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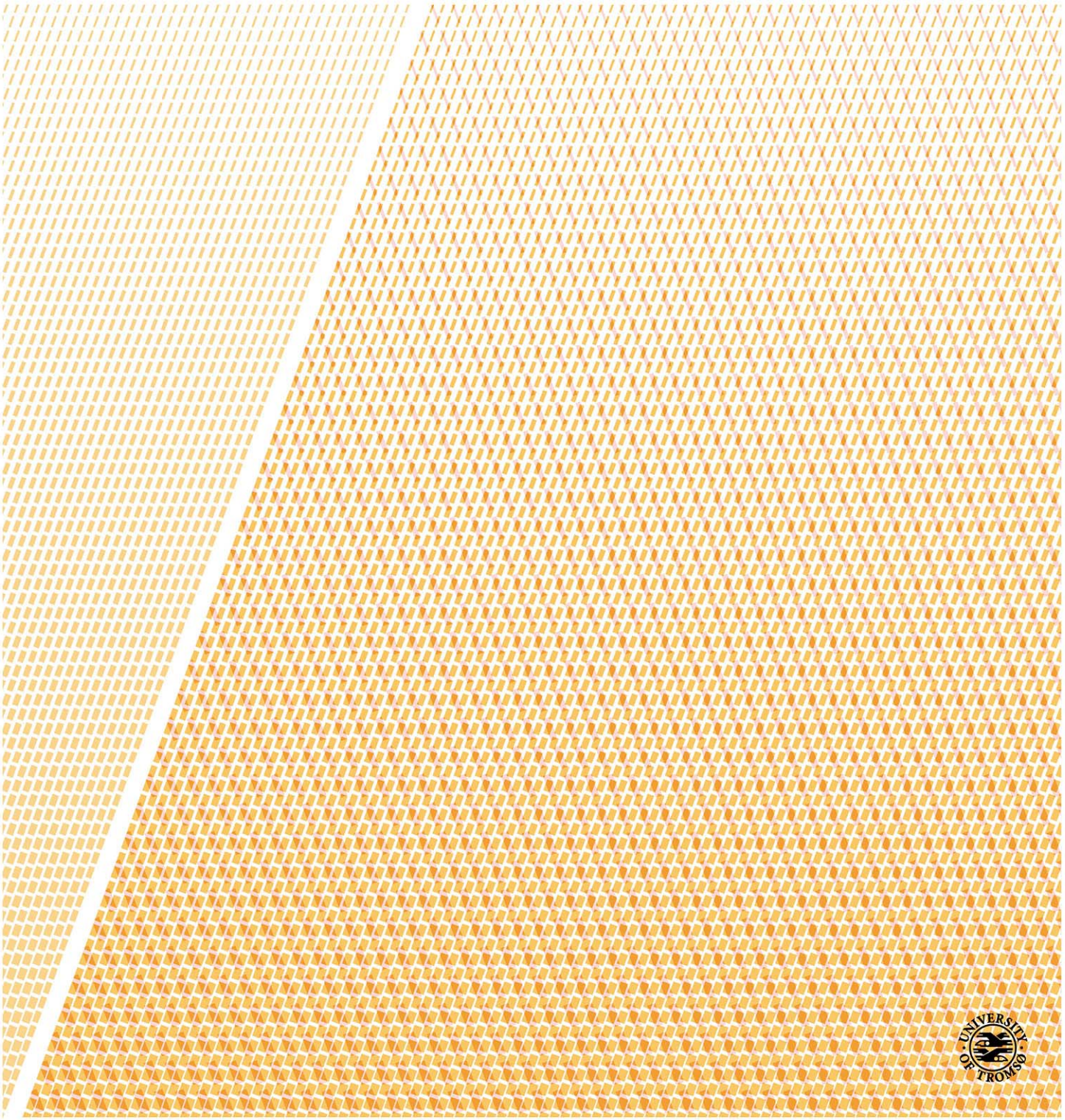
Vitaly Postoev

A dissertation for the degree of Philosophiae Doctor – June 2016



Using medical birth registries in the Kola Peninsula for birth defects surveillance and investigation of their risk factors

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2016

ISM skriftserie
blir utgitt av Institutt for samfunnsmedisin
Universitetet i Tromsø.

Abstract (in English)

Birth defects are important public health issues. They often cause a reduction in the quality of life and are responsible for a significant proportion of infant deaths in developed countries. Ongoing monitoring of birth defects occurrence and temporal trends in them are key investigative components. In Russia, their registration became mandatory in 1999. However, the registered details were different from European systems in the types and number of defects and age limit for registration. Moreover, the number of regional territories covered has been limited, and diverse estimates of birth defect prevalence rates occur. Unfortunately, it is difficult to analyze the available surveillance data for long-term trends because of the short observation period.

Medical birth registries are valuable sources of information about birth defects, and are widely used for the monitoring and surveillance over long periods of observation. Medical birth registration in North-West of Russia began in 1997 in the city of Monchegorsk and for all of Murmansk County in 2005. Birth defect data for 1973-1996 obtained retrospectively in Monchegorsk allowed an investigation of changes in prevalence over a forty-year period. Interestingly, this observation window coincided with both extensive socio-economic changes and in medical care services, primarily, because of the implementation of prenatal screening.

The aim of the current research project was to demonstrate the effectiveness of using existing medical birth registries in Murmansk County for the surveillance of birth defects with the following objectives: (i) investigate changes in the prevalence of birth defects for the period 1973-2011 in the city of Monchegorsk (located in Murmansk County); (ii) identify reasons for these trends, with special emphasis on the influence of prenatal ultrasound screening (promulgated in 2000); and (iii), analyze the perinatal factors associated with congenital anomalies of the kidney and the urinary tract in Murmansk County during 2006-2011.

The registry-based study with data from both the Kola Birth Registry and the Murmansk County Birth Registry from 1973 to 2011 showed that the total prevalence of birth defects at birth was comparable with European data, with almost a quarter of the cases constituting

minor malformations of the genital organs and musculoskeletal system. The birth prevalence exhibited a two-fold increase in the city of Monchegorsk during 1973-2011, and was primarily due to an increase in prevalence among livebirths. The most prominent increase occurred for congenital malformations of the kidney and the urinary tract, and the implementation of prenatal screening was the most likely reason for such changes. Although the total birth prevalence of all defects increased after establishing mandatory ultrasound screening in Russia, the birth prevalence of the most severe anomalies has been stable, while congenital malformations of the circulatory system and deformations of the musculoskeletal system declined.

The prenatal screening also had an impact on the perinatal mortality among newborns affected with birth defects. We observed a five-fold decrease in perinatal mortality among such newborns, while the total perinatal mortality declined only twofold. Moreover, the mothers who had undergone at least one ultrasound examination during pregnancy had a decreased risk of having a newborn die during the perinatal period.

The congenital anomalies of the kidney and the urinary tract were associated with maternal diabetes mellitus or gestational diabetes, infections during pregnancy, the use of any medication during pregnancy and conception during summer increased the risks of these birth defects.

Even though induced abortions were not registered, the medical birth registries in Murmansk County provided a powerful tool for birth defect research and surveillance. The observed increase in the total prevalence of birth defects in Murmansk County was due to prenatal screening. Antenatal detection of severe malformations with subsequent terminations of such pregnancies was the main reason for the downward trend in perinatal mortality among affected newborns. Our findings emphasize that detrimental risk factors associated with maternal lifestyle and health status constitute potential risks for birth defects.

Sammendrag (in Norwegian)

Medfødte misdannelser er viktige i folkehelsesammenheng. De kan redusere livskvalitet og er årsaker til en betydelig andel av den globale barnedødelighet. Overvåking og registrering av misdannelser og utviklingstrender for misdannelser er viktige verktøy. Systematisk registrering ble innført i Russland i 1999. Registreringen er imidlertid svært forskjellig fra de europeiske systemer i måte å registrere, definisjon av defekter og aldersgrense for registrering. Det er også mangelfull geografisk utbredelse av registreringen, med den følge at estimater av misdannelsesfrekvens er varierende og ufullstendige. På denne bakgrunn er det vanskelig å analysere tilgjengelige data i et lenger perspektiv, også på grunn av korte og varierende observasjonsperioder.

Medisinske fødselsregistre er viktige kilder for informasjon om misdannelser, og blir brukt i stort omfang for monitorering og overvåking over lengre tidsperioder. Medisinsk fødselsregistrering i Nord-Vest Russland begynte i 1997 i Monchegorsk (Kola fødselsregister), og for hele Murmansk fylke (Murmansk fylkes fødselsregister) i 2005. Data for perioden 1973 til 1996 ble innhentet i ettertid og gav grunnlag for undersøkelser av endringer i forekomst over en førti-års periode. Denne tidsperioden falt sammen med en periode i Russland med store sosio-økonomiske endringer, med tilhørende store endringer i helsevesenet. For svangerskapsomsorgen var innføringen av prenatal screening den viktigste endring.

Formålet med dette prosjektet var å vise hvordan det eksisterende fødselsregisteret i Murmansk fylke kunne brukes effektivt til overvåking av medfødte misdannelser med følgende formål: (i) å undersøke endringer i forekomst av medfødte misdannelser i perioden 1973-2011 i Monchegorsk (i Murmansk fylke); (ii) å kartlegge årsaker til denne utviklingen, med spesiell vekt på innføringen av prenatal screening (innført i 2000); og (iii), analysere perinatale faktorers sammenheng med medfødte misdannelser i urinvegene hos barn født i Murmansk fylke i perioden 2006-2011.

Den registerbaserte studien med data fra både Kola fødselsregister og Murmansk fylkes fødelsregister fra 1973 til 2011 viste at den totale forekomst av misdannelser var sammenlignbar med europeiske data, med rundt en fjerdedel av tilfellene knyttet til genitalia og muskel-skjelettsystemet. Forekomsten i Monchegorsk i perioden 1973 til 2011 ble fordoblet, først og fremst gjennom en bedre registrering av de levende fødte. Den viktigste

endringen skjedde for misdannelser i nyrer og resten av urinvegene. Innføring av prenatal sceening var den sannsynlige årsak til disse endringene. Selv om den totale forekomst av alle misdannelsene øket etter at prenatal screening ble innført har forekomsten av de mest alvorlige misdannelser vært stabil, mens misdannelser i hjerte-karsystemet og muskel-skjelettsystemet har minket.

Prenatal screening hadde også effekt på perinatal dødelighet hos nyfødte med påviste misdannelser. Det ble påvist en femdobbel reduksjon av perinatal dødelighet hos denne gruppen, mens den totale perinatale dødelighet bare ble halvert. Likeledes hadde de gravide som fikk en ultralydundersøkelse i løpet av svangerskapet en redusert risiko for at barnet døde i løpet av perinatalperioden.

Medfødte misdannelser av nyrer og urinveger var assosiert med mors diabetes og svangerskapsdiabetes, infeksjoner i løpet av svangerskapet, medisinbruk gjennom svangerskapet og unnfangelse i sommerhalvåret.

Selv om provoserte aborter ikke ble registrert er fødselsregistrene et viktig verktøy for forskning og overvåking knyttet til medfødte misdannelser. Den observerte økning i total forekomst av fødselsdefekter er basert på den prenatale screening. Påvisning av alvorlige misdannelser med påfølgende terminering av svangerskap var den dominerende årsak til den påviste reduksjon i perinatal dødelighet hos de affiserte barn. Våre studier gir også grunnlag for at risikofaktorer knyttet til mors livsstil og helse før og under svangerskapet har stor betydning for utfallet av svangerskapet og risiko for medfødte misdannelser.

Абстракт (in Russian)

Врожденные пороки развития являются важной медицинской проблемой: они вызывают снижение качества жизни и непосредственно связаны со значительной частью младенческих смертей в развитых странах. Непрерывный мониторинг распространенности врожденных пороков наряду с анализом временных трендов являются ключевыми компонетами исследования тератогенных факторов риска. Порядок мониторинга врожденных пороков в России был законодательно определен в 1999 году, однако порядок их регистрации отличается от такового в европейских странах по числу учитываемых аномалий и возрастным ограничениям. Кроме того, количество территорий, представляющих данные по распространенности, ограничено, ее оценки сильно варьирует. Необходимо также отметить, что анализ временных трендов распространенности с использованием данных национального мониторинга является затруднительным в связи с коротким периодом наблюдения.

Известно, что медицинские регистры родов являются ценным источником информации о врожденных дефектах и широко используются для целей мониторинга и контроля. Регистрация медицинской информации о беременности и родах была начата в 1997 в Мончегорске, а с 2006 года в систему обязательной регистрации родов была включена вся Мурманская область. В настоящее время медицинские регистры родов в Мурманской области с ретроспективными данными с 1973 года позволяют изучать изменение частот врожденных пороков в течение сороколетнего периода, включающего период социо-экономических преобразований и изменений в медицинской практике, связанных в первую очередь, с внедрением методов пренатальной диагностики.

Целью настоящего исследования явилась демострация возможностей медицинских регистров родов, созданных в Мурманской области, для мониторинга и контроля за распространенностью врожденных пороков развития. Для этого были поставлены следующие задачи: (1) изучить изменение распространенности врожденных пороков в Мончегорске (Мурманская область) за период 1973-2011; (2) определить причины

изменения распространенности с течением времени с изучением эффекта от внедрения пренатального скринига беременных; (3) провести анализ перинатальных факторов, связанных с врожденными аномалиями почек и мочевыделительной системы, как группы с максимальным ростом распространенности за исследуемый период.

Исследование, основанное на Кольском регистре родов и Мурманском областном регистре родов, выявило, что общая распространенность пороков развития при рождении в период 1973-2011 гг была сопоставима с данными европейских регистров, при этом около четверти всех пороков составили так называемые «малые аномалии развития» половых органов и костно-мышечной системы. Общая распространенность пороков развития, определенная при рождении, увеличилась в два раза в Мончегорске за исследуемый период, в первую очередь, за счет увеличения распространенности среди живорожденных. Наибольший рост продемонстрировали врожденные аномалии почек и мочевыделительной системы, и внедрение пренатального ультразвукового скрининга является наиболее вероятной причиной таких изменений. Несмотря на то, что общая распространенность врожденных дефектов увеличилась после внедрения обязательного пренатального скрининга, распространенность наиболее тяжелых пороков (подлежащих обязательной регистрации в России) не изменилась, а распространенность пороков сердечно-сосудистой и костно-мышечной систем даже снизилась.

