may result in reduction of SGA birth [163]. Higher risk of both SGA_W and SGA_{WL} birth of boys was associated with maternal alcohol abuse. These results correspond to

other researchers' findings [163-165]. Tobacco use and alcohol consumption are associated with a toxic effect on the placenta and the fetus, which could lead to fetal growth retardation and consequently low infant BW [166, 167].

Babies with fetal growth retardation, diagnosed as fetus and newborn affected by maternal use of tobacco (ICD-10 code P04.2) or maternal use of alcohol (ICD-10 code P04.3) as well as fetal alcohol syndrome (ICD-10 code Q86.0), were extremely rare in the MCBR. There were no babies with fetal alcohol syndrome as main cause of death. In 52 806 births, only ten liveborn infants had some pathology caused by maternal alcohol consumption (coded as Q86.0). Eleven infants were defined as affected by maternal cigarette smoking.

There are two probable explanations for this phenomena. First of all, there may be a misclassification regarding the pathology which really caused the toxic effects of alcohol and tobacco on the fetus. These cases of fetal or newborn dysmorphic disorders could be classified as isolated congenital malformations not associated with maternal alcohol abuse. Second, there may be underreporting of tobacco smoking and alcohol abuse as both variables in the MCBR are based partly on self-reporting by pregnant women. In both cases, health care providers as well as medical staff at delivery hospitals need more awareness and knowledge on adverse effects of maternal smoking and alcohol use on pregnancy outcome.

Is any difference in SGA$_W$ and SGA$_{WL}$ risk factors?

In this thesis, no difference in contribution of studied risk factors to SGA$_W$ and SGA$_{WL}$ was found. Two types of fetal growth restriction are used in perinatal medicine. Fetal head/abdomen circumference ratio determined by ultrasound was suggested to differentiate symmetrical and asymmetrical growth restriction [168]. Decrease of fetal growth occurred during the first and second trimesters results in symmetric fetal growth restriction. Small head and abdominal size are typical for this type of growth restriction [169]. Fetal body is proportionally small [170]. Decrease in fetal growth in the third trimester can result to

asymmetric fetal growth restriction [169]. Congenital malformations and chromosomal abnormalities were defined as main etiological factors of symmetric fetal growth restriction. In contrast, asymmetric intrauterine growth restriction is mostly caused by placental insufficiency [169, 170].

No difference was found in environmental and medical risk factors between symmetric and asymmetric fetal growth restriction. Gestational age, at which pregnant woman is exposed to definite risk factor, was more important than the specific risk factor [171].

5.2 Ethical considerations

Birth registry-based studies are intensively used to address research issues in perinatal epidemiology. Such population-based registries, and the MCBR in particular, contain an array of individual information about infants and their parents, mostly, mothers. Therefore, ethical concerns should be addressed using data from birth registries. The linkage of birth registries with other databases even strengthens the need to adhere to ethical principles for scientific research [172].

The four general ethical principles are: respect for autonomy, benefice, non-maleficence, and justice [173]. In science, these principles are translated to issues the researcher has to define before and during the research process. First of all, informed consent reflects the "autonomy" or the right of a person to freely make his or her own choice to participate in a research study. In most studies, researchers therefore need to obtain informed consent from the study participants. In a birth registry such as the MCBR, there is no information on maternal personal identifiers (names, surnames, exact home address, etc.). The absence of such personal identifiers provides confidentiality and privacy for the participants and the possibility to identify an individual in the database of the MCBR is limited. No personal consent is therefore needed for a birth registry-based study as it is presented in this thesis.

Second, no discrimination was done in this thesis, as all mothers who

delivered a baby in Murmansk County in 2008-2011 were included into the MCBR irrespective of race, ethnicity and residence.

Third, research protocols that apart from a description of study design also contain an overview of ethical issues of the planned study, contribute to protect participants before the study begins. Approval from a local ethics committee is required before a medical or public health project is initiated [172] and all research involving humans must follow the Declaration of Helsinki [174].

