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Epidemiology and new opportunities of investigating risk factors for congenital malformations in Northwest Russia: a registry-based linkage study

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Anton Kovalenko

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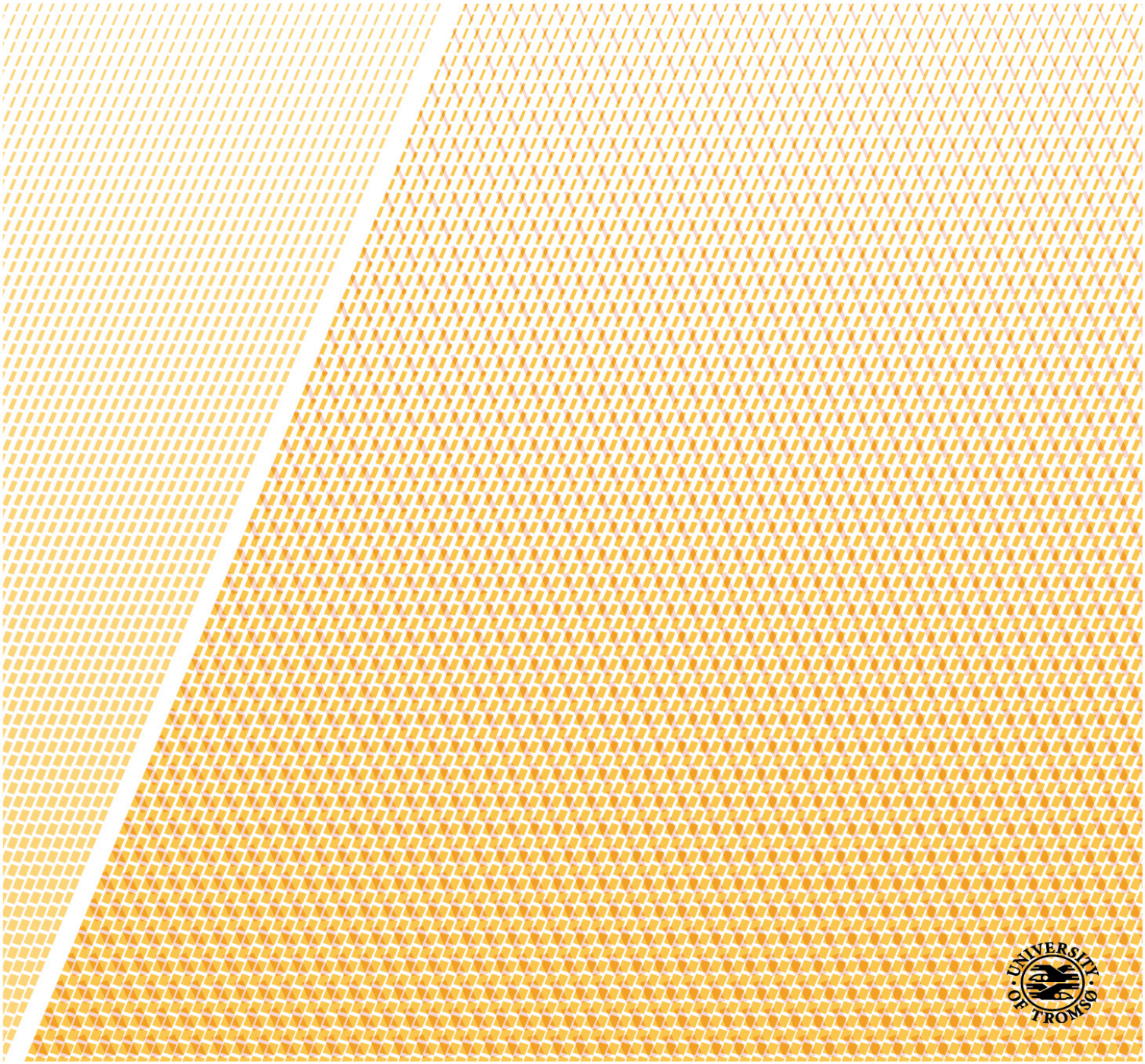

Epidemiology and new opportunities of investigating risk factors for congenital malformations in Northwest Russia: a registry-based linkage study

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A dissertation for the degree of Philosophiae Doctor (PhD)

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ABSTRACT (in English)

Background: To date, there is a lack of population-based health registries in Russia. Without availability of such data, estimating the size of a public health problem is challenging. Birth defects constitute an important public health issue as they are the main causes of perinatal and infant mortality. Using several medical sources for birth defects' surveillance may therefore help improve public health. To address incomplete data coverage, the studies described in this thesis all have a registry-based study design, and were based on the linkage of the Murmansk County Birth Registry (MCBR) and the Murmansk Regional Congenital Defects Registry (MRCDR) to investigate the epidemiology and selected risk factors for congenital malformations.