Пренатальная диагностика оказала также влияние на показатель перинатальной смертности среди новорожденных с пороками развития. Мы наблюдали пятикратное уменьшение перинатальной смертности среди таких новорожденных, тогда как общая перинатальная смертность снизилась в два раза. Кроме того, беременные женщины, прошедшие как минимум одно ультразвуковое обследование в течение беременности, имели значимо более низкий риск смерти новорожденного в перинатальном периоде.

Врожденные аномалии почек и мочевыделительной системы были изучены детально в связи со значительным увеличением распространенности, и были определены перинатальные факторы риска данной группы дефектов. По результатам регрессионного анализа, наличие сахарного или гестационного диабета у матери,

инфекционные заболевания или прием медикаментов во время беременности, а также зачатие в летние месяцы значимо увеличивало риск развития данной группы аномалий у новорожденных.

Несмотря на отсутствие регистрации искусственных прерываний беременности по медицинским показаниям, медицинские регистры родов в Мурманской области являются мощным источником данных для мониторинга и контроля распространенности врожденых пороков. Увеличение общей распространенности врожденных пороков, выявленное нами, является, по нашему мнению, результатом повышения качества их диагностики из-за введения пренатального скринига. Кроме того, диагностика аномалий до родов с последующим прерыванием беременности явилась главной причиной снижения уровня пренатальной смертности. Необходимо также отметить, что эффект негативных изменений в образе жизни беременных женщин и изменение распространенности хронических заболеваний до и во время беременности также должен быть изучен.

Preface

The idea to study congenital malformation in North-West Russia occurred to me in 2009 during my Master of Public Health Program studies at the International School of Public Health (ISPHA, Arkhangelsk, Russia). Arild Vaktskjold involved me in a registry-based research project devoted to children's health in the Kola Peninsula. This activity made me aware of the opportunity to study birth outcomes in Murmansk County.

The first step in this direction was the completion of my master thesis that focused on congenital heart diseases among children in Monchegorsk. It became clear to me that the research potential of medical birth registries allows one to investigate much more. When a new PhD-position became available, I decided to apply for the current project. This application was successful and changed my life. Being a medical doctor in Arkhangelsk, I plunged into perinatal epidemiology and continued to study patterns and risk factors of birth defects.

The project and current position would never have been possible without a joint PhD program between the Northern State Medical University in Arkhangelsk and UiT-The Arctic University of Norway in Tromsø, established in 2011 by the Arctic Health Research Group (UiT) with financial support of The Arctic University of Norway. Moreover, two birth registries that had been set up in the Kola Peninsula within the Russian-Norwegian collaboration provided the basis for the search summarized in thesis.

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List of Papers

The thesis is based on the following papers, which are referred to Arabic numerals in this dissertation:

1. Postoev VA, Nieboer E, Grjibovski AM, Odland JO. Prevalence of birth defects in an Arctic Russian setting from 1973 to 2011: a register-based study. Reproductive Health. 2015;12:3.
2. Postoev VA, Grjibovski AM, Nieboer E, Odland JO. Changes in detection of birth defects and perinatal mortality after introduction of prenatal ultrasound screening in the Kola Peninsula (North-West Russia): combination of two birth registries. BMC Pregnancy and Childbirth. 2015;15(1):308.
3. Postoev VA, Grjibovski AM, Kovalenko AA, Anda EE, Nieboer E, Odland JO. Congenital anomalies of the kidney and the urinary tract: A Murmansk County birth registry study. Birth Defects Research Part A, Clinical and Molecular Teratology. 2016;106(3):185-93.

List of Abbreviations

ACBR – Arkhangelsk County Birth Registry

BD – birth defect

CAKUT – congenital anomaly of kidney and urinary tract

CHD – congenital heart disease

EUROCAT – European Surveillance of Congenital Anomalies

FD – fetal death

ICBDSR – International Clearinghouse of Birth Defects Surveillance

KBR – Kola Birth Registry

LB – livebirth

MCBR – Murmansk Birth Registry

NTD – neural tube defect

PS – prenatal screening

SB – stillborn

TOPFA – termination of pregnancy due to fetal anomaly

Acknowledgements

Firstly, I want to express my gratitude to my supervisors: Jon Øyvind Odland and Andrej Grjibovski. Jon Øyvind believed in me and in my research project and granted me an enormous amount of trust and high independence, which I have tried to justify. His great experience both as a medical doctor and as an epidemiologist allowed me to receive new knowledge through valuable advice and comments. Considering that my PhD-position consisted mostly of working in Arkhangelsk, I especially appreciated the continuous contact with Jon Øyvind, who was available every day and at any time. I usually got immediate responses to my letters full of questions independent of his working location: Tromsø (Norway), Pretoria (South Africa) or Lilongwe (Malawi). He has also given me access to his scientific network and introduced me to Evert Nieboer.

Andrej Grjibovski was my co-supervisor and he followed my work closely. He always had time for fruitful discussions about articles and his critical comments constituted opportunities to learn more and rendered my published papers more academic and interesting. I very much appreciated and benefited from his knowledge in the field of perinatal epidemiology and registry-based research, which he has shared with me.

In extend my sincere appreciation to Evert Nieboer who was a co-author of all three articles that form the basis for my doctoral thesis. However, the word "co-author" does not reflect his impact. His comments, suggestions and editorial advice were indispensable.

I also want to acknowledge Erik Anda as the "creator" of the Murmansk County Birth Registry and for his support and help with the interpretation of registry data.

I also need to convey my thanks to all PhD students involved in the Arkhangelsk-Tromsø PhD program, and our senior colleagues in the Arctic research groups, especially Tormod Brenn. We worked together as a team and could always expect a helping hand. Our annual meetings, the weekly meetings in Arkhangelsk and those during every Tromsø visit were always replete with valuable discussions and were extremely helpful.

I would be remiss not to mention the dedicated staff at the Kola Birth Registry and the Murmansk County Birth Registry, as well as researchers at the Kola Research Center and Alexander Voitov, the Chief-doctor at the Monchegorsk City Hospital.

Lastly, I owe my family a very special thank you for their support throughout my years of education.

1. Introduction

1.1 Medical registries as a tool for birth defects surveillance and research

Investigations based on health registries play an important role in the development of new medical knowledge. Related research questions often require long study periods or large sample sizes for detecting rare outcomes (1). Birth defects (BDs) constitute an important public health issue for which registry-based investigations are helpful. Moreover, establishing appropriate surveillance systems for BDs has been mentioned by the World Health Organization (WHO) as a key activity at the country level that could support "the development of services for the prevention and care of BDs" (2). The aims of surveillance programs are often two-fold: to define changes in prevalence of BDs and to investigate associations between such changes and any factors that serve as potential teratogens.

The first population-based study of BDs was performed in 1951 by Book, who summarized about 44,000 births in the interval 1927–1946 in the city of Lund in Sweden and calculated their incidence (3). Since that time, most of BD investigations have been conducted based on health registries in order to obtain large sample sizes. Two types of medical registries are suitable for such objectives: medical birth registries (MBRs) and registries of birth defects (i.e., registries of congenital anomalies). MBRs are useful for clarifying the causes and consequences of health problems related to pregnancy and childbirth and, as a rule, contain data about all pregnancy outcomes in a specific geographical area. At the same time, birth defect registries usually collect information about affected children only. Historically, they have been the primary sources of information for the epidemiology of BDs; they often have a wider age limit for registering diagnoses, and the process of data collection about perinatal risk factors is usually retrospective.

Even though being different in structure and information collection, both approaches are suitable for BDs surveillance and research. Each approach has inherent advantages and limitations. This thesis constitutes the first attempt to demonstrate the effectiveness of two MBRs set up in the Kola Peninsula (North-West Russia) with the dual objectives of BDs surveillance and research.

1.1.1 Medical birth registries: the world experience

MBRs are usually set up for surveillance of perinatal conditions, epidemiological research, the planning and quality assurance of health services and their administration/management. MBRs provide information for defining any increase in prevalence of adverse pregnancy outcomes and for exploring causes of such temporal trends. Moreover, perinatal conditions such as BDs, cerebral palsy and prematurity can cause long lasting disability and thus high disability-adjusted years of life. There are also some theories about intrauterine programming of diabetes, cardiovascular diseases and cancer (4-8), and the MBRs and cause-of-death registries facilitate related research.

The history of birth registries started in the 1960s after the thalidomide catastrophe. The first MBR in Europe was initiated in Norway in 1967 by collecting, processing and analyzing all medical birth certificates with a linkage to the death certificates (9). The primary aim of the registry was epidemiological surveillance of BDs and other perinatal conditions, especially for early detection of upward trends in prevalences (9). Comparable programs were also initiated in South America and Atlanta (USA) in the same year (9).

In the strict sense, initially the MBR of Norway was not officially "a registry" but only "a register" (database) of birth certificates. However, it has been gradually modified to ongoing registration of births with two primary objectives: (i) epidemiological surveillance of birth defects and other perinatal conditions, with health services connected to pregnancy and childbearing; and (ii), conducting epidemiological research in perinatal health (9).

Since terminations of pregnancy due to fetal anomaly (TOPFAs) constitute one of the major problems in the epidemiology of BDs, their registration was included in the MBR of Norway from January 1, 1999 on. This development allowed a more effective ongoing monitoring of BDs.

Currently, the Norwegian MBR operates under the 2001 Norwegian Act of Health Registries, and it contains information about all deliveries and all pregnancy terminations after 12 weeks of gestation. It is mandatory for midwifes and obstetricians to report all births to the MBR of

Norway *via* a notification form (10). Today all reports are in electronic form, which minimizes errors in data transfer. It is important that the MBR of Norway provides data for both health policy-makers and scientists, while maintaining its affiliation with the central health authority. A unique personal identification number (assigned for each person living in the country permanently) allows data links to other health databases without personal identifiers like a name or maternal/baby date of birth, thereby increasing the research capacity of the registry (11, 12). Moreover, the possibility to link information between health registries allows ongoing validation of collected data.

Some examples of findings provided by the MBR of Norway involving perinatal surveillance are: an increase in prevalence of hip dysplasia related to new diagnostic criteria (9); identification of adverse birth effects of antiepileptic drugs (13); and defining the effects of the Chernobyl accident on newborns' health (14-16). The registry is useful not only for surveillance of adverse pregnancy outcomes, but also for the monitoring of maternal diseases and conditions. For example, an upward temporal trend in occurrence of diabetes in pregnancy was observed (9).

By 2016, the MBR of Norway included information on 2,817,468 pregnancy outcomes (10). Besides ongoing surveillance, it provides an enormous potential for perinatal registry-based research. We found 633 publications in the PubMed database with key words "Medical Birth Registry of Norway". Thirty six of them were directly devoted to BDs, including studies on trends in the prevalence of BDs (17) and causes of the defects [e.g., a study on BDs among offspring of Norwegian farmers (18) and the association between parental age and BDs (19)]. Evaluation of the validity of the registry has also been among the research objectives, and a number of studies have estimated the completeness of the registration of both defects (20, 21) and maternal conditions (22, 23). These various assessments have established that the validity is satisfactory for data on Down syndrome (21), cleft lip and palate (20), as well as for maternal diabetes type 1 (22) and rheumatic diseases (23). By contrast, the registrations of isolated cleft palate for newborns (20) and of asthma, epilepsy and diabetes type 2 (22) among mothers were deemed incomplete.

There are other examples of birth registries which coverage of an entire country (e.g., Denmark, Finland, Sweden, Iceland, and Estonia), but they were created later. The Swedish MBR was established in 1973 by an Act of the Swedish parliament and it is the largest one, with 108,211 births in 2011 (24). Among the former Soviet countries, only Estonia has promulgated mandatory reporting of births with the establishment of an MBR ─ it covers 327,904 births (25) to date. The latter, together with the Estonian abortion registry (established in 1994), allows epidemiological research and provide information about post-delivery health services and birth statistics (26). In Table 1 more details about the Estonian MBR and other MBRs in European countries that emphasize BDs are provided.

As mentioned above, systematic validation of collected data is important for epidemiological research (27). The total coverage and proportion of missing data are the most important issues of quality assessment and control. Speaking generally, the Nordic MBRs have reported statistics about missing data such as: 0.1-0.6% (gestational age), 0.02-0.2% (birthweight) and 0.005-0.2% (parity) in 2011 (24). The proportion of missing data about newborns and mothers, as well as about pregnancy complications, varies between registries. For example, the Swedish MBR report in 2003 indicated that 9% data on smoking was missing, as well as 15-25% for pre-pregnancy body mass index and 25% for occupational status. Moreover, the records for about 0.5-3.0% of newborns born in 2003 were completely lost by antenatal-care clinics and pediatric wards (28). The validity of data on BDs was previously estimated for Finnish registries by comparing data collected in the country's malformation registry with that in the MBR of Finland (29). The reported number of infants with BDs was three-fold higher in the MBR, while only severe defects such as anencephaly and orofacial clefts were equally reported (29).

Table 1. Overview of medical birth registries in Europe (10, 24, 25, 28, 30, 31)

Name of the medical birth registry	Year of foundation	Annual number of birth registered (year)	Registration of TOPFAs	Period of BDs registration	Membership in any international surveillance system
The Medical Birth Registry of Norway	1967	60,026 (2014)	Yes (from 1999)	Neonatal, but may be registered until one year	EUROCAT (full member) ICBDSR
The Danish National Birth Cohort	1973	58,717 (2011)	Yes	Neonatal	-
The Swedish Medical Birth Registry	1973	113,780 (2014)	No, but a special surveillance system for TOPFAs registration was initiated in 1999	Neonatal cases among children up to 6 months of age (up to 1 year for heart defects) are registered in the Swedish Birth Defects Register	ICBDSR (together with the Swedish Birth Defects Register) The MBR provides data on exposure for the Swedish Birth Defects Register, which is an affiliate member of EUROCAT

The Medical Birth Registry of Finland	1987	57,805 (2014)	No, but there is a separate Induced Abortion Registry	Neonatal cases among children up to 1 year are collected by the Registry of Congenital Anomalies	-
The Iceland National Register of Birth	1972	13,830 (2015)	No, but TOPFAs > 12 weeks are registered in the Abortion Register	Neonatal, but later cases are registered in the central hospital	-
The Estonian Medical Birth Registry	1991	13,830 (2014)	No, but since 1996 they are registered in the Estonian Abortion Registry	Neonatal	-

1.1.2 Medical birth registries in the North-West Russia: history and comparison with the Nordic registries

Kola Birth Registry

The birth registries in Murmansk County in North-West Russia had their beginning in 1995. It was a component of an investigation of the effect of occupational exposure to nickel on adverse pregnancy and delivery outcomes among female workers at the nickel-refinery complexes in the cities of Nikel, Zapolyarny and Monchegorsk (all are located in Murmansk

County) (32). These three cities had high proportions of women who were nickel-refinery workers, which is unusual (33). Critical evaluation of routinely collected medical documentations for these epidemiological studies was conducted (32), and pregnancy and delivery related information was collected from the three mentioned towns. Subsequently, the city of Monchegorsk became the research focus because the metal-refining complex, the workforce and the population were the largest. The Kola Birth Registry (KBR) was established in 1997 (34). Information about each livebirth (LB) and stillbirth (SB) after 28 week of gestation came from the delivery histories, the general medical, the hospital obstetrics journals and delivery department journals. All data were stored in a computerized database, and from 1997 on were collected prospectively. Moreover, in-clinic spontaneous abortions before 28 weeks of gestation were also registered (34).