Fourth, data protection is provided by the storage of paper registration forms as well as electronic data of the MCBR in locked cabinets in the Registry Office in Murmansk. External parties have only limited access to the database of the registry [71].

A birth registry provides a wide perspective for studies in the field of perinatal epidemiology, the findings of which could be further applied to improve antenatal, labour, postpartum, and neonatal care. In this thesis, the benefit overweighs the risks for the population of mothers and infants in Murmansk County. In fact, the work in this thesis does not pose any risk to the participants as the work is based on already collected data in a birth registry. The overall aim of the thesis is to study risk factors of adverse pregnancy outcomes. The results will be helpful to devise strategies to reduce prevalence of PTB, PM, and SGA births by diminishing risk factors that might have negative impact.

5.3 Methodological considerations

The MCBR serves as an example for the implementation of future birth registries in the Russian Federation in general and in Northwest Russia in particular. Its establishment provides several suggestions for the development of future birth registries.

Quality controls of the MCBR conducted in 2006 and 2007 revealed less than 1% errors [71] however it is important to avoid mistakes also in further data collection. Particular attention should be paid to information based on self-

reporting, in particular to smoking before and during pregnancy which includes number of cigarettes, and maternal education. Beside this, complete and as much as possible precise information on LMP is required. Early pregnancy ultrasound examination must include records of GA assessment in weeks and days of pregnancy as well as expected date of birth. Proper instructions for health care providers and regular control could help avoid missing data on the abovementioned variables.

It is also important to thoroughly collect data on pre-pregnancy weight in women who visit delivery hospitals late in pregnancy. Furthermore, there is currently no information on artificial reproductive technology available in the MCBR. Such information must be recorded to provide possibility for further research.

To date, the registry form of the MCBR does not contain information about precise intake period of folic acid and multivitamins in pregnancy. The records "intake before pregnancy" and "intake during pregnancy" in the registration form are not enough as this information is mostly copied from medical records and does not reflect intake but the occurrence of prescription. To date, the lack of precise information on multivitamins and folic acid intake makes it difficult, if not even impossible, to study the impact of these interventions on pregnancy outcome. Public health institutions should attempt to oblige hospitals to record this information properly in medical histories.

Data on amniotomy during the first stage of labour are important to study labour induction in connection with induced term and preterm deliveries. Information on amniotomy should therefore be included in the MCBR registration form for future data collection.

Information on pre-pregnancy diseases and complications or diseases during pregnancy should be recorded in separate boxes for each health condition. A check-box format demonstrates better validity of some variables in a birth registry quality control study [47]. Only using records of IDC-10 codes is not enough for variables of maternal diseases. Changing the recording to a check-

box format could potentially reduce the amount of missing data and positively affect under- or overreporting information.

A regular quality control is suggested once a year or every second year with consequent report of results accessible for regional health care providers and medical staff at delivery hospitals. Written detailed guidelines should be available for establishing a birth registry. Furthermore, its continuation must determine the exact procedure of data collection to avoid missing data on stillbirths, infant deaths, and perinatal deaths. These could be potentially extracted from delivery hospitals for perinatal and infant mortality audit.

5.4 Epidemiological considerations

5.4.1 Study design of this thesis

The design of the birth registry-based studies in Papers I-III equals a prospective cohort study design. To date, no other birth registry-based prospective study in Russia investigated adverse pregnancy outcomes.

Birth registry-based studies are unsuitable for infant diseases with a long latent period as databases of medical birth registries contains information on short-term infant outcomes [4]. The period of observation on infant health from the perspective of the birth registry stops at the time of the baby's discharge. A similar approach was used in the MCBR. Additional data can be added only if

any major birth defects or confirmed diagnoses are established after a baby is transferred to a hospital of higher level. The procedure of how such additional records should be entered into the birth registry database is not officially established and can to date be regarded as more or less arbitrary.

The possibility to link registry databases with other registries gives an opportunity to investigate infant diseases and delivery complications with late clinical appearance. However to date, both in Russia in general and in Murmansk County in particular, there are no registries besides the registry of birth defects and the registry of rare diseases in children.