Aims: The specific aims of this thesis were to: 1) combine data from the MCBR and MRCDR to identify possible under-reporting of birth defects and comparing their prevalence in Murmansk County with those of Norway and Archangelsk County; 2) explore potential risk factors that may help explain the high occurrence of hypospadias in Murmansk County; 3) identify maternal risk factors for the most frequent cardiovascular malformations, namely ventricular septal heart defects.

Methods: The study population included all 52 806 live- and stillbirths recorded in the MCBR during 2006-2011. To capture cases diagnosed after the perinatal period, data for the same years were extracted from the MRCDR to follow babies up to two years after birth. Chi-squared tests were applied to evaluate differences in distribution of selected risk factors between babies with and without birth defects. Logistic regression was used to estimate the effect of risk factors on the occurrence of some defects, specifically hypospadias and ventricular septal defects.

Results: Routine under-reporting of major birth defects to the MRCDR of 40% cases occurred in Murmansk County. Linkage of the two registries allowed better prevalence estimates for 21 types of major defects for which registering and reporting are obligatory in Russia. Due to this, the prevalence of major birth defects increased from 50 to 77 per 10 000

newborns after registry linkage. Hypospadias was the most common birth defect in Murmansk County with a prevalence of 25.7 per 10 000 newborns and the cases were associated with cervical erosion, low infant birthweight and preeclampsia. Smoking, alcohol abuse during pregnancy and maternal diabetes mellitus were also risk factors for delivering infants with ventricular septal defects. Male sex was a protective factor and reduced the risk to be born with such a defect.

Conclusion: The studies in this thesis demonstrate that linking data from the MCBR and MRCDR improved both case ascertainment and the official assessment of prevalence, thereby reducing the potential of under-reporting by physicians. These findings have direct implications for improving perinatal care in Murmansk County. Potentially numerous cases of hypospadias and ventricular septal defects are preventable in Russia if health policy makers were to give more attention to established risks. Public health efforts should therefore focus on reducing smoking and alcohol consumption, as well as improving diabetes control in pregnant women.

SAMMENDRUG (in Norwegian)

Bakgrunn: Fram til nå har det vært en stor mangel på befolkningsbaserte helseregistre i Russland. Uten tilgang til denne type data er det vanskelig å vurdere omfanget av mange forskjellige folkehelseproblemer og utfordringer. Medfødte misdannelser er et alvorlig helseproblem og er forbundet med sykelighet og dødelighet ved fødsel og i tidlige barneår. Bruken av flere informasjonskilder for medfødte misdannelser kan medføre en betydelig forbedring av barnehelsen i en befolkning. I denne studien er det brukt registerdata knyttet til Murmansk County Birth Registry (MCBR) og Murmansk Regional Congenital Defects Registry (MRCDR) for å undersøke forekomst og risikofaktorer knyttet til medfødte misdannelser.

Formål: De spesifikke formål med denne studien var: 1) å kombinere data fra MCBR og MRCDR for å påvise eventuell under-rapportering av misdannelser og å sammenlikne forekomst i Murmansk fylke med norske data og data fra Arkhangelsk fylke; 2) å undersøke mulige risikofaktorer som kan gi en forklaring på den høye forekomst av hypospadi i Murmansk fylke; 3) å identifisere maternelle risikofaktorer for den hyppigste hjerte-kar misdannelsen; ventrikkel septum defekter.

Metode: Studiematerialet bestod av alle 52 806 levende- og dødfødte registrert i MCBR i tidsrommet 2006-2011. For å finne alle kasus diagnostisert etter perinatalperioden ble data fra de samme år hentet fra MRCDR for å følge barna opp til 2-årsalder. Kji-kvadrat tester ble brukt for å analysere eventuelle forskjeller i risikofaktorer mellom barn med og uten påviste misdannelser. Logistisk regresjon ble brukt for å estimere effekten av risikofaktorer på forekomsten av noen misdannelser, spesielt hypospadi og ventrikkel septum defekter.