The KBR contains data about 26,841 newborns (LB+SB) in the city of Monchegorsk born from 1973 through to 2005. Strictly speaking, it was not a "true" MBR by comparison to the Norwegian one because it was set up for research purposes, even though it constituted a register/database of all births rather than a planned system of ongoing registration.

The KBR database contains information about the following: parents (age, occupation, nationality, maternal diseases before pregnancy); previous pregnancies and related outcomes; current pregnancy (diseases, other complications, prenatal screening (PS) results, and exposures during pregnancy); delivery details (gestational age, type, complications); and the newborns [status (LB or SB), Apgar score, anthropometric measures, conditions and diseases during perinatal period, diagnosed BDs].

The validity of the primary medical documentation was recognized as satisfactory for epidemiological research (32). Moreover, the quality and content of the registry's database was evaluated by Vaktskjold et al. (33) and was found sufficient for perinatal epidemiological investigations.

Many studies were completed using KBR data, of which most examined the effect of occupational exposures on different perinatal conditions, including BDs (35-38). No significant associations were observed between nickel exposure during early pregnancy and

incidence of spontaneous abortions (39) and small for gestational age infants (40), as well as between nickel exposure and genital (38) and musculoskeletal anomalies (37). An assessment of the relationship between organic solvent exposure and birth weight was also carried out, and a higher risk of low birth weight for newborns whose mothers had been exposed to organic solvents was found (41).

Unfortunately, local health authorities did not show much interest in the data provided by the KBR, and thus its conversion to a tool for ongoing surveillance/monitoring did not occur.

Murmansk County Birth Registry

The annual number of deliveries in the city of Monchegorsk was relatively small in comparison with Murmansk County (about 7% of all births) and thus did not permit the investigation of rare outcomes. The Murmansk County Birth Registry (MCBR), a cooperative project between the Murmansk Health Authority and the University of Tromsø, was established by an administrative edict: specifically, the mandatory prospective registration of all births in Murmansk County as of the 1st of January, 2006 (42).

Data about pregnancy and delivery involved four sources in the County's 15 obstetric departments: mother's medical history documents; the obstetric journals; medical delivery documents for the newborn; and an interview with the mother. The primary form for collecting the information about the mother, pregnancy and newborn was similar to that used by the MBR of Norway, although some fields were enlarged with the aim of collecting more information about perinatal exposures, especially by way of the mother's occupation (43).

After the first year of operation (2006), 8,401 deliveries and 8,468 newborns were registered in the MCBR; it constituted 99% of all births in Murmansk County (43). By 2011, it contained data on about 52,000 of pregnancy outcomes in the County.

The MCBR includes information about the parents of the newborn (age and occupation), maternal characteristics/habits (residence; smoking habits; alcohol consumption; medication and drug use during pregnancy; intake of multivitamins and folic acid before and during pregnancy; previous pregnancies and their outcomes; diseases prior to and during pregnancy;

and pregnancy complications), PS results, method of delivery and related complications, and the newborn (gender; Apgar score; anthropometric measures; gestational age at birth; BDs diagnosed perinatally; and conditions/treatment during the perinatal period). The entire birth registration form was included in Erik Eik Anda's doctoral thesis (42).

The MCBR is close to "a registry" in terms of a system of ongoing registration carried out by an official organization with its own staff. Moreover, as indicated earlier, the process of mandatory registration of pregnancy outcomes was promulgated by local law (42).

By comparison with the Nordic registries, the MCBR had differences that could affect data collation. All induced termination of pregnancies and spontaneous abortions before 22 weeks were not included, so information about BDs among terminated pregnancies was lost. In addition, the absence of a personal identification number makes the linkage with other databases challenging, but is still possible by maternal or/and child date of birth. However, there are some advantages of the Kola and the Murmansk County registries. Because they were set up for research purposes, detailed information about some exposures (especially occupational) was registered.

1.1.3 Registries of birth defects and international surveillance systems

The first registries for BDs in Europe date back to the 1960s, as do the first MBRs. They had the adverse effects of thalidomide (44) as a common premise. Because they were regional, they could not be very effective, as only small populations were covered. Since only a few defects were registered, they did not allow temporal and etiological analyses, or investigations of rare defects. Since the primary objectives were to establish trends in rare and multiple malformations, coverage of large populations was crucial. The International Clearinghouse for Birth Defects Monitoring Systems was set up in Helsinki in 1974 to address these issues, with some of the existing MBRs as founding members. More than 30 regional registers from America, Asia and Europe (45) contribute and since 2004 it is known as the International Clearinghouse of Birth Defects Surveillance (ICBDSR). The purpose of this organization was not to combine the registration of BDs, but was to exchange and systematize data collection by local registries to increase the probability of detecting new

teratogens (46). The Center was located in Bergen (Norway) in 1989 and moved to Rome (Italy) in 1992, where it currently carries out its activity.

In 1974, the European Economic Community's Committee on Medical and Public Health Research established a workshop which aimed to improve "the methodology of population studies throughout the Community"(44). The first topic of such an action concerned the investigation of congenital anomalies. This workshop was reorganized in 1979 and retitled as the European Network of Population-based Registries for the Epidemiologic Surveillance of Congenital Anomalies (EUROCAT) (44). The main goal of the EUROCAT project was an integration of regional registries across Europe into a pooled database in accordance with standard definitions, diagnosis and terminology. Primary objectives for establishing this standardized data set were to control prevalence of BDs in Europe and to enhance understanding of regional differences.

Standard operation procedures of EUROCAT include:

- Standard data about newborn, diagnosis, parents;
- Unified coding system for any collected information; and
- Standard computer data entry and validation program.

EUROCAT now covers one-third of all births annually in the European Union (47, 48) and collects data about more than 80 BD forms, excluding minor ones, which are listed in special guidelines (48, 49). The ICBDSR reports the prevalences of the 35 most severe and easily observed forms of BDs (45).

There are some MBRs among the ICBDSR and EUROCAT members. Specifically, the Medical Birth Registries of Norway is a member of the ICBDSR and a full member of EUROCAT. The Swedish Medical Birth Registry and the Swedish Birth Defects Register are members of ICBDSR as well. The latter organization is also an associate member of EUROCAT, but the Swedish MBR also provides information on risk factors (50). This indirectly attests to their comprehensiveness and validity for BDs surveillance and epidemiological investigations.

As mentioned by Vaktskjold (33), the KBR could not be a member of either the ICBDSR or EUROCAT because of the small annual number of births. However, the MCBR met the criteria of an affiliate member of EUROCAT or a member of the ICBDSR. In any case, full membership by the MCBR would not have been possible because induced abortions were not registered.

1.2 Epidemiology of birth defects worldwide

The World Health Organization (WHO) recognizes BDs as "structural or functional anomalies (e.g., metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life" (2). The International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) includes BDs in Chapter XVII: Congenital malformations, deformations and chromosomal abnormalities. The two terms "birth defects" and "congenital malformations" seem to be interchangeable by epidemiologists. However, one could argue, that "congenital malformations" represent only structural anomalies, while "birth defects" have a more broad meaning and include both structural defects and functional or metabolic disorders (51). Nevertheless, in our context we consider them interchangeable.

BDs are an important public health issue, because they are responsible for 10% of neonatal deaths worldwide (52) . They are the most prominent cause of infant deaths in countries with low overall mortality rates, and constitute 25% of neonatal deaths in Europe and 2.5% among affected newborns who die during the first week of life (53). There is also a higher proportion of preterm newborns among those with BDs, which further increases the risk of mortality (51). According to EUROCAT, in Europe one newborn per 1000 dies during the first week of life because of BDs (54). Congenital anomalies also have a significant impact on life expectancy and the quality of life of affected children (2).

The burden of BDs is also evident in Russia. According to official statistics, 2,677 children under one year (or 13.8 per 10,000 newborns) died from BDs in 2015 (55), and constituted the second most common reason of infant mortality.

According to EUROCAT data, the total prevalence of BDs in Europe was 25 per 1,000 newborns in 2012, with 79.8% of LB among them (56). The most common subgroup was congenital heart disease (CHD) with a prevalence of 7.9 per 1,000 newborns, followed by BDs of limbs (4.0 per 1,000), chromosomal anomalies (3.8 per 1,000) and BDs of the urinary system (3.4 per 1,000) (56). Among the Nordic countries, the total prevalence of BDs in 2011 was the highest in Finland (52.8/1,000), with those in Norway and Sweden being 27.4/1,000 and 22.2/1,000 respectively (56). This difference might reflect a higher age-limit for registering malformations (up to one year) in Finland.

The ongoing surveillance of BDs in Europe allows the assessment of changes in prevalence over time. According to EUROCAT, there is an increase in total prevalence of Down syndrome and gastroschisis since 1980, whereas those of oral clefts and omphalocele decreased (48). Positive trends also occurred for gastroschisis, hypospadias, renal dysplasia and Trisomy 18. By contrast, the total prevalence of BDs of the nervous system, severe CHD, respiratory defects, clef palate, most anomalies of the digestive system and limb defects decreased (57).

1.3 Surveillance and prevalence of birth defects in Russia

The Russian Ministry of health care initiated a national BD monitoring system in 1999. Twenty isolated forms of BDs, Down syndrome and multiple BDs became mandatory for reporting and the total prevalence of all BDs were to be determined (58). The federal monitoring is conducted by the Research Clinical Institute of Pediatrics in Moscow. Interestingly, only 43 regions of Russia participate in the federal monitoring program that reports data about prevalence rates. Murmansk County is not included (59). Information (although limited) about every BD case is collected according to a prescribed protocol. Maternal age, residence, parity are collected for the mother, while date of birth, birthweight, sex and status (LB or FD) are included in the neonate information (the notification form in Russian and its translation into English is presented in Appendix A and B, respectively). Reporting for all LB and FD with signs of BD after 22 weeks of gestation is obligatory (60).

The statistics of BDs in Russia are not fully comparable with those compiled by the international registers, because of the short list of defects for which reporting is mandatory and the small number of counties covered. There is only one registry of congenital malformations in Russia, which became a member of the ICBDSR in 2001; it provided data for about 35 of the most severe BDs in Moscow County until 2009. However, we could not find information about its current activity. It is important to emphasize that diagnoses made in maternity wards and during the first year of life were considered, which makes these prevalence estimates more reliable (61). According to the last published data, the prevalence of the 35 forms of BDs reported by the ICBDSR for Moscow County was 12.3 per 1,000 newborns in 2001 and 6.1 per 1,000 newborns in 2009 (45).

We have mentioned that the Russian national system monitors BDs, which from our prospective is distinct from surveillance. The former is often episodic or intermittent, whereas the latter is ongoing and continuous, implying a greater commitment to interpret and disseminate the recorded information. Surveillance is the analysis of health-related information that is communicated in a timely manner to all whom need to know, and includes health problems that require action in the community (62). Limited information about cases, incomplete coverage of a country's territory, as well as an absence of individual information about risk factors make analysis of national data a challenge.

We suspect that the Russian official data about prevalence of the most severe defects (reporting of which is mandatory) are comparable with EUROCAT data about the same defects for LB and SB (with exclusion of TOPFAs). These BDs are characterized by clear diagnostics and coding, and are usually detected during the first days of life. The compatibility of data about the total prevalence is questionable because there are no strict national guidelines that define phenotypes for all registered malformations, nor is there a list of minor malformations that are not reportable; neither should the latter be included in prevalence calculations. There are therefore possibilities for both under- and overestimation of prevalence and for the misclassification of defects in data provided by national statistics.

Our assessment in the previous paragraph receives support from the great variation in total prevalence of BDs in Russia, which unlikely is due to natural variability. The total

prevalence of BDs spanned from 7.0/1,000 in Stavropol County to 49.9/1,000 in Severnaya Osetia-Alanya County in Russia with an average all-Russian indicator of 23.2/1,000 newborns in 2011 (63) ─ a seven-fold difference. By comparison, EUROCAT reported that the highest total prevalence occurred in Hungary (40.7/1,000), and the lowest in Portugal (11.0/1,000) in the same year (56) reflecting a four-fold range. Moreover, differences in data might also imply different age-limits for BDs in registration across the EUROCAT members and different PS policies. These specific discrepancies do not occur between regions of Russia.

The prevalence of the mandatory reporting defects in Russia was 7.0/1,000 newborns and ranged from 2.8/1,000 newborns in Magadan County to 13.5/1,000 in Ivanvo County in 2011. The rates in Arkhangelsk County (one of the northernmost regions of Russia) were 10.5/1,000 for all BDs, and 7.0/1,000 for the group requiring mandatory reporting (63) .

The change in prevalence of BDs across the 1999-2011 period is evident from the data in Table 2. The total prevalence has tendency to increase during the observation period, whereas the prevalence of BDs which requiring reporting appears stable.