5.4.2 Selection bias in the thesis

In research, bias means that an error is systematically introduced into research often without the knowledge of the researcher. There are several biases that can occur during the research process, but for a registry-based study selection bias is a critical aspect. For Papers I-III all births, with the exception of several defined exclusions, were included into the study population. The registry-based design in this thesis reduced the risk of selection bias. However, risk of selection bias could still exist in this thesis and is mostly related mostly to the initial database. A quality control study concluded satisfactory quality of the data collected for the MCBR during 2006-2007 [71]. However, there is no published information about the procedure of postponed inclusion of some births into the database. The reason for such delayed data entry or even missing cases could be explained by withdrawal of medical documents (both maternal and infant paper medical histories) by official institutions including the prosecutor's office, Bureau of Forensic Medicine, and Ministry of Health. Most of these withdrawals are explained by the necessity of detailed analyses of any adverse pregnancy outcome, i.e., stillbirth, maternal death, as well as early neonatal death.

There is also the possibility that primary medical documents have been withdrawn from delivery units upon an infant's death. This might contribute to selection bias only if the data on any particular birth was collected retrospectively and not immediately after birth. Information about postponed collected data on births with initially withdrawn documentation is not available. Therefore, in this thesis, one could assume underreporting of stillbirths and infant deaths that could potentially contribute to the prevalence estimations of all studied outcomes.

5.4.3 Validity and reliability of the results in the thesis

Data in the MCBR were validated [71]. In 2006 and 2007, two quality controls showed that the prevalence of errors was less than 1% and the database was

considered having satisfactory quality [71]. Records on 98.9% of all still- and liveborn births in Murmansk County for 2006-2011 were included in the database [71] which strengthens external validity and generalizability of the findings in this thesis.

However, data on some risk factors are probably under- or overreported. In the registration form, data on smoking is recorded based partly on maternal self-reporting. Data on alcohol abuse is based on self-reporting and mostly on medical records. Self-reporting may therefore contribute to a lower prevalence of these two important risk factors.

In Paper II, the relatively high prevalence of chronic infections of the genitourinary tract among mothers both at term birth (24.8%) and for all spontaneous PTB groups (21.6-26.7%) may be due to overreporting since it was partly based on self-reporting. Nevertheless, its prevalence might be even higher as there were 7 627 cases in the MCBR for which this information was missing. However, Chi-squared testing indicated that chronic genitourinary infections were uniformly distributed between study groups in the current thesis. Therefore, this variable was not included in the logistic regression modeling. Consequently, this thesis could not confirm whether infections (predominantly of the genitourinary tract) resulted in spontaneous PTBs. Intrauterine infections have indeed been identified in 38% of idiopathic preterm labor cases [175]. In fact, their contribution to PTBs may be underestimated [176, 177] due to poor detection technology [177]. Analysis of vaginal microbiota reveals an association between PTB and low levels of Lactobacillius and high levels of Gardnerella or Ureaplasma [178]. The most common pathway for microorganisms to the amniotic cavity is the ascending route [176]. Colonized women have a high risk of early PTB [179] and infection as a PTB risk factor is more common at GA <30-32 weeks [179, 180].

5.4.4 Limitations and strengths

This thesis has several limitations. The absence of data on ultrasound-estimated

GA, which were not included into the registry routinely before January 1, 2009, is a limitation. In this thesis, an approach was applied to unify the data for 2006-2011 and to calculate GA for all births in the MCBR. LMP and first ultrasound data were used to determine GA. It was earlier found that the first trimester report of LMP corresponds to GA based on data of first trimester ultrasound [116]. However, the approach applied in this thesis may limit the accuracy of the GA assessment.

In this thesis, maternal BMI recorded at the first antenatal care visit was used. Fattah et al. [181] demonstrate that BMI does not change during the first 14 weeks of pregnancy, and accurate early pregnancy measurements are recommended as preferable compared to data based on self-reports or pre-pregnancy measurements. Pre-pregnancy data on BMI was not available in the MCBR and therefore information recorded at the fist antenatal care visit was applied in this thesis.