Resultater: Rutinemessig under-rapportering av alvorlige misdannelser til MRCDR på rundt 40 % ble påvist i Murmansk fylke. Kobling av de to registrene ga et betydelig bedre estimat for 21 typer av alvorlige misdannelser der registrering og rapportering er obligatorisk i Russland. På grunn av dette økte forekomsten av alvorlige misdannelser fra 50 til 77 per 10 000 nyfødte etter kobling av registrene. Hypospadi var den mest vanlige medfødte misdannelsen i Murmansk fylke, med forekomst 25.7 per 10 000 nyfødte. Påviste

risikofaktorer var cervix erosjon, lav fødselsvekt, og pre-eklampsi. Røyking, alkoholmisbruk og maternell diabetes mellitus var også risikofaktorer for barn med ventrikkel septum defekter. Å være gutt var en beskyttende faktor i denne sammenheng.

Konklusjon: Vår undersøkelse viser at å koble data fra MCBR og MRCDR bedrer sikkerheten i både påvisning av misdannelsene og vurderingen av data, med påfølgende reduksjon av både over- og under-rapportering av forekomsten. Disse funn kan medvirke til en stor forbedring av den perinatale omsorg i Murmansk fylke. Flere tilfeller av hypospadi og ventrikkel septum defekter kan forebygges i Russland om helsemyndighetene vil vie mer oppmerksomhet til etablerte risikofaktorer. Folkehelsetiltak bør derfor fokusere på reduksjon av røyking og alkoholmisbruk, samt øket oppmerksomhet mot og behandling av diabetes mellitus i svangerskapet.

АБСТРАКТ (in Russian)

Введение: В настоящее время в России имеется недостаток регистров, основанных на популяционной основе. В условиях недоступности таких данных, оценка проблем общественного здоровья является сложной задачей. Врожденные пороки развития представляют важную составляющую общественного здоровья, так как они являются основой причиной перинатальной и младенческой смертности. Использование нескольких медицинских источников данных для мониторинга врожденных пороков могут помочь улучшить общественное здоровье. Для устранения неполноты данных, исследования описанные в этом тезисе имеют популяционный подход и дизайн; Мурманский Областной Регистр Родов и Мурманский Региональный Регистр Врожденных Пороков Развития были объединены для изучения эпидемиологии и некоторых факторов риска врожденных пороков.

Цели и задачи исследования: Специфическими задачами исследования являлись: 1) объединить данные из Мурманского Областного Регистра Родов и Регионального Регистра Врожденных Пороков, выявить возможное занижение регистрации пороков, сравнить распространенность пороков с Норвегией и Архангельской областью; 2) изучить возможные факторы риска, которые могли бы помочь объяснить высокую распространенность гипоспадии в Мурманской области; 3) идентифицировать материнские факторы риска для пороков межжелудочковой перегородки, которые являются преобладающей группой среди всех врожденных пороков сердечно-сосудистой системы.

Методы: Исследуемая группа включала 52 806 живо- и мертворожденных зарегистрированных в Мурманском Областном Регистре Родов в течение 2006-2011 гг. С целью охвата врожденных пороков, диагностированных после перинатального периода, были использованы данные Регионального Регистра Врожденных Пороков, таким образом дети, рожденные в 2006-2011, были прослежены на протяжении 2-х лет. Хи квадрат тест был использован для оценки разницы в распределении выбранных факторов риска в группах с и без врожденных пороков. Логистическая регрессия

использовалась для оценки эффекта влияния факторов риска и вероятности рождения ребенка с некоторыми врожденными пороками, а именно с гипоспадией и межжелудочковыми дефектами перегородки сердца.

Результаты: На территории Мурманской области было выявлено занижение регистрации пороков до 40%. Объединение 2-х регистров позволило лучше оценить распространённость 21 вида пороков, входящих в группу обязательного учета. Благодаря этому, зарегистрированная распространенность этих пороков увеличилась с 50 до 77 на 10 000 новорожденных. Из группы обязательного учета, гипоспадия с распространенностью 25.7 на 10 000 новорожденных, оказалась самым часто встречающимся пороком и была ассоциирована с эрозией шейки матки, низким весом новорожденного и преэклампсией. Курение, употребление алкоголя во время беременности и сахарный диабет тип 1 и 2 являлись факторами риска, повышающими вероятность рождения ребенка с дефектом межжелудочковой перегородки. Мужской пол ребенка являлся защитным фактором, снижающим вероятность рождения ребенка с данным видом порока.