Table 2. Prevalence of all BDs and of BD forms that are mandatory for reporting, 1999-2011 (63)

Prevalence, per 1,000	**1999-2000**	**2001-2002**	**2003-2004**	**2005-2006**	**2007-2008**	**2009-2011**
All BDs	16.0	17.5	20.4	22.2	22.6	22.3
BDs, mandatory for reporting	NA	NA	6.2	6.1	5.9	6.3

Since information from the Russian national monitoring service is only available for the last 15 years, little information is available about the prevalence of BDs in the 1970s and 1980s nor for temporal trends therein. Historically speaking, the early studies during this the Soviet Union period report a wide range in estimates of prevalence. Kulakova (64) reported a total prevalence of BDs in the city of Omsk of 21.9 per 1,000 newborns in 1966-1976. At the same time, it was reported to be only 7.0 per 1,000 newborns in the Armenian republic in 1977 (65) and 27.2 per 1,000 in the Beloruskaja republic in 1984 (66).

Only a few studies have investigated changes in the prevalence of BDs over time and the results are contradictory. In Tomsk County (Western Siberia), the total prevalence of BDs was 22.7 per 1,000 in 1979-1992, and the year-by-year variation ranged from 13.9 to 30.2 per 1,000 (67). In the city of Omsk (68), the prevalence increased three-fold between 1956 and 2005 from 16.8/1,000 to 41.7/1,000, whereas in the Republic of Tuva there were no significant changes reported for the 1984-1994 and 1999-2003 periods (69, 70).

1.4 Sources of variability in prevalence rate of birth defects

The main objective of the surveillance of BDs is to define significant changes in their prevalence, especially the identification of upward trends. Prevalences of BDs vary with time and place, as mentioned above and by others (71, 72). It seems important to identify changes in diagnostic practices, case ascertainment and effects of population-based interventions as sources of variability before making decisions about potential linkage to a teratogenic agent or other causes.

PS as a major population-based intervention for BDs that can lead to the termination of pregnancy for severe anomalies. This link depends on two factors: a national BD screening policy and local legislation about pregnancy terminations. It appears that the birth prevalences of severe anomalies, such as of neural tube defects (NTDs), reduction limb defects and Down syndrome, were reduced after the introduction of screening in countries with liberal legislation about abortions. The prevalence of Down syndrome among LB decreased in 1980-2013 in Australia, because the majority of women decided to terminate their pregnancies when prenatally diagnosed (73). Declines in the prevalences of all non-chromosomal, urinary and limb anomalies were also reported in Basque Country (Spain) for 2006-2008 in comparison to 1996-1998 (74).

On the other hand, improved diagnoses of BDs at birth would improve antenatal diagnoses of minor defects, although this would increase the total prevalence (75-77).

In Russia, reported rates of antenatal diagnoses of BDs varied from 26.1% [Republic of Bashkortostan, 2010 (78)] to 44.0% [Krasnodar County, 2007 (79)]. There are few studies,

which have estimated the influence of initiating PS on prevalence rates in Russia and on antenatal diagnoses of BDs. All such studies depend on regional monitoring systems. Interestingly, the birth prevalence of BDs in Primorsky County increased by 27.5% during 2000-2014, mostly due to better antenatal diagnostic practices (80).

There are other examples of population-based interventions to prevent BDs. A primary strategy is the introduction of primary prevention of BDs by folic acid supplementation. The prevalence of severe CHD decreased 6% annually in Quebec (Canada) after implementing the mandatory fortification of flour and pasta products with folate (81). The same trend, but lower in magnitude, was found for orofacial clefts in the United States (82) and for CHD in Europe (83). The authors explained their findings by an "undocumented increase" of folic acid intake among women following the recommendations for folic acid supplementation. They also did not exclude environmental changes, nor were the decline in maternal smoking prevalence and improved control of chronic maternal diseases during pregnancy (83). A 42% decline in the birth prevalence of anencephaly has also been reported when comparing the periods before and after the introduction of folate fortification of wheat flower in Chile (84). However, a more recent study employing EUROCAT data for all NTDs did not confirm these findings (85).

Another possible reason behind prevalence variability is a shift in risk factor distribution. Advanced maternal age (86-89), tobacco smoking (90-92), alcohol consumption (93) and obesity (94) have been associated with higher risks of BDs, as well as maternal diabetes mellitus or gestational diabetes (95-99) among others. The prevalences of these factors also vary and consequently this could affect the occurrence of BDs. Interestingly, the proportion of mothers in advanced age increased from 13% in 1990 to 19% in 2008 among all members of EUROCAT (100). In Norway, there were 6.2% of mothers aged 35 and older in 1973, but this proportion increased to 19.8% in 2011 (101). The increasing average maternal age is considered as the main factor responsible for the upward trend in the prevalence of Down syndrome in Europe (48). The prevalence of smoking has declined in Scandinavian countries in the last decades (102-105), while many studies report increases in the prevalence of gestational diabetes (106) and preexisting diabetes mellitus (107). It is also interesting, that

the prevalence of adverse life-style factors, including smoking and alcohol consumption, can increase when severe socio-economic transition occurs in a country (108).

Clearly, registry-based research constitutes a significant component of investigating BDs. A large representative study-sample and detailed information about various perinatal exposures are required for the investigation of causal relationships for relatively rare events. Consequently, MBRs have become indispensable sources of data. Even though registries of congenital anomalies contain detailed information about the cases and have a wider neonatal age limit, their role in investigating effects of perinatal risk factors appears uncertain. Reasons for this include the need to collect retrospective information about conditions before and during pregnancy, thereby introducing the possibilities of recall bias and limited access to information about potential confounders (46).

2. Aims of the thesis

The overall goal of the thesis was to assess the usefulness and quality of two birth registries established in the Kola Peninsula for surveillance BDs and related research. This task had three specific research components.

1. Estimation of the prevalence at birth and structure of BDs in Monchegorsk in 1973-2011, with a focus on temporal trends in their prevalence (Paper 1).

2. An assessment of the impact of implementing PS in Murmansk County on the birth prevalence of BDs and perinatal mortality among affected newborns by combining data from both registries with pregnancy termination information (Paper 2).

3. Investigation of prenatal risk factors using MCBR data for congenital anomalies of the kidney and the urinary tract (CAKUTs) in Murmansk County, the group of BDs with the highest growth in prevalence during the study period (Paper 3).

3. Material and methods

3.1 Context of the research

Murmansk County ("Oblast") is a federal subject in the Northwest of Russia with an area of 144,900 square km (see Figure 1), and constitutes 0.85% of Russia's territory. The County includes the Kola Peninsula and borders Karelia, Finnmark fylke in Norway and the Lapland Region of Finland. Its western border extends a little beyond the 100,000 square km covered by the Kola Peninsula. The County's administrative center is the city of Murmansk. A significant part of the County is located above the Arctic Circle and has a unique climate and daylight regimen.

Figure 1. Murmansk County and adjoining regions

The region had 766,300 inhabitants in 2015, of whom 92.6% were urbanites (109). The population has decreased by 30,000 during the last five years. (109). According to the 2010

Census, the most prevalent ethnic groups were: Russians, 89.0%; Ukrainians, 4.8%; Belarusians, 1.7%; Tatars, 0.8%; Azeris, 0.5% (110) . The indigenous people of the area primarily were Saami, but today they constitute only a tiny minority; most are citizens of the Lovozero settlement (see map).

Murmansk County features a high level of mining and metal refining industries that emit multiple metals and nonmetals, as well as sulfur dioxide (SO_2). These emissions impair the local air quality and acidify/contaminate the soil, which potentially could influence maternal and children's health. However, this is not reflected in official 2014 perinatal statistics for Murmansk County (see Table 3) when compared with all-Russian data and those for the North-West Federal District (the northern part of European Russia).

Table 3. Perinatal statistics data (Federal State Statistical Service, 2014)

Indicator	**Russia**	**North-West Federal District**	**Murmansk County**
Birth rate, per 1,000 inhabitants	13.3	12.3	11.7
Perinatal mortality rate, per 1,000 newborns	8.8	8.9	7.3
Stillborn rate, per 1,000 newborns	6.0	6.8	4.8
Infant mortality, per 1,000 livebirths	7.4	5.8	6.4
Infant mortality associated with BDs, per 10,000 livebirths	16.0	13.6	12.2

Economic activities of Murmansk County consist of the extraction and processing of minerals (iron, apatite, vermiculite, phlogopite, loparite, baddeleyite and nepheline concentrates), and the refining of copper, nickel, cobalt and aluminum. More specifically

100% of the Russian production of apatite (a phosphate mineral used in fertilizers) concentrate, 44% of the nickel and 7% of copper come from Murmansk County.

Interestingly, the towns in the County are relatively small (by Russian standards) and most of them have unique economic specialization: apatite mining in Kirovsk and production in Apatiti; nickel mining/refining in Nikel and Zapolyarny, nickel refining in Monchegorsk, and aluminium production in Kandalaksha; as well as iron mining and processing in Olenegorsk and Kovdor. There is also a nuclear power plant in Polarnije Zori and naval military zones are located in the northern Barents region (111). The city of Monchegorsk was the focus of the KBR and in 2015 had 46,426 inhabitants; it is the fourth largest city in Murmansk County (109). Its main employer was/is the local nickel/copper/cobalt refinery complex.

3.2 Study design, data sources and sample size

Details of the registry-based studies shown in Figure 2 indicate that the Kola Birth Registry (KBR) and the Murmansk County Birth Registry (MCBR) were the primary data sources.

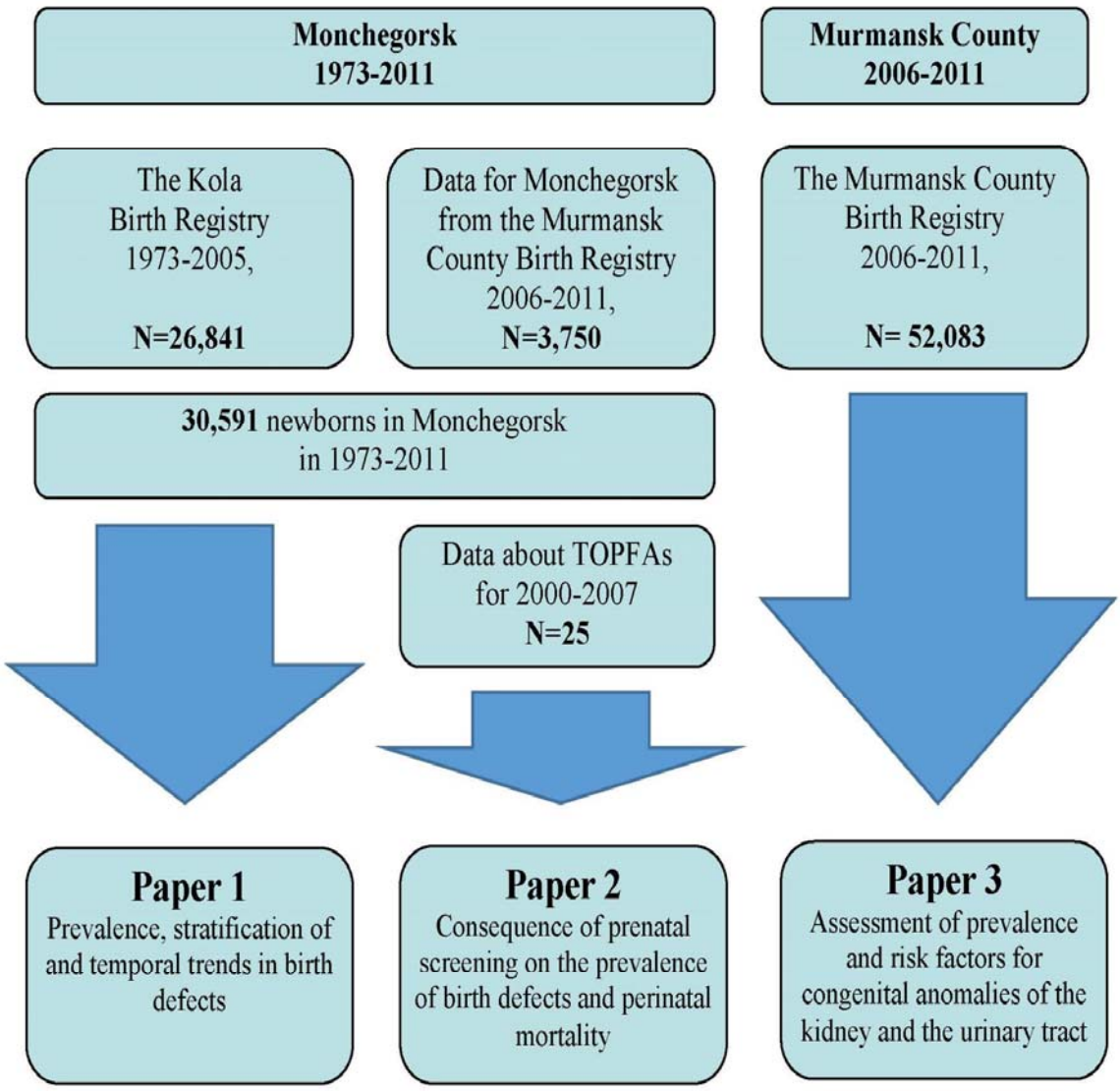

Figure 2. Study populations and sources of data

3.2.1 Papers 1 & 2

The study population consisted of all newborns (LB+SB) born in the city of Monchegorsk in 1973-2011, registered either in the KBR or the MCBR and for whom there was no missing information about the variables of interest (date of birth, birth defect presence, status at birth). In all, 30,448 newborns were included in the analyses out of 30,591 newborns registered in either registry.

Altogether, 10,317 newborns out of 10,502 who were born in the years ultrasound technology was available in the County (1994 or later) were included in the analysis of the effect of PS on perinatal mortality.

To assess the prenatal detection rates as well as the effect of PS on the continuation of pregnancies and perinatal mortality, the registry data were supplemented with information about early pregnancy terminations due to fetal anomalies (N=25) for the years 2000-2007 (provided by the Monchegorsk City Hospital).

3.2.2 Paper 3

To increase power of the study sample and exclude systematic errors caused by differences in coding practice between the two birth registries, we only used data from the MCBR. Thus the study population included all newborns born in Murmansk County in 2006-2011 and registered in the MCBR to carry out the assessment of risk factors (total N=52,086). The MCBR was also the source of information about perinatal risk factors. Altogether, 50,936 singletons without missing information about diagnosis at birth and perinatal status were included in the stratification by ICD-10 codes and the calculation of prevalence and proportional distribution of the CAKUTs; 39,322 of them (185 cases) had no missing information about the variables of interest, and thus were included in the multivariate analysis of potential risk factors.