This thesis did not include some maternal diseases and pregnancy complications that might be significant for the studied pregnancy outcomes. As described in Section 3.4, labour complications were not included in the assessment of PM risk factors.

The major strength of this thesis is that studies were done based on a large study population; the MCBR database includes records on 52 806 births. The MCBR form includes many potential risk factors; therefore it was possible to study the impact of socio-demographic, lifestyle, as well as medical risk factors on adverse pregnancy outcomes.

6 CONCLUDING REMARKS

The Murmansk County Birth Registry was established in 2006 and collected data on all births in Murmansk County until the end of 2011, which makes it a valuable tool to study prevalence and risk factors of adverse pregnancy outcomes. This thesis demonstrated an overall PM prevalence of 8.8 per 1 000 births, which decreased to 6.9 per 1 000 births after the exclusion criteria were applied. The overall prevalence of PTB was 6.9% with a downward trend during 2006-2011. Both socio-demographic, lifestyle factors as well as prior adverse pregnancy outcomes and complications during the current pregnancy contributed to PM and PTB in Northwest Russia. Prevalence of SGA_{WL} and SGA_W comprised 4.1% and 9.7% of all births, respectively. Social determinants such as low education, unmarried status, maternal unemployment, low BMI, smoking, and alcohol consumption increased the risk for a baby to be born both SGA_{WL} and SGA_W. As maternal smoking and alcohol consumption are behavioral factors, public health initiatives and efforts should be strengthened to reduce their prevalence.

The results in this thesis suggest that it is particularly important to monitor the health status during pregnancy in underweight women who are at high risk of SGA birth. This intervention can prevent birth complications due to SGA fetuses. It is advisable to provide targeted help to this category of pregnant women to avoid SGA births and its future health consequences for the baby's life.

7 PRACTICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Given the differences between underweight and normal weight pregnant women regarding SGA birth, regional healthcare institutions should develop strategies to prevent underweight in women who plan to become pregnant. Overweight and obesity are statistically significant factors for PM and PTB. It is therefore vital that public health institutions on a regular basis organize and focus educational healthcare programs to young women who are planning to become pregnant.

Greater public health efforts should also be undertaken to reduce smoking and alcohol consumption during pregnancy. Furthermore, efforts must be undertaken to reduce abortions in Northwest Russia. In this context, it is important to improve awareness both among health providers and women concerning consequences of induced abortions for PM and PTB. Attempts should also be done to prevent PTB, as prior PTB is a risk factor for PTB and PM in current pregnancy.

The most essential future perspective is a continuation of the MCBR. To date, data until December 2011 are available. In 2012-2016, no data collection was done because of organizational and financial difficulties. Data from these years could therefore be collected only retrospectively. It predisposes different study designs (both prospective and retrospective) that in turn could result in missing data and difficulties in data comparison.

One more perspective is to link already collected data with other databases such as the regional cancer registry, death records, registry of orphan diseases, data of air pollution monitoring, data on preterm babies follow-up etc. Data from birth registries, such as the MCBR, could be linked to databases of infant deaths to study factors predisposing infant mortality in Northern Russia.

Linkage with other birth registries can be used for the study of rare exposures and rare outcomes. Both need a large sample size. In 2012, the Arkhangelsk

County Birth Registry was implemented based on the same registration form as the MCBR. Data collection algorithm as well as all variables in electronic database in both birth registries were identical. Records on almost 45 000 births in Arkhangelsk County, neighboring to Murmansk County, were collected during 2012-2014 (data unpublished).

Combination of databases that have the same variables provides an opportunity for further epidemiological studies. A perspective for further development of perinatal epidemiology in Northwest Russia includes improvements of the registration form of the MCBR, dissemination of experiences related to the establishment of the MCBR to neighboring regions, as well as linkage of the MCBR with data of other registries and records from official institutions.

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