Заключение: Наши данные демонстрируют, что объединение 2-х регистров улучшило оценку случаев врожденных пороков развития и их распространенность, тем самым снижая возможность пропуска регистрации пороков врачами. Результаты нашего исследования имеют прямое влияние на улучшение перинатальной помощи в Мурманской области. Потенциально, множество случаев гипоспадии и межжелудочковых пороков перегородки сердца можно предотвратить, если организаторы здравоохранения будут уделять больше внимания выявленным факторам риска. В этом случае, усилия здравоохранения должны сконцентрироваться на борьбе с курением и приемом алкоголя беременными женщинами, а также над улучшением гликемического контроля у беременных с диабетом.

PREFACE

After graduating from Pavlov State Medical University of St. Petersburg, I started my internship in general surgery in July 2005. Already in September 2005, my mother Ludmila Kovalenko, who was then Head of the Department of Obstetrics-Gynaecology and Paediatric Care of the Murmansk Region, involved me in the international project “Murmansk County Birth Registry” which was a collaboration with University of Tromsø. During that time, I participated in a seminar where I met two wonderful individuals from Northern Norway – Jon Øyvind Odland and Erik Anda. Later in 2005, I got a 50% position in the central office of the Murmansk County Birth Registry (MCBR) together with two of my colleagues Elena Voitova and Yana Lapina. Those were wonderful but intense years for me, as I worked full-time as a practical doctor at Murmansk Regional Clinical Hospital as a cardiovascular surgeon while concurrently working at the MCBR.

The first year in setting up the MCBR was quite difficult. We experienced some problems both at the organisational and local levels. I was partially responsible for data entry as well as internal data validity, creation of the database, data extraction, storage and security issues. Regular international contacts were also part of my duties. In fact already 3 September 2007, which was the next week after my marriage, I participated as speaker at the International Epidemiology Congress in Mexico City together with my Norwegian partners and friends. In the session on Circumpolar Health Issues, I presented the first results from the MCBR for 2006. It was also my first experience at the international level. That inspired me so much.

During the following years from 2007 to 2012, I tried to spend as much time in the MCBR office as I could. I got a unique experience and understanding of how to conduct such a project in Russia. Within that period, there were also several conferences in Russia and Norway on relevant topics to the MCBR. The annual working trips of the central MCBR office staff to Tromsø were unforgettable. Working closely with various databases each year, the idea of combining registries came to me. The most suitable registries for this purpose were the MCBR and the Murmansk Regional Congenital Defects Registry.

In 2010, I participated in organising the “Arkhangelsk County Birth Registry” which was designed as a copy of MCBR, using the same database and paper form as in Murmansk County. I spent some time in Arkhangelsk, teaching the central office staff there concerning practical questions on how to operate a registry.

At the end of 2012, I officially became a PhD-student at UiT The Arctic University of Norway (then the University of Tromsø). To date, the topic concerning birth defects is still important to me. I am therefore happy that I have been able to work on this topic intensely during my thesis research.

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LIST OF PAPERS

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

Paper I

Kovalenko A, Brenn T, Odland JØ, Nieboer E, Krettek A, Anda EE.
Underreporting of major birth defects in Northwest Russia: a registry-based study.
Int J Circumpolar Health 2017; 2017;76(1): 1366785.

Paper II

Kovalenko A, Brenn T, Odland JØ, Nieboer E, Krettek A, Anda EE.
Risk Factors for Hypospadias in Northwest Russia: a Murmansk County Birth Registry Study.
Submitted.

Paper III

Kovalenko A, Anda EE, Odland JØ, Nieboer E, Brenn T, Krettek A.
Risk Factors for Ventricular Septal Defects in Murmansk County, Russia: A Registry-Based Study.
Int J Environ Res Public Health 2018;15(7):e1320.