3.3 Information about birth defects and risk factors/exposures available in the KBR and the MCBR

3.3.1 Information about birth defects

Information about BDs recorded in the registries included the presence of BDs (coded as "Y", "N" or "A" or missing in the KBR, and "0" or "1" in the MCBR) and fields for diagnoses. The KBR included both written diagnoses and ICD-10 codes, while the MCBR only had ICD-10 codes. Only newborns with diagnoses belonging to the "Q" chapter of ICD-10 codes were included in the analyses as cases. The number of newborns with missing or uncertain data about BDs was 56 in the KBR and 99 in the MCBR, which together constituted 0.2%. The majority of such cases were diagnostic misclassifications. For example, the codes K42.0 (physiological umbilical hernia) and N 47.0 (phimosis) in the KBR identify these as BDs but they are not classified so by ICD-10.

3.3.2 Information about exposures before and during pregnancy

All information about the pregnancy course and preexisting diseases among mothers in both registries include occupational status and exposures; history of previous pregnancies; lifestyle habits; chronic diseases before the pregnancy; acute conditions during current pregnancy; and pregnancy complications. ICD-10 codes for diseases are given. With some differences in field titles, the gathered information from the two registries was more or less the same. However, some differences existed. Since the KBR was set up to assess occupational exposures, it provided additional fields for information about organic solvent exposures during pregnancy. At the same time, the KBR contained information only about smoking during pregnancy, while this section in the MCBR included information about smoking before pregnancy, as well as the number of cigarettes smoked daily. Moreover, the KBR did not provide information about folic acid and multivitamin supplementation, while the MCBR contained this information for use before and during pregnancy.

Details about prenatal ultrasound screening were included in both databases, as well as gestational age at examinations and all findings had ICD-10 codes. The KBR provided

gestational ages at all examinations, while the MCBR did so for the first ultrasound and all pathological findings from scans.

3.4 Statistical analysis

The prevalence (and the 95% confidence intervals) for the total and each malformation subgroup were calculated using Wald's method. The temporal trends in prevalence and mortality were estimated using four 10-year time intervals from 1973 to 2012 and evaluated using the chi-square test for trend.

Assessment of the effects of ultrasound screening on perinatal deaths and identification of risk factors for urinary malformations involved logistic regression modelling. The multicollinearity of the independent variables were tested, and adjusted risks ratio (approximated by odds ratios) were calculated using regression of risk factors. The final regression model for Paper 2 included the following variables as independent: maternal age, prenatal screening, gestational age, BDs present, year of birth, and previous history of prenatal deaths). In Paper 3, the final model was established by inclusion of the following independent variables: maternal age, age of father, maternal body-mass index; use during pregnancy of medication, multivitamin intake, folic acid intake, cigarette smoking; evidence of alcohol abuse, chronic sex tract or urinary infections before pregnancy; other infections during pregnancy; and season of conception. The backward stepwise regression model using the likelihood-ratio method for inclusion of all studied factors and the probability criteria for removal of 0.1were used.

All the statistical analyses employed the IBM SPSS 21.0 software package.

3.5 Ethical considerations

No personal maternal information (i.e., such as first name, surname or address) was recorded in the registries, so written consent could not be obtained from the mothers. The KBR was established retrospectively, with approval from the Murmansk County Health Authority (33). In case of the MCBR, the local health authority passed legislation making birth registration and collection of medical data from hospital records mandatory (42). At the first antenatal

visit, all prospective mothers were informed that information about their pregnancy and neonates would be included in the registry database.

Both registries and their protocols received approval from the Murmansk County Committee for Research Ethics (Murmansk, Russia) and the Regional Committee for Medical and Health Research Ethics (Tromsø, Norway). The latter and the Committee for Research Ethics at the Northern State Medical University (Arkhangelsk, Russia) approved the current project.

4. Main results

4.1 Paper 1: Prevalence of birth defects in an Arctic Russian setting from 1973 to 2011: a register-based study

The total prevalence of BDs at birth and of those stratified by defect groups were calculated using all defects as the numerator (before and after excluding minor defects, according to the EUROCAT guidelines) with the total number of newborns as the denominator.

Newborns with BDs born in Monchegorsk in 1973-2011 (N=1,099) were registered either in the KBR or the MCBR. The prevalence of BDs at birth was 36.1 per 1,000 newborns (95% CI = 34.0-38.2) and, as per the EUROCAT guidelines, decreased to 26.5 per 1,000 newborns (95% CI = 24.6-28.3) when excluding minor malformation (most of them were malformations of genital organs and the musculoskeletal system). The prevalence of BDs among FDs was five times higher than for LB (167.3 per 1,000 *versus* 34.7 per 1,000). For those requiring mandatory reporting, the prevalence was 7.3/1,000 newborns (95% CI = 6.4-8.3) ─ for LB it was 6.8/1,000 (95% CI = 5.8-7.7) and 67.2/1,000 (95% CI = 38.1-97.2) among FDs.

The most prevalent group of defects was congenital malformations and deformations of the musculoskeletal system and accounted for 35.4% of all BDs. Multiple malformations represented 8.7%.

Significant positive time-trends were evident ($p<0.0001$) when comparing results for 1973-1982 and 2003-2011 for the total prevalence of BDs among newborns (23.5/1,000 to 46.3/1,000) and LB (21.9/1,000 to 45.6/1,000). By contrast, those among FDs had a tendency to decline from 169.8 per 1,000 (95% CI = 97.2–242.5) to 46.5 per 1,000 (95% CI = 0-112.1), but this trend did not reach statistical significance (p for trend = 0.12). When comparing the temporal trends for the same time interval of the stratified prevalences, they were positive for nervous system malformations and those of the eye, ear, face and neck, the genital organs and the urinary system. The last group showed the highest increase: 0.2/1,000 newborns (95% CI = 0-0.5) to 19.1/1,000 newborns (95% CI = 15.4-22.7).

4.2 Paper 2: Changes in detection of birth defects and perinatal mortality after introduction of prenatal ultrasound screening in the Kola Peninsula (North-West Russia): combination of two birth registries

The impact of implementing prenatal ultrasound screening on the birth prevalence of BDs and on perinatal mortality in Monchegorsk were evaluated using the registry data supplemented by information about terminations of pregnancy due to fetal anomalies (TOPFAs) for the period 2000-2007.

The total prevalence of BDs at birth increased 24% [34.2/1,000 (95% CI = 31.9-36.5) to 42.8/1,000 (95% CI = 38.0-47.7)] after the prenatal ultrasound screening was formally implemented, as well that among LBs [32.8/1,000 (95% CI = 30.6-35.1) to 42.3/1,000 (95% CI = 37.4-47.2)]. By contrast, the corresponding prevalence of BDs among FDs had a tendency to decrease, although the downward trend did not reach significance [172.1/1,000 (95% CI = 124.4–219.8) to 94.3/1,000 (95% CI = 13.0-175.7), with F= 1.97 and p for trend of 0.16]. Concomitantly, the prevalence of the most severe defects (reporting of which is mandatory in Russia) among all newborns did not change.

Significant declines in the prevalence at birth of congenital malformations occurred for the circulatory system, the musculoskeletal system (including deformations) and the group of other congenital malformations. A substantial increase was evident only for BDs of the group of CAKUTs.

There were 572 cases of perinatal deaths in 1973-2011 in Monchegorsk, of which 297 were SB. Out the perinatal deaths, 506 (including 244 FDs) were registered during 1973-2000 and 66 (including 53 FDs) in 2001-2011. Consequently, the perinatal mortality rate decreased from 21.2 per 1,000 newborns (95% CI = 19.4-23.1) in 1973-2000 to 10.0 per 1,000 (95% CI = 7.6-12.3) in 2001-2011, while stillborn rate decreased from 10.2 per 1,000 newborns (95% CI = 9.0-11.5) to 8.0 per 1,000 newborns (95% CI = 5.9-10.1). Clearly, the perinatal mortality for all newborns decreased two-fold during 2001-2011. At the same time, the perinatal mortality among newborns with any kind of malformation decreased from 106.6 per 1,000 newborns with BDs (95% CI = 84.3-129.1) to 21.2 per 1,000 newborns with BDs (95%

CI = 4.3-38.1), that reflected a five-fold decline. Moreover, the logistic regression analysis indicated that mothers who had undergone at least one ultrasound examination during pregnancy had a lower risk of having a newborn die during the perinatal period [adjusted OR = 0.49 (95% CI: 0.27-0.89)].

During 2000-2007, the termination of 25 pregnancies before the gestational age of 22 weeks due to severe fetal anomalies, and were not recorded in the registries. After their inclusion in the mortality rate calculations, the stillborn rate in 2000-2007 increased to 13.8/1,000 (95% CI = 10.9-13.6) from 8.5/1,000 (95% CI = 5.8-11.1); similarly, the perinatal mortality increased to 17.7/1,000 (95% CI = 14.7-22.0) from 12.4/1,000 (95% CI = 9.2-15.6). Thus, the absolute reduction of perinatal mortality due to TOPFAs in 2000-2007 was 5.3 per 1,000 newborns.

Of the 232 BDs, 81 were diagnosed prenatally and this corresponds to an overall prenatal detection rate of 34.9%.

4.3 Paper 3: Congenital anomalies of the kidney and the urinary tract: A Murmansk county birth registry (MCBR) study

Based on Paper 1, congenital malformations of the kidney and the urinary tract (CAKUTs) as a group of BDs showed the highest increase in prevalence during 1973-2011 in the city of Monchegorsk. A detailed examination of this group of BDs for the period 2006-2011 is described, with special focus on potential risk factors.

There were 203 registered newborns with CAKUTs in Murmansk County during 2006-2011, 10% of whom had multiple malformations of the urinary system. The prevalence at birth was 4.0 per 1,000 newborns (95% CI = 3.4-4.5). There were six cases of isolated single kidney cyst (Q61.0). These birth defects according to EUROCAT are minor anomalies. Thus, the prevalence at birth calculated excluding minor anomalies was 3.9 (95% CI = 3.3–4.4). Congenital hydronephrosis was the most prevalent malformation and represented 14.2% of all registered CAKUTs, although more than half of these were included in the “other congenital anomalies of the kidney” category.

In spite of the absence of significant temporal trends in the birth prevalence of CAKUTs, there was fluctuation that ranged 2.4 per 1,000 in 2006 to 5.6 per 1,000 in 2008. The observed prevalence of CAKUTs (stratified by year) in Murmansk County is compared to the EUROCAT data in Figure 3.

Newborns with missing information about potential risk factors of BDs were not included in the multivariate analysis (total n = 39,322). Among the excluded variables, the largest proportion pertained to chronic sex or urinary tract infections (n=7,380), fathers' age (n=4,367) and maternal body mass index (n=1,026). For these variables, the prevalence of CAKUTs was higher only for newborn of mothers with chronic sex or urinary tract infections in the univariate analyses.

Based on the multivariate analysis results, diabetes mellitus or gestational diabetes [adjusted OR = 4.77 (95% CI = 1.16-19.65)], infections during pregnancy [adjusted OR = 2.03 (95% CI = 1.44-2.82)], the use of any medication during pregnancy [adjusted OR = 1.83 (95% CI = 1.14-2.94)], and conception during summer [adjusted OR = 1.75 (95% CI = 1.15-2.66)], were significantly associated with CAKUTs.

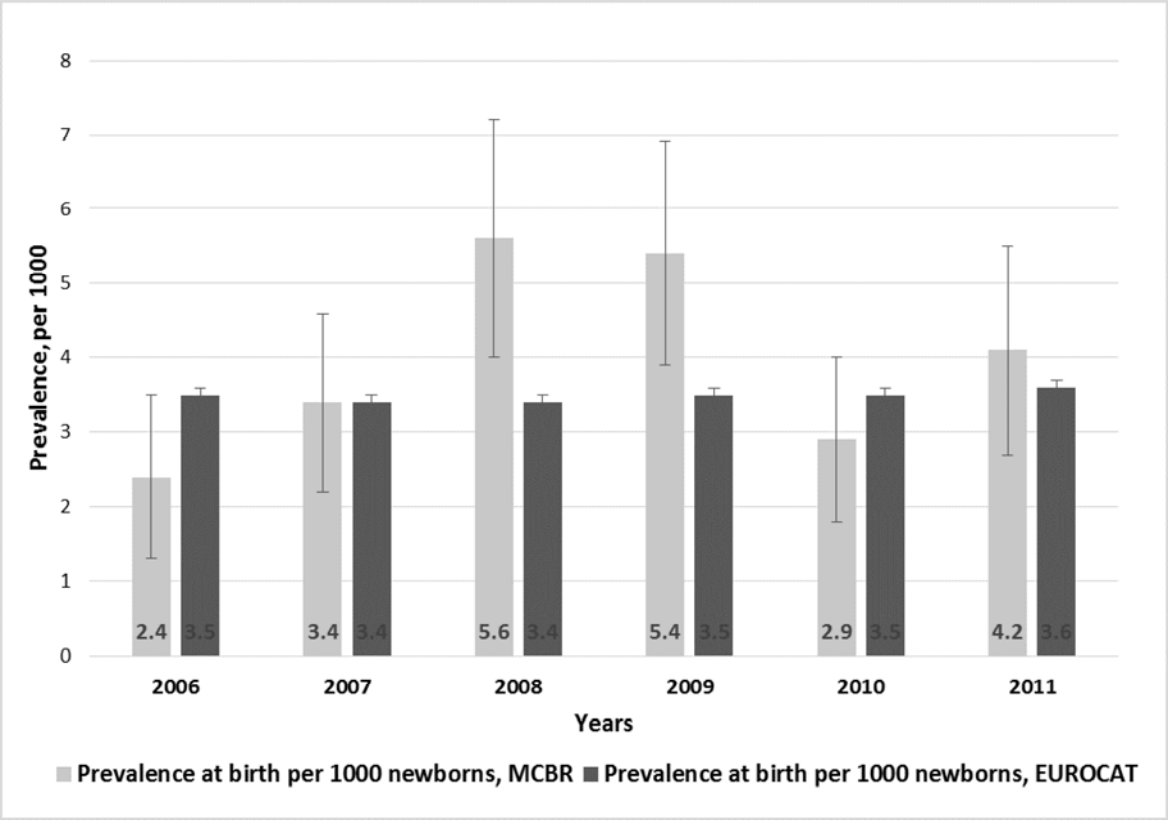

Figure 3. Comparison of the annual prevalence of congenital anomalies of the kidney and the urinary tract in Murmansk County with EUROCAT data

5. Discussion

5.1 Discussion of main results

5.1.1 Prevalence of BDs: estimation by registries *versus* official data

The observed prevalence in Monchegorsk was higher when compared to EUROCAT data (56). Since minor malformation represented a large part of the defects, after their exclusion the prevalence became comparable but remained higher for 2003-2011. We consider that the total prevalence in our study seems underestimated, likely because the period of observation short and the absence of information about TOPFAs in our registry-based prevalence calculations. Comparisons of our results with data from neighboring countries that also used MBRs for BD surveillance appear somewhat incongruent. Our 1973-2011 findings (36.1 per 1,000 newborns) are comparable with the 1967-2013 Norwegian results (33.4 per 1000 newborns, excluding TOPFAs) (112), while the prevalence of BDs in Sweden in 1992-2012 was lower (31.4 per 1,000 newborns) (113) than in Monchegorsk for the same time period in spite of a difference in antenatal screening policies.