LIST OF ABBREVIATIONS

ACBR	Arkhangelsk County Birth Registry
ASD	Atrial septal defects
BD	Birth defect
BMRN	Medical Birth Registry of Norway
BW	Birthweight
CI	Confidence interval
CVMs	Cardiovascular malformations
EUROCAT	European Surveillance of Congenital Anomalies
FD	Foetal death
GA	Gestational age
IA	Induced abortion
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
KBR	Kola Birth Registry
LB	Live born
MCBR	Murmansk County Birth Registry
MIAC	Murmansk Analytic Informational Centre
MRCDR	Murmansk Regional Congenital Defects Registry
SA	Spontaneous abortion
SB	Stillborn
SGA	Small for gestational age
SHD	Septal heart defects
TA	Therapeutic abortion
TOPFA	Termination of pregnancy due to foetal anomaly
VSD	Ventricular septal defects
WHO	World Health Organisation

ACKNOWLEDGEMENTS

First of all, I would like to thank my main supervisor Alexandra Krettek for granting me the freedom to work independently, and am grateful for all the help you gave me along the way. We needed to work by long distance because of me being in Murmansk most of the time. Your advice and comments were always valuable and your patience was unlimited. Thank you for providing me with new knowledge, especially in scientific writing.

I wish to express my sincerest gratitude to my co-supervisor Erik Anda, who was not only a co-supervisor but also a friend. Your critical comments were always to the point and helpful. We spent a lot of good times together before and during the PhD process. Fishing and outdoor rest in between working sessions were also part of our routines.

I also need to acknowledge the help I received throughout the years from my co-supervisor Tormod Brenn. You assisted me a lot in all questions concerning statistics. You clarified all statistical issues which remained unclear to me, even after completing my PhD courses. Moreover, Tormod also opened the door for me to appreciate the cultural differences between Russia and Norway.

My deepest appreciation and respect are extended to Jon Øyvind Odland. He always answered my questions quickly and in a succinct and concrete manner. Thank you for the financial support that allowed me to attend conferences in Mexico, Sweden and Norway. I learned from you the best balance between work and rest/fun.

In extend my sincere appreciation to Evert Nieboer, who edited my manuscripts multiple times to improve them and render them publishable. Your professional skills are fantastic. Thank you for the opportunity to improve my English with a native speaking person.

To my colleagues and friends in Arkhangelsk and Tromsø, namely Alexander Voitov, Elena Voitova, Yana Lapina, Anna Usynina, Elena Roik, Olga Kharkova, Vitaly Postoev, Sergey Drachev, Yriy Sumarokov, Alexander Kudryavtsev, Ekaterina Sharashova, Torkjel Sandager

and Odd Nielsen, I consider our communications to have been a very useful and important part of the PhD process, as you created an enjoyable microclimate for my scientific work.

I am also grateful for support in many different ways from my parents Ludmila and Alexander Kovalenko and my oldest brother Dmitry, especially their care for my children while I was in Tromsø. Finally, I would like to thank my wife Maria and my three children Anya, Lesya and Ilusha for their incredible patience and psychological support throughout my life, and especially during the preparation and writing of this thesis.

1. INTRODUCTION

1.1 Data sources for birth defects surveillance

The ultimate value of any public health surveillance program lies in the ways in which the data collected are used to improve the health of the public. In that regard, programs that are targeting birth defects surveillance are no exception; they too exist to improve public health. No matter the target area, every program must have clear goals and objectives that drive how the use of surveillance data toward improving public health. Population-based registries are a particularly powerful tool for the evaluation of health services (1), as they represent the experience of a whole community. By contrast, the data in hospital registries are more limited as they pertain to admitted patients.

Both medical birth and congenital defects registries are suitable tools for birth defects surveillance and for exploring associations between birth defects and related potential risks. They were started many years ago in the Nordic Countries (2-5) for monitoring the health of pregnant women and their offspring, and to contribute to the quality of perinatal care. Linkage of related registries can be effective in enhancing the surveillance of birth defects and case ascertainment.

Indeed, linkage of registries is a successful way of addressing various public health issues. To date, most studies based on linked information from registries have been conducted in the Nordic countries. Their focus has been on diseases such as cancer, coronary heart disease, birth defects, pneumonia, obesity and depression (3, 6-12). International examples include linking the Surveillance, Epidemiology and End Results (SEER) program of cancer registries with Medicare data in the USA (13).

1.2 Thalidomide disaster

In 1957, the immunomodulatory drug thalidomide (known as “Countergan”) was marketed by the German company Chemie-Grünenthal which also had developed it. The drug was first prescribed as a sedative or hypnotic, and later was also claimed to cure conditions such

as anxiety, gastritis, tension and insomnia. Subsequently, it was also used for nausea and to alleviate morning sickness in pregnant women. In this later capacity, its use was worldwide (14).

Unfortunately, strong pressure from the pharmaceutical industry eagerly awaiting new medicines facilitated the marketing of Countergan despite being inadequately tested. Subsequent to its launch, targeted outsourcing rapidly expanded the customer base, and strong market forces prevented a timely withdrawal of Countergan when evidence emerged of disastrous side-effects (15). Worldwide, about 10 000 cases of infants born with malformed limbs have been reported to be linked to maternal thalidomide use; of these, only 50% survived (16). Other birth defects associated with the use of this drug include: malformed eyes, hearts, alimentary and urinary tracts, as well as blindness and deafness. The negative effects of thalidomide led to the development of more structured drug regulations and stricter control over drug use and development.

1.3 Nordic birth registries

1.3.1 Medical Birth Registry of Norway

Established in 1967, the Medical Birth Registry of Norway (MBRN) was organized in the wake of the thalidomide catastrophe. In 1984, two main objectives of the MBRN were formulated and enacted into law. Specifically, the aims were to: a) conduct epidemiological surveillance of birth defects and other perinatal health problems, with a focus on prevention and health services related to pregnancy, childbirth and the neonatal period, and quality assurance; and b) conduct epidemiological research on causes and consequences of perinatal health problems (4). To date, all pregnancies ending after week 12 must be reported to the MBRN (including terminations after week 12). The Norwegian Institute of Public Health manages the MBRN and is the controller of both the registry and the compiled data. The use of a unique personal identification number, assigned at birth, allows data linkage directly between the registry and databases without using personal or other “sensitive” data. To ensure data quality, the MBRN is routinely linked with the Central Population Register. For the production of statistics and in connection with research projects, the MBRN can be linked with other central health registries (Cancer Registry of Norway; Cause of Death Registry;

Norwegian Prescription Database; Norwegian Surveillance System for Communicable Diseases; and the Central Tuberculosis Registry and the Norwegian Immunisation Registry). In 2010, the MBRN project was initiated with the aim to develop and implement new versions of electronic forms pertaining to maternity, child and abortion notifications, and other forms for which pre-coded information can be used (17). Today, all reports to the MBRN are in electronic format.

1.3.2 Danish Medical Birth Registry

The Danish Medical Birth Registry is a key component of the Danish health information system; it was established in 1973 using paper forms for birth registration (18). Systematic data collection was started in 1968, and related statistical analyses were published that same year. However, no data were collected in electronic form before 1973.

Since 1968, all residents in Denmark are registered in the Danish Civil Registration System with a unique 10-digit civil registration number (CPR number), which is used in all official registrations. Thus, all newborns are assigned a CPR number at delivery, as well as all persons upon immigrating to Denmark. The unique CPR number of the child is linked to those of the parents in the Civil Registration System. Since 2002, stillbirths have also received a CPR number for administrative purposes.

In 1997, the electronic registration of births replaced paper forms. Due to changes in clinical practices, as well as the goal to add supplementary information to the Register, new variables were added during the last 20 years. From 1 January 1997 to 31 December 2017, the population cohort includes data on 1 338 665 newborn infants from 1 311 085 pregnancies. The registry also provides data for Statistics Denmark and eSundhed.dk ─ the institutions responsible for annual publishing of official data.

1.3.3 Swedish Medical Birth Registry

The Swedish Medical Birth Registry was established in 1973 through an act of the Swedish Parliament (19). Its purpose was to combine information on ante- and perinatal factors because of their importance for the health of the infant. Even though the basic structure of

the registry has remained unchanged over the years, there have been major modifications to both its content and methods for data collection.

During 1973-1982, the register was constructed from summarizing documents prepared by secretaries at obstetric clinics. These documents were called "Medical Birth Reports" and summarized the contents of the medical records on a standard form. In 1976, the registry's information content was critically examined. One result was to discontinue the use of the natal medical reports. Copies of the three medical records of primary interest were now to be sent to the National Board of Health for computerization in order to eliminate uncertainty in data transfer to the Medical Birth Registry. The records of primary interest pertained to the antenatal care of the mother, the delivery, and the pediatric examination results. This revised procedure took effect in 1982 and the Registry's content was expanded concurrently. One of the changes concerned diseases during pregnancy. Previously, specific diagnoses had been noted with ICD codes. Check boxes for eight serious conditions were included in the new registry form, as well as for other items of information (e.g., use of analgesics).