Since the official monitoring data for Murmansk County were unavailable, we compared our birth prevalence rates with information (see Table 4) provided by the Murmansk Medical Analytical Center (MMAC) for 2002-2009 (Kovalenko AA, personal communication). Data from the MMAC include all BDs registered at birth and during the first year of life (collected according to the National Russian monitoring rules). Based on our registry data, there were 207 affected newborns in Monchegorsk in the 2003-2009 period, which corresponds with a birth prevalence of 50.6 per 1,000 newborns. The MMAC data might be higher because of the higher age limit, but were actually lower: 168 newborns or 41.1 per 1,000 children under one year. These findings correspond with comparison done in Finland, where the number of newborns with BDs reported by the MBR was higher than registered in the malformation registry (29). There are two possible explanations for this: either over reporting of BDs in the registries due to the large proportion of minor malformations not confirmed, or unsatisfactory collection of information about newborns with “non-mandatory for reporting defects” by maternity and children hospitals to the official statistics providers due to uncertainty in definition of a malformation. We suppose that a combination of the both factors occurred.

Table 4. The absolute number and prevalence (per 1,000) of BDs among children under one year in Murmansk County and for newborns in Monchegorsk in 2002-2009 (data from the KBR, MCBR and MMAC)

Year	2002	2003	2004	2005	2006	2007	2008	2009
Murmansk County (official statistics)								
N	481	402	454	442	353	369	522	460
prevalence	57.2	46.1	50.8	51.9	41.7	42.0	45.2	50.7
The city of Monchegorsk								
Data of official statistics, N	NA	8	36	31	27	20	22	24
prevalence	37.2	13.6	67.7	55.9	44.8	33.9	24.2	39.7
Registries, N	22	26	39	51	21	15	28	27
prevalence	35.4	43.1	74.0	94.1	35.6	25.4	44.8	44.0

5.1.2 Temporal trends in prevalence and sources of variability

The monitoring of temporal trends in prevalence is a main aim of surveillance. However, the prevalence fluctuations do not necessarily reflect variation of true incidences.

The total prevalence of BDs at birth increased during the 40-year observation period in Monchegorsk, but this general tendency was only valid for LBs. This is similar with EUROCAT data on birth prevalence (LB+FD) of BDs, that increased from 18.2/1000 in 1980-1989 to 21.7/1000 in 2001-2011(56). Other epidemiological studies that reported an increase in prevalence of BDs usually included early pregnancy terminations due to BDs in the calculations (74, 76, 77, 114).

The prevalence of severe BDs in the current study did not show significant changes with time, but showed a tendency to increase during 1973-2002 followed by a substantial decline in 2002-2011. Contrary to these results, investigations that estimated the birth prevalence of severe BDs without the inclusion of TOPFAs in the analysis have observed a decline in the

prevalence during the 1990s (85, 115, 116). Note that our decrease occurred for the years after implementation of PS and seems to be the primary consequence of better antenatal diagnosis of severe defects, with subsequent pregnancy termination. Moreover, the prevalence of BDs among FDs, which we presume were often incompatible with those of LBs, also had a tendency to decline.

The implementation of PS appears to explain the temporal trends in the prevalence at birth of CHD (117) and neural tube defects (85). Salvador et al (77) found a significant rise in the prevalences of nervous, respiratory, digestive and urinary defects and suggested that: "true increases in the prevalence of BDs are not expected in absence of epidemiological factors" and thus "the rise is likely due to the improvement in the detection rate of prenatal ultrasound". Better detection of BDs by using antenatal ultrasound with better documentation of the diagnoses was also mentioned as the primary explanation for an artificial increase in the prevalence of total BDs in a study carried out in Texas (USA) (75).

In our study, the highest growth in prevalence occurred for CAKUTs. It constitutes a heterogeneous group of defects, although the majority of them can be visualized easily (relatively speaking) by prenatal ultrasound. Detection rates prior to birth could be as high as 82% for CAKUTs (118), although we found it to be 42.1% in Monchegorsk (Paper 2). Nevertheless, the observed antenatal prevalence of CAKUTs was the highest among all groups of malformations (7.2 per 1,000 newborns, whose mothers had undergone at least one ultrasound examination); they represented 39.5% of the BDs recognized before birth. The upward trend in the prevalence of CAKUTs during the last decades has also been reported by others (77, 119, 120), but they did not cover long observation periods, and the growth in prevalence was not so dramatic. Thus, Chinese researchers reported a two-fold increase in the perinatal prevalence of urinary malformations in 2005-2014, with the highest being 1.46 per 1,000 in 2014 (120) . This is almost three times lower than what we have observed in Murmansk County in 2006-2011, and thirteen times lower than in Monchegorsk during 2003-2011.

A finding of potential interest is the substantial variation in the prevalence of CAKUTs between clinics in Murmansk County. It was highest in Monchegorsk and in one of the

Murmansk hospitals. Out of 203 cases with CAKUTs, 140 (68.9%) occurred in these two neonatal delivery units, even though they handled only 23.8% of all deliveries in the County. Interestingly, comparable discrepancies in prevalence appear to occur between registries but not clinics: they found large regional differences in the prevalence of congenital hydronephrosis in Europe that ranged 2 to 29 per 10,000 births (121). The authors explain this variation by a difference in the prevalence of prenatally diagnosed cases due to contrasting screening policies and interpretation of the results. The latter seems to be an appropriate reason in our case as well. Garne et al (121) did not exclude over diagnosis as a potential reason. Even though we also embrace that the quality of ultrasound examination and operator experience are key issues, we cannot not exclude an artificial concentration of complicated pregnancies in relatively large hospitals like Murmansk Hospital № 2. Presumably, better detection of BDs (including antenatal) occurs in hospitals conducting a large annual number of ultrasound examinations and multiple deliveries because of better equipment and more experienced doctors.

Speaking generally, the main contributor of the observed increase in prevalence of CAKUTs was the implementation of prenatal ultrasound screening. This improved their antenatal detection in the early neonatal period. A lower birth prevalence of CAKUTs for newborns whose mothers did not undergo ultrasound screening supports this conclusion.

5.1.3 Perinatal mortality decline

We observed a five-fold decline in perinatal mortality among newborns with BDs, and the logistic regression analysis confirmed an impact of PS. There appear to be two main reasons for this.

Firstly, early detection of malformations permitted intervention during the first hours of life in large perinatal centers with well-developed neonatal surgical care units. We analyzed data from Monchegorsk, as indicated is a relatively small city and the local hospital did not provide specialized medical care. We suspect that pregnant women prenatally diagnosed with severe fetal defects that could be surgically corrected were transferred for deliveries to the central clinics (specifically, Murmansk, Moscow or Saint-Petersburg). In consequence, a

decline in the perinatal mortality would occur in district hospitals such (such as Monchegorsk) and thereby increasing it in the central hospitals. We did not have registry data earlier than 2006 for the city of Murmansk, and therefore could not quantify this dimension.

The second and more likely reason for the observed decline is the antenatal detection of severe defects with subsequent pregnancy termination. In many countries, the wide implementation of PS has resulted in raised pregnancy terminations. For example, TOPFAs due to prenatal diagnosis of trisomy 21 and anencephaly are estimated to be 92% and 82% respectively (122). Therefore, the perinatal mortality due to congenital anomalies is lower in countries with a high proportion of pregnancy terminations following PS (123). For example, researchers in Australia have estimated that the effect of TOPFAs on the perinatal mortality rate was a 10.6% decrease in the period 1989-2000 (124).

Our termination rate of 5.4 per 1000 birth and 86.1% for pregnancies with incompatible-with-life defects corresponds well with the Australian data, which showed an increase in the TOPFAs rate from 0.6 per 1000 birth in 1982 to 6.0 per 1000 birth in 2000 (124). In our study, the reduction in occurrence of FDs resulted in a 30% decline in perinatal mortality. This is higher than in the Australian study for which it was estimated to be 15.4% in 1997 (124), but similar to data for 1987-1990 reported by Gissler et al (125) based on the Finnish Medical Birth and the Finnish Abortion Registries; they attributed one third of the decline to terminations of pregnancy due to medical reasons.

When re-calculating our perinatal mortality and stillborn rates by including the TOPFAs data for 2000-2007, the respective increases were 43% and 63%. This demonstrates the high impact TOPFAs have in the decline of both perinatal mortality and FDs. Consequently, the exclusion of TOPFAs from an analysis of perinatal mortality leads to an underestimation of this key indicator of perinatal health. The magnitude of this underestimation depends on PS policy and legislation about abortions in a country and, consequently, the difference between true and observed perinatal mortality rate is the highest in countries with mandatory ultrasound screening during pregnancy and with the availability of pregnancy terminations. EUROCAT data (54), for which the proportion of infant deaths with malformations ranged

from 23 to 44% of all infant deaths in Europe, support these interpretations; the highest proportion occurred in Dublin (Ireland) where induced abortions are not allowed and prenatal ultrasound screening is not practiced.

5.1.4 Assessment of risk factors

The assessment of BD risk factors was a primary aim of the MBRs. Since most of the pertinent information concerning maternal socio-demographic, anthropometric and life-style characteristics was collected from the expectant mother before delivery, recall and interviewer bias were minimized (126). Källen (46) considers that only prospective data collection about perinatal exposure allows the investigation of BD predisposing factors. Moreover, a large study sample permits the revelation of risk determinants, even those having moderate effects. Although the MCBR contains more than fifty thousand pregnancy outcomes, this is considerably lower in comparison to the Nordic MBRs reviewed earlier. Nevertheless, the KBR and the MCBR make up the largest dataset in Russia that contains information about various perinatal exposure to risks in relation to BD cases. Consequently, they constitute important tools for investigating causation.

Researchers are aware of the importance of reliable and valid measurements. However, registry studies based on data collected by individuals other than research team members represent the main limitation of MBRs, as they are initiated for surveillance and monitoring (127). Even when individuals collecting the data are well trained and highly motivated to document procedures correctly, many of the variables measured contain a subjective component ─ especially in terms of the classification of perinatal maternal conditions and risk factors.

In spite of some limitations connected with missing data and the possibility for misclassification, we considered our data about potential risk factors for CAKUTs suitable for a detailed analysis of our study population. For chronic infections of the sex and urinary tract and fathers' age,14.4% and 8.5% of the data were missing respectively, while all other variables had a lower proportion of missing items when compared to the Nordic registries (24). Specifically, the proportion of missing data in our study was 1.8% for smoking during

pregnancy, 2.0% for maternal weight and height, 0.7% for folic acid intake and 0.4% for multivitamin use.

As indicated in the Section 4.3, we found that diabetes mellitus or gestational diabetes, infections during pregnancy, usage of any kind of medication and conception during summer months associated with CAKUTs. While increased risks due to diabetes and acute infections are (128-132), summer conception seems less explored. Perhaps this is due to the geographical location of Murmansk County. A previous study based on EUROCAT data (133) has also reported a higher prevalence of congenital hydronephrosis and of other urinary defects among newborns conceived during the summer. However, the latter study pertains to countries located considerably south of Murmansk County, and thus would have different temperature and daylight regimens.

We also assessed an effect of folic acid and multivitamin supplementation during pregnancy, and found no association of folic acid use nor of multivitamin during pregnancy with risk of CAKUTs. This is inconsistent with a more recent case-control study that reports an increased probability of such anomalies among women using folic acid supplement and the decreased risk of CAKUTs among newborns whose mothers use multivitamin intake (130).

We did not examine changes in prevalence of the mentioned risk determinants over time, but one can suppose that such changes in the health status of pregnant women exist. Increased mean maternal age, proportion of obesity, diabetes and smoking are likely examples of such changes, and these could be partly responsible for the observed increase in the prevalence of CAKUTs and other groups of malformations.

5.2 Methodological challenges

The thesis has some limitations, which could have led to possible underestimation of the total prevalences of BDs and misclassification of their structure, such as overestimation of unspecified malformations and underestimation of others.

5.2.1 Case assessment and prevalence estimation

The main problem in BD investigations includes difficulties in the determination of ratios (51, 134), because of impossibility to exactly define the population at risk and an inability to include all unknown FDs and unknown pregnancies. Many embryos with BDs die at small gestational age, and their survival depends on the severity of defects. The proportion of FDs caused by chromosomal anomalies or structural BDs varies in different data sets from 3.3% (135) to 50% (136). It is important that FDs at early gestational ages are usually associated with chromosomal anomalies, while structural defects (for example NTD) are responsible for FDs at more advanced gestational ages (135). Since we are not able to study the entire population at risk, the denominator for incidence calculations is unknown. Consequently, prevalence is considered as the recommended entity for assessing the frequency of BDs (137). In addition, Mason et al (137) recommend that the number of SBs not be included in the denominator, but acknowledged that not doing so "has relatively little impact on the final prevalence estimate". At the same time, Forrester et al (135) suggests including all known FDs, even those with early gestational ages. He also supposes, that identification of "as many infants and fetuses with BDs as possible … may be useful for BDs activities other than surveillance" (135).