Most women are identified by their unique personal identification numbers (PIN). Every legal resident of Sweden is assigned a PIN, which is used in a wide variety of contexts, including health care. This facilitates linkages between different registers.

1.3.4 Medical Birth Register of Finland

The Medical Birth Register of Finland was established in 1987 (20). It includes data on live births and stillbirths with a weight of at least 500 g or a gestational age of at least 22 weeks, as well as information on the mothers. Some quality control studies showed that the Register had insufficient data quality, which led to reforms in 1990, 1996 and 2004 to improve its reliability. The introduction of check-boxes in the registration form has also improved the quality and validity of this registry (21).

Based on data from the Finnish Register data, perinatal deaths and very preterm birth suggested worse outcomes after the mother had gone through an earlier induced abortion. Increased odds for very preterm birth exhibited a dose-response relationship as follows: 1.19

[95% confidence interval (CI) of 0.98-1.44] after one induced abortion, 1.69 (1.14-2.51) after two, and 2.78 (1.48-5.24) after three (22). Another study has shown that placenta previa was associated with an increased risk of major congenital malformations in singleton births (adjusted odds ratio = 1.55; 95% confidence interval, 1.27-1.90) (23).

1.3.5 Medical Birth Registry of Iceland

The Medical Birth Registry of Iceland is a population-based registry that contains information on all pregnancies and deliveries in Iceland since 1972 (7). Registered data include parental information, pregnancy details, labour and delivery characteristics, as well as birth and neonatal outcomes data. Despite the richness of the data, information on maternal weight and smoking is not registered. However these details are available from the maternity records taken during a women's first antenatal visit (7). By 2012, all 10 delivering units in Iceland transmitted pertinent data to the Registry electronically (20). The Medical Birth Registry of Iceland is widely used in linkage-studies with other Nordic registries (24).

Interestingly, the 2008 economic collapse in Iceland has been shown to associate with risks of adverse birth outcomes. Interestingly, an increase in the adjusted odds of having low-birth weight deliveries followed this national development, namely with an OR = 1.24, 95% CI [1.02, 1.52], and especially so among infants born to mothers younger than 25 years (aOR = 1.85, 95% CI [1.25, 2.72]) and those unemployed (aOR = 1.61, 95% CI [1.10, 2.35]) (25). Another study (26) suggested that a transient increase in gestational hypertension and use of β-blockers among pregnant women occurred in the first year following the Islandic economic collapse. The severity of the aggregate economic climate was followed by a slow but gradual recovery, and likely constitute an explanation for this observation (26).

Furthermore, the prevalence of smoking during pregnancy decreased from 12.4% in 2001 to 7.9% in 2010, particularly among women with Icelandic citizenship whereas obesity levels were not affected (7).

1.4 Birth/congenital defects surveillance in the World

1.4.1 Surveillance in the Nordic countries

As outlined above, birth registries and congenital defects registries have been established in the Nordic Countries. A detailed summary of how birth defects are registered in the registries discussed above is provided in Table 1.

Table 1. Overview of how birth and congenital defects are registered in the Nordic countries.

Country, name - membership	Period of birth defect (BD) registration	Birth defect in stillbirth	Abortions*	Data sources
The Medical Birth Registry of Norway - EUROCAT (full member) ICBDSR	Neonatal, but may be registered up to 1 year	Yes	Yes, SA>12 weeks, all IAs with the indication of prenatally diagnosed BD	Form completed by physician or midwife. Data added to MBRN notification form at birth
Danish Medical Birth Register	Neonatal	Yes	SA yes, TA at any gestational age	Form completed by midwives, hospital discharge records
Danish Congenital Anomalies Surveillance	Up to 5 years of age	Yes, from 22 weeks	SA from 20 weeks, after 12 weeks malformations recorded for termination of pregnancy	Discharge diagnosis and hospital records from obstetric and paediatric departments, birth notifications, death certificates, data from cytogenic laboratory
The Medical Birth Register of Sweden - ICBDSR	Neonatal	Yes	No	Care records, delivery record, paediatric exam