In the current project, we have described only the prevalence of BDs at the time of diagnosis. We used birth for the estimation of prevalence, even though some of the BDs were evident before the delivery. Since we investigated the registries as a surveillance tool, we did not exclude FDs registered in the KBR or the MCBR. The number of FDs in our study sample was less than 1%, and thus our findings are consistent with Mason's statement quoted above (137). TOPFAs under 22 weeks of gestation and early spontaneous FDs were not included in the KBR or in the MCBR. Consequently, the true prevalence could be higher than calculated, especially for the period subsequent to the establishment of PS (years 2001-2011). However, we included data on TOPFAs in the prenatal detection rate calculations (Paper 2) to render the estimates of antenatal detection rate more precise.

Birth surveillance systems have a tendency to underestimate the true prevalence of BDs among delivered newborns, since the short follow-up period between the birth and the

mother's discharge prevents the capture of all BDs. Their ascertainment is often incomplete, even for severe or easy visualized defects. For example, of all cases only 94% of cleft lip and palate, 83% of cleft lip, and 57% of cleft palate were reported in the MBR of Norway (20). Neither do birth defect registries have 100% ascertainment of severe defects, and for example, the under-ascertainment of spina bifida and cleft palate for the Swedish MBR was 6% and 13%, respectively (138). The estimated rates in such cases are functions of the degree of PS and of early neonatal diagnostic measures, while the true rates also include children who have malformations revealed later in life. Only 67% of birth anomalies appear to be identifiable prenatally or during the first month (139). For example, the average age for CHD diagnosis is between the first and the second year of life, but most of the late diagnoses are minor defects (140).

The experience of the operators and the quality of ultrasound examinations could also influence the estimation of prevalence. During the first years of the screening implementation, there were no clear standard operating procedures or unified interpretations of results in Russia, nor for indications for postnatal ultrasound examination period. For example, there were no exact criteria for differential diagnosis between the two most common diagnosed conditions during the prenatal period, namely: pyelectasis (slight dilatation of kidney pelvis with normal parenchyma, which is the first sign of urine outflow disturbance) and hydronephrosis (distension of the kidney pelvis with atrophic parenchyma). The recommended normal size of the renal pelvis has varied from 4 mm to 10 mm during last ten years (141). Interestingly, the Russian National Association of Prenatal Diagnostics recommends using a pelvis size of 5 mm as a cut-off for the second trimester of pregnancy and 7-8 mm for the third (141). Since there were no strict ultrasound criteria for this condition, prevalence estimates for hydronephrosis varied between clinics.

The transfer of pregnant women in cases of suspected fetal BDs to central regional or Moscow clinics constituted an additional source for underestimating the prevalence. Hence, based on the data from the Monchegorsk polyclinic (Voitov A.A., 2014, personal communication), during 2000-2007 two newborns with hypoplasia of the left heart were delivered to Moscow in 2002 and 2003. Although the deliveries from mothers transferred to

Murmansk were included in the MCBR in the years 2006-2011, they have "Murmansk" as the place of birth and thus if from Monchegorsk were not included in the analysis for this city. Neither were neonates prenatally diagnosed with severe BDs but born in other major clinics (Moscow or St-Petersburg) because the mothers were transferred there were not recorded in the KBR or the MCBR. The proportion of such cases was not high and represented less than 1% among all newborns with BDs, and thereby had a minor impact on our analyses. Misclassifications linked to such transfers from secondary hospitals could impede investigations of geographical variation in BD prevalence, but this was beyond the scope of the thesis.

Since TOPFAs were not registered and the follow-up period was short, we conclude that the total prevalence may have been underestimated but was adequate for severe malformations among LBs.

5.2.2 The problem of confounding

In our study, we controlled for confounding at the statistical analysis stage. Our investigations of associations between PS and perinatal mortality (Paper 2) and between risk factors during pregnancy and the occurrence of CAKUTs (Paper 3) were potentially subject to bias from confounding variables. Adjustment for confounders was our primary tool for addressing this source of bias.

As a first step in the estimation of BD risk factors, univariate analysis identified variables that potentially could be associated with malformations of the kidney and the urinary tract. Backward stepwise multivariate regression analysis that applied a probability criterion of ≥ 0.1 for removal then followed. Inclusion of all independent variables as categorical in the model could potentially lead to imperfect adjustment (134), and thereby introduce bias due to residual confounding. We therefore employed stratification with more than two categories for age and body mass index.

Our regression model for assessing the effect of PS (Paper 2) included only gestational age, maternal age, year of delivery and history of previous perinatal deaths, and presence of BDs

among newborns as main confounders. We did not control for all possible confounders such as comorbidities of mothers and complications of pregnancy, previous history of stillbirth, and maternal socio-economic status. This was due to differences in coding between the registries, and up to 5% of the data was missing for some variables. Moreover, our sample size for the estimation of PS was relatively small and the number of variables for use in the final regression model was limited.

Another issue pertaining to multivariate analysis is that often birth registries are limited in statistical power for detecting teratogens with moderate effects (1), leading to an incomplete estimation of risk factors.

5.2.3 Influence of bias

Of the two major types of systematic error, namely selection and information bias, the latter has more relevance for our research. We concluded that selection bias did not directly apply to the MCBR, as the registry covered about 99% of the deliveries in Murmansk County each year (43). Nevertheless, we might suspect that the unregistered pregnancies (1%) had different characteristics or outcomes compared to the registered women or children, but we had no possibility of checking this suspicion.

Information bias pertains to different assessment of risk factors or defining outcomes for the comparison groups (134). In our work, the main source of informational bias connected with outcome was the historical difference in coding practices of defects. In part the data in the KBR were retrieved retrospectively (back to 1973) using existing medical documentation and prospectively from 1995 on. For the early years, the classification of diagnosed BDs involved the conversion of ICD-9 to ICD-10 codes (32, 34). This could be a reason for non-differential misclassification of BDs in the KBR, although we consider that this did not influence the total prevalence estimates. All coding for the MBCR conformed to the ICD-10 classification. Another possible source of information bias was the difference in coding practices between hospitals in the Murmansk County health network. To minimize this, hospital staff recording data for the MCBR were regularly trained to make coding practice more uniform (43).

However, we could not exclude the possibility of some differences, especially regarding maternal conditions before and during pregnancy.

Information bias was not limited to mothers and infants. Underreporting of sensitive information like maternal smoking is also critical. Alcohol and drug consumption were not self-reported by mothers, but noted by a doctor when signs of alcohol or drug abuse were evident or noted in primary medical documentation (43). Such information biases could lead to non-differential misclassification of an exposure, and would most likely attenuate the estimate of risk (e.g., BDs among smoking mothers).

Possible measurement errors may also have occurred in estimating the gestational ages recorded in the registries. To minimize quality assurance, exercises were done that minimized misclassification bias. To make the definition of gestational age uniform, we used gestational age defined by the first day of last menstrual period.

5.2.4 Missing data

Missing observations are an important issue when working with registries. In general, the validity of the KBR and the MCBR appears satisfactory for the epidemiological research conducted. Most of the information, such as gestational age and newborn's body weight, has more than one source and could thus still be recorded in the database even if such information was missing in one of the primary data sources (e.g., history of delivery). According to Vaktskjold et al. (34), the proportion of records in the KBR with missing information exceeded 5% for only six of the registered descriptors, namely about the fathers (29.0%), employer (10.3%) and occupation (14.8%). These omissions occurred mainly in the oldest delivery records. A similar situation was observed for the MCBR, as the identity of the father was unknown for 9.1% of the deliveries in 2007 (43), and was confirmed in Paper 3, as for 8.3 % of the cases the age of the father was not available. This variable was a predictor in the univariate analysis. Its inclusion in the multivariate analysis could potentially have influenced the results due to the missing data. Indeed, we checked the prevalence of urinary malformations among newborns with missing information about fathers and found a lower prevalence of CAKUTs in this group.

Another variable for which a large proportion of information was missing in the MCBR was maternal chronic genital and urinary tract infections. The exclusion of all newborns with missing information led to insufficient statistical power to detect an effect of this variable on the risk of CAKUTs. Related issues were the misclassification of this risk factor due to different diagnostic practices and an inherent reluctance to report these (i.e., non-differential bias). Inclusion of missing values in the variable "maternal chronic sex and urinary tract infections" as non-exposure led to increased risk ratios for this exposure.

5.3 Public health implication of the findings

This thesis is the first epidemiological study to investigate the total birth prevalence of BDs, their stratification by ICD-10 codes and temporal trends, as well as the impact of PS in North-West Russia. The results demonstrate the advantages and disadvantages of the existing MBRs for both research and surveillance of BDs. Our research activities provide an overview and insight of the distribution and temporal variability in the prevalence of BDs in Murmansk County, but also provides a focus on one city with unique occupational and environmental exposures. We tried to perform our data analyses in accordance with EUROCAT guidelines, which allows a comparison of the findings with European countries.

We believe that the results obtained will be of interest not only for researchers but will also be used by practicing doctors for identifying the group of pregnant women with increased risk of CAKUTs, and for promoting prenatal screening programs and their effectiveness. Moreover, additional knowledge about the burden of BDs among the newborn population should help in the planning of health care for affected children and implementation of health care programs that focus on BDs.

We have demonstrated that the Murmansk County MBRs constituted powerful tools for investigating BDs, especially from the historical perspective. Combining BD data for the MBRs with diagnoses made after hospital discharge seems to be realistic. It would improve the BD surveillance system and opens up the possibility of integration with international surveillance systems. The existing problem of linkage between databases in the absence of personal identification numbers could be solved by using the birthdates of both the child and

mother, along with the name of the delivery hospital for identification as suggested by Anda (42).

Based on our results, we endorse the current system of PS employed in Russia and recommend the establishment and promulgation of strict criteria for antenatal and postnatal diagnoses of BDs and of clinical protocols for the management of such newborns. Moreover, the idea of placing most of the screening procedures in large medical centers with high annual number of examinations and experienced staff seems rational.

5.4 Future activities and research

5.4.1 Future of birth registries in North-West Russia as an instrument of perinatal surveillance

To our knowledge, the birth two registries in the Kola Peninsula were the only operational examples in Russia when due to lack of funding the MCBR was terminated in 2011 (Kovalenko AA, personal communication). Another attempt to create a county-based MBR was undertaken in Arkhangelsk in 2011 (namely the Arkhangelsk County Birth Registry, ACBR) as a cooperative project between UiT-The Arctic University of Norway, the Norwegian Institute of Public Health and the Ministry of Health Care of Arkhangelsk County represented by the Arkhangelsk Regional Medical Analytical Center (Grjibovski AM, Usynina AA, personal communication). The prospective registration of births started on the January 1, 2012. However, it also stopped operating in 2015 due to the discontinuation of financial support from abroad.

As indicated earlier the Monchegorsk, Murmansk County and Arkhangelsk county-based birth registries were dependent on foreign (mostly Norwegian) financial and research personnel support. They were set up for epidemiological investigations rather than surveillance. In our assessment, a lack of sharing/promoting of data in the registries with health-care professionals and policy-makers and the absence of All-Russian legislation about the establishment of birth registries and their use appear to have been responsible. The medical statistics in Russia mostly constitute summarized data without the possibility of linkage outcomes to risk factors or detrimental exposures at the individual level. We hope

that our work together with other projects based on these two birth registries will increase the understanding of their necessity and use in perinatal surveillance and essential research of risk factors, perhaps even restarting their operation. At the time of writing the thesis, the future of the MBRs in Russia remains vague. We hope that the published research papers and the PhD theses based on it demonstrate the necessity and usefulness of the MBRs in various fields of public health.

5.4.2 Practical recommendations to increase the validity and research potential of the Murmansk County Birth Registry

Based on the findings of this doctoral work, some practical suggestions are stated below that could increase the validity and application of the MCBR as a tool for the surveillance of BDs. Implementing some of the suggestions outlined below is recommended if the MCBR were to be resumed,

1. Mandatory registration of all pregnancy terminations in case of prenatally diagnosed BDs. The process of data collection in such cases might be limited by the most important fields, namely information about prenatal and autopsy diagnosis, parental age and occupation. It could constitute a separate database (register) of pregnancy terminations as done in Estonia (26).
2. Continuation of the registration of BDs after hospital discharge and adding this information to the MCBR, by linkage to the National system of monitoring BDs. Linkage between databases might best be done by maternal and child birthdate and delivery hospital location (name).
3. Only diagnoses belonging to the Q-chapter of ICD-10 constitute “birth defects”. To make data collection and transferring more reliable, we suggest that all such diagnoses be registered and not to exclude the minor ones, since this could better be done during any subsequent data analysis.
4. Using a code manual to harmonize data transfer from primary documentation seems a prudent measure to protect against bias and consequent misclassifications. Although not a novel concept, the use of such manual seems pertinent in terms of ensuring

methodological soundness and repeated emphasis on one's ethical obligations to conduct research with maximum reliability and validity.

5. Information about chronic diseases before pregnancy needs to be more thorough by adding an additional field about exacerbations of any chronic conditions during pregnancy. We suggest that acute infections during pregnancy and exacerbation of chronic infections noted separately in order to avoid misclassification of these risk factors.
6. Medication used in pregnancy should only involve international non-proprietary names (i.e., INN; not tradenames). We understand that it might be problematic to achieve 100% coverage of all medications used during pregnancy, since most are available without a prescription in Russia. All medications mentioned in the primary medical documentation should be also be recorded.
7. Finally, formal systematic validation of the database is critical. We recommend that all fields about BDs and risk factors be included in routine quality assessment and control.

5.4.3 Future research potential of an ongoing birth registries in Northwest Russia

Besides being a surveillance tool, the continuation of birth registration by the MCBR has enormous research potential to investigate all possible pregnancy outcomes. As the number of registered pregnancy outcomes increases, the improved statistical power of the data opens up the possibility of estimating the prevalence of rare events and their variability. In case of BDs, this would generate the possibility to delineate additional forms of defects and to study more risk factors.

As mentioned above, prenatal risk factors and temporality of maternal health status or habits need investigation, including the possibility that the increasing trend in mean maternal age is a factor underlying the temporal trends in prevalence of BDs. We also suspect the increase in the prevalence of smoking among pregnant women during the last decades. For example, recent studies show it to be as high as 18.9% (142). Moreover, the prevalences of such adverse maternal factors as obesity, diabetes and chronic genital or urinary infections could

also change over time. Current studies from other countries report their upward trends (106, 107). Furthermore, the compliance and effect of periconceptional folic acid supplementation among Arctic populations need further study.

The geographical variation in the distribution of BDs has not been a surveillance objective. As indicted earlier, Murmansk County has a high concentration of specialized industries and represents unique research potential for ecological and cohort studies of environmental and occupational impacts of industries including the refining/production of nickel, copper, cobalt, iron, aluminum and apatite. Arkhangelsk County has many pulp and paper plants, which potentially could affect pregnancy outcomes and seem worthy of investigation using the ACBR. Preliminary comparison of total BDs prevalence using the MCBR data showed that the total rates varied between communities, with the highest in Kandalaksha (56 per 1,000) and the lowest in Zaozersk (7 per 1,000). It is interesting, that the prevalences of BDs in Monchegorsk, Apatity and Kirovsk were also higher in comparison with All-County levels: 41/1,000, 38/1,000, 38/1,000 *versus* 29/1,000 respectively. A problem of such geographical surveillance is a small sample-size. In the MCBR, there are 3,743 births in Monchegorsk, 2,922 in Kirovsk, 3,390 in Apatiti, and 3,397 in Kandalaksha during 2006-2011. We need more registered deliveries to detect geographical variability in the prevalence of BDs to be able to detect the role of industrial and ambient exposure to pollutants. Continuation of the birth registration process is essential for success. Using occupational status and place of residence, individual exposure might be assessed using occupational exposure data and results from local pollution monitors, and this would allow risk assessments. Clearly, such considerations would require large data sets. The need for such studies constitutes an additional objective for restarting birth registration in North-West of Russia.

6. Concluding remarks

It is clear that the medical birth registries set up in the Kola Peninsula are useful in the surveillance of BDs and related epidemiological research (including associated risk factors). One of the inherent limitations could be resolved by including the registration of TOPFAs and a linkage between the MCBR and national monitoring of BDs. Based on our studies using the KBR and MCBR we conclude that:

- The observed prevalence of BDs in Monchegorsk was higher than in Europe, although a quarter of cases was represented by minor malformations of the genital organs and the musculoskeletal system;
- An increase in the total prevalence of BDs from 1973 to 2011 occurred among LBs, with that for CAKUTs exhibiting the highest growth;
- The primary contributor to changes in prevalence was the implementation of prenatal ultrasound screening, nevertheless, BD risk factors associated with maternal lifestyle and health status need more investigation.
- Diabetes mellitus or gestational diabetes, infections during pregnancy, usage of any kind of medication and conception during summer months were associated with increased risk of CAKUTs.

Our findings have direct implication for improving perinatal care in Murmansk County. They also provide a framework for restoring ongoing registration of pregnancy outcomes in Murmansk County by integrating birth registration and perinatal surveillance. The hope is that the doctoral research described constitutes an incentive for the recommencement of ongoing birth registration in the region.

7. References

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Paper I

Prevalence of birth defects in an Arctic Russian setting from 1973 to 2011: a register-based study

Vitaly A Postoev, Evert Nieboer, Andrej M Grjibovski and Jon Øyvind Odland

Paper II

Changes in detection of birth defects and perinatal mortality after introduction of prenatal ultrasound screening in the Kola Peninsula (North-West Russia): combination of two birth registries

Vitaly A. Postoev, Andrej M. Grjibovski, Evert Nieboer and Jon Øyvind Odland

Paper III

Congenital Anomalies of the Kidney and the Urinary Tract: A Murmansk County Birth Registry Study

Vitaly A. Postoev, Andrej M. Grjibovski, Anton A. Kovalenko, Erik Eik Anda,
Evert Nieboer, and Jon Øyvind Odland

Appendix A

Notification about newborn with congenital birth defects (original document in Russian)

УТВЕРЖДЕНО
Приказ Минздрава России
от 10.09.98 №268
Медицинская документация
форма №025-11/у-98

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ
РОССИЙСКОЙ ФЕДЕРАЦИИ

Полное наименование и адрес учреждения_____
_____
_____
_____
_____
_____

ИЗВЕЩЕНИЕ НА РЕБЕНКА С ВРОЖДЕННЫМИ ПОРОКАМИ РАЗВИТИЯ

ФИО ребенка: □□□□□□□□□□□□□□□□ □□□□□□□□□□□□□ □□□□□□□□□□□□□□□□ Дата рождения: □□□□□□□□ Дата смерти: □□□□□□□□ ФИО матери: □□□□□□□□□□□□□□□□ □□□□□□□□□□□□□ □□□□□□□□□□□□□□□□	Место проживания матери во время беременности: респ./ край/ обл. _____ авт. обл./ округ _____ р-н _____ гор./ пос./ с./ дер._____ _____

Возраст матери □□	Порядковый номер родов □□	Масса тела при рождении: □□□□ г

Состояние при рождении:	живорожденный □		мертворожденный □	
Пол ребенка:	М □	Ж □	интерсекс □	неизвестен □
Близнецовость:	да □		нет □	
Выписан (переведен):	домой □		в больницу □	
	жив □		умер □	
Направление на аутопсию:	да □		нет □	

Описание врожденных пороков и аномалий развития:

Диагноз: Код по МКБ □□□□

Выявлен впервые да □ нет □

Примечание: информация роддома о врожденном пороке (пороках)
развития подтверждается: да □ нет □

Подпись _____(_____) Дата « »_____19 __г.

Appendix B

Notification about newborn with congenital birth defects (translated into English)

APPROVED
Ministry of Health Care Order №268 dated 10.09.1998

Medical documentation
Form №025-11/y-98

Ministry of Health Care of Russian Federation

Hospital name and address_____
_____
_____
_____
_____
_____

NOTIFICATION ABOUT CHILD WITH CONGENITAL BIRTH DEFECTS

Child name, surname: □□□□□□□□□□□□□□□□ □□□□□□□□□□□□□ □□□□□□□□□□□□□□□□ Date of birth: □□□□□□□□ Date of death: □□□□□□□□ Mother's name, surname: □□□□□□□□□□□□□□□□ □□□□□□□□□□□□□ □□□□□□□□□□□□□□□□	Mother's address during the pregnancy: Region _____ District_____ City_____

Maternal age □□	Delivery's number □□	Birth weight: □□□□ г

Newborn's status:	livebirth □	stillborn □		
Newborn's sex:	M □	F □	intermediate □	unknown □
Twins:	yes □	no □		
Discharged:	to home □	to hospital □		
	alive □	died □		
Autopsy:	yes □	no □		

Description of all congenital anomalies:

Diagnosis: ICD-10 code □□□□

Primary diagnosed yes □ no □

Information about birth defects from maternity hospital is confirmed: yes □ no □

Signature _____(_____) Date « » _____19 __г.

Appendix C

Prevalence of selected birth defects according to the Kola Birth Registry and the Murmansk County Birth Registry

Table A1. Prevalence of selected malformations in Monchegorsk in 1973-2005 (according to the Kola Birth Registry)

Anomaly	LB N	FD N	Total N	Total Prevalence	LB Prevalence	FD Prevalence
Anencephalus and similar	2	5	7	0.27	0.08	21.83
Encephalocele	0	0	0	0.00	0.00	0.00
Spina Bifida	14	3	17	0.66	0.55	13.10
Hydrocephalus	28	3	31	1.21	1.10	13.10
Microcephaly	12	1	13	0.51	0.47	4.37
Anophthalmos/micropthalmos	2	0	2	0.08	0.08	0.00
Congenital cataract	1	0	1	0.04	0.04	0.00
Anotia	2	0	2	0.08	0.08	0.00
Common arterial truncus	1	0	1	0.04	0.04	0.00
Transposition of great vessels	1	0	1	0.04	0.04	0.00
Single ventricle	2	2	4	0.16	0.08	8.73
Ventricular septal defect	9	2	11	0.43	0.35	8.73
Atrial septal defect	8	1	9	0.35	0.31	4.37
Atrioventricular septal defect	3	0	3	0.12	0.12	0.00
Tetralogy of Fallot	0	0	0	0.00	0.00	0.00
Tricuspid atresia and stenosis	0	0	0	0.00	0.00	0.00
Ebstein's anomaly	0	0	0	0.00	0.00	0.00
Pulmonary valve stenosis	0	0	0	0.00	0.00	0.00
Aortic valve atresia/stenosis	0	0	0	0.00	0.00	0.00
Mitral valve anomalies	0	0	0	0.00	0.00	0.00
Coarctation of aorta	0	0	0	0.00	0.00	0.00
Aortic atresia/interrupted aortic arch	0	0	0	0.00	0.00	0.00
Patient ductus arteriosus	20	0	2	0.08	0.08	0.00
Choanal atresia	12	0	12	0.47	0.47	0.00
Cleft lip	25	2	27	1.05	0.98	8.73
Cleft palate	15	0	15	0.58	0.59	0.00
Oesophageal atresia	5	1	6	0.23	0.20	4.37
Duodenal atresia or stenosis	1	0	1	0.04	0.04	0.00
Atresia or stenosis of other parts of small intestine	3	0	3	0.12	0.12	0.00
Ano-rectal atresia and stenosis	2	0	2	0.08	0.08	0.00
Atresia of bile ducts	2	0	2	0.08	0.08	0.00
Diaphragmatic hernia	1	0	1	0.04	0.04	0.00
Gastroschisis	2	0	2	0.08	0.08	0.00
Omphalocele	4	0	4	0.16	0.16	0.00
Multicystic renal dysplasia	1	0	1	0.04	0.04	0.00
Congenital hydronephrosis	10	0	10	0.39	0.39	0.00
Bladder exstrophy and/or epispadia	2	1	3	0.12	0.08	4.37
Posterior urethral valve and/or prune belly	2	0	2	0.08	0.08	0.00
Hypospadias	45	0	45	1.75	1.77	0.00
Indeterminate sex	0	0	0	0.00	0.00	0.00
Limb reduction defects	11	0	11	0.42	0.43	0.00
Club foot - talipes equinovarus	0	0	0	0.00	0.00	0.00
Hip dislocation and/or dysplasia	24	0	24	0.93	0.94	0.00
Polydactyly	48	0	48	1.87	1.89	0.00
Syndactyly	13	0	13	0.51	0.51	0.00

Anomaly	LB N	FD N	Total N	Total Prevalence	LB Prevalence	FD Prevalence
Congenital constriction bands/amniotic band	0	0	0	0.00	0.00	0.00
Situs inversus	1	0	1	0.04	0.04	0.00
Conjoined twins	0	2	2	0.08	0.00	8.73
Congenital skin disorders	79	0	79	3.08	3.10	0.00
Down syndrome	26	2	28	1.09	1.02	8.73
Patau syndrome/trisomy 13	0	1	1	0.04	0.00	4.37
Edward syndrome/trisomy 18	1	0	1	0.04	0.04	0.00
Turner syndrome	1	0	1	0.04	0.04	0.00

Table A2. Prevalence of selected malformations in Murmansk County in 2006-2011 (according to the Murmansk County Birth Registry)

Anomaly	LB N	FD N	Total N	Total Prevalence	LB Prevalence	FD Prevalence
Anencephalus and similar	2	0	2	0.04	0.04	2
Encephalocele	2	0	2	0.04	0.04	2
Spina Bifida	4	0	4	0.08	0.08	4
Hydrocephalus	26	0	26	0.51	0.51	26
Microcephaly	1	0	1	0.02	0.02	1
Anophthalmos/micropthalmos	2	0	2	0.04	0.04	2
Congenital cataract	1	0	1	0.02	0.02	1
Anotia	5	0	5	0.10	0.10	5
Common arterial truncus	2	0	2	0.04	0.04	2
Transposition of great vessels	0	2	2	0.04	0.00	0
Single ventricle	1	0	1	0.02	0.02	1
Ventricular septal defect	154	3	157	3.06	3.02	154
Atrial septal defect	99	1	100	1.95	1.94	99
Atrioventricular septal defect	7	0	7	0.14	0.14	7
Tetralogy of Fallot	6	1	7	0.14	0.12	6
Tricuspid atresia and stenosis	1	0	1	0.02	0.02	1
Ebstein's anomaly	1	0	1	0.02	0.02	1
Pulmonary valve stenosis	9	0	9	0.18	0.18	9
Aortic valve atresia/stenosis	4	0	4	0.08	0.08	4
Mitral valve anomalies	0	1	1	0.02	0.00	0
Coarctation of aorta	3	0	3	0.06	0.06	3
Aortic atresia/interrupted aortic arch	10	0	10	0.19	0.20	10
Patient ductus arteriosus	35	0	35	0.68	0.69	35
Choanal atresia	4	0	4	0.08	0.08	4
Cleft lip	18	1	19	0.37	0.35	18
Cleft palate	38	0	38	0.74	0.75	38
Oesophageal atresia	12	0	12	0.23	0.24	12
Duodenal atresia or stenosis	5	0	5	0.10	0.10	5
Atresia or stenosis of other parts of small intestine	2	0	2	0.04	0.04	2
Ano-rectal atresia and stenosis	9	0	9	0.18	0.18	9
Atresia of bile ducts	0	0	0	0.00	0.00	
Diaphragmatic hernia	6	0	6	0.12	0.12	6
Gastroschisis	6	0	6	0.12	0.12	6
Omphalocele	5	0	5	0.10	0.10	5
Multicystic renal dysplasia	1	0	1	0.02	0.02	1
Congenital hydronephrosis	43	0	43	0.84	0.84	43
Bladder exstrophy and/or epispadia	2	0	2	0.04	0.04	2
Posterior urethral valve and/or prune belly	7	0	7	0.14	0.14	7
Hypospadias	69	1	70	1.36	1.35	69
Indeterminate sex	1	0	1	0.02	0.02	1
Limb reduction defects	11	0	11	0.21	0.22	11
Club foot - talipes equinovarus	7	0	7	0.14	0.14	7
Hip dislocation and/or dysplasia	22	0	22	0.43	0.43	22
Polydactyly	68	0	68	1.33	1.33	68
Syndactyly	61	0	61	1.19	1.20	61

Anomaly	LB N	FD N	Total N	Total Prevalence	LB Prevalence	FD Prevalence
Congenital constriction bands/amniotic band	1	0	1	0.02	0.02	1
Situs inversus	1	0	1	0.02	0.02	1
Conjoined twins	0	0	0	0.00	0.00	0
Congenital skin disorders	22	0	22	0.43	0.43	22
Down syndrome	37	0	37	0.72	0.73	37
Patau syndrome/trisomy 13	0	0	0	0.00	0.00	0
Edward syndrome/trisomy 18	0	0	0	0.00	0.00	0
Turner syndrome	0	0	0	0.00	0.00	0