Swedish Birth Defects Register - ICBDSR, EUROCAT(affiliate)	Up to 6 months of age, heart defects up to 1 year	Yes, all deaths with congenital anomalies >22 weeks	No SA, Yes TA	Reports are compulsory and obtained from departments of paediatrics, obstetrics and clinical genetics
National Birth Register of Finland	Neonatal	Yes	Yes	Doctor's notice of birth, discharge summaries, death certificate
National Register of Congenital Malformations of Finland + prenatal registry	Up to 1 year of age	Yes	Yes TA	Doctor's report, cytogenetics laboratories, MBR, other registries, death certificates
Iceland National Register of Birth within National Register of Persons	At birth. BD after that are collected at central hospital	Yes	No, TA with BD registered in the abortion register (>12 weeks)	Maternity providers fill out a birth report

* TA=therapeutic abortions, SA=spontaneous abortions

1.4.2 Surveillance in Europe

1.4.2.1 The European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT)

EUROCAT covers 1.7 million births in 23 European countries (27). To date, 43 registries annually provide data to EUROCAT. It was established in 1979 with the goal of improving

and standardizing the collection of data about congenital disorders. The current objectives of EUROCAT are to provide essential epidemiologic information on congenital anomalies in Europe. This is done to facilitate early warning of new teratogenic exposures and to evaluate the effectiveness of primary prevention. To meet these objectives, EUROCAT annually performs statistical monitoring for both trends and clusters in time to detect signals of new or increasing teratogenic exposures and to monitor progress in the prevention of congenital anomalies. Total prevalence rates of 81 subgroups of congenital anomalies, including all cases of livebirths, stillbirths/ late foetal deaths from 20 weeks gestational age, and terminations of pregnancy for foetal anomaly are monitored and reported. As of 2016, approximately 30% of new births in the European Union are reported to EUROCAT (27).

1.4.2.2 The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

ICBDSR is an international, voluntary and non-profit organisation affiliated with the World Health Organisation (WHO). The ICBDSR was first established in 1974, at a meeting in Helsinki/Finland where representatives of malformation registries from 10 countries were present (28). This non-profit organisation brings together birth defect surveillance and research programs from around the world, with the aim of investigating and preventing birth defects and lessening the impact of their consequences. ICBDSR now has 42 member programs worldwide and covers 4 million births per year (28).

1.4.3 Surveillance in Russia

In Russia, the systematic epidemiological monitoring of birth defects has been done since 1998 (29). When the birth defects registry was created, it used resources that already existed within the Russian health care system. Thus, the basis for the Russian birth defects monitoring was a population-based approach to collect data using multiple sources of information, with subdivision by geographical areas. By using various sources of information, it would be possible to identify additional cases and perform a more accurate case ascertainment which is necessary for accurate determination of prevalence. Of course, multisource systems are more complex than direct data collection from one source or hospital, and thus require more time to obtain additional data. However, they provide better

diagnostic accuracy. For example, heart defects which are detected in hospitals are not fully described or only poorly so, while diagnoses at cardiology centres are more quantitative and accurate, which undoubtedly enhances the quality of monitoring registers.

The basic principles of the Russian monitoring registers were designed by taking into account the experience of monitoring systems in European countries as well as the organization and regulations of the national Russian health care system. Thus, the Russian Birth Defects Register was created based on experiences from two international systems, namely EUROCAT and Clearinghouse (30). For data storage and processing issues, an automated information system ("Monitoring") was created based on knowledge and experience from the Research Institute of Paediatrics and Paediatric Surgery in Moscow. It collected and integrated data from various sources (maternity hospitals, polyclinics, and hospitals) and supported multiple sources of registration. In 2009, the Russian Federation initiated the transition to the new electronic system, which allowed the registration of not only newborn but also of foetuses with birth defects identified during prenatal screening.

The Russian Birth Defects Registry collects data through information gathered by existing health facilities. Thus, collecting information about malformations in different geographical regions is done by local birth defects registries. However, the creation and support of a unified database and related processing and subsequent comparative analyses of the data is carried out by the Information-Analytical Federal Centre in Moscow (31).

Data from the Russian Birth Defects Registry shows that the coverage of registered newborn children is 100% in 14 regions (they constitute 41.2% of all regions), while 12 regions (35.3%) have 90-99% of infants registered and in 8 regions (23.5%) the level ranges from 70-90%.

Figure 1 shows a schematic overview of the Russian monitoring system. Such monitoring system was introduced in 1999 and initially involved 19 regions. Annually, the number of regional registers working on the monitoring program increased and in 2009, the Russian monitoring for birth defects involves 48 registers of the Russian Federation (31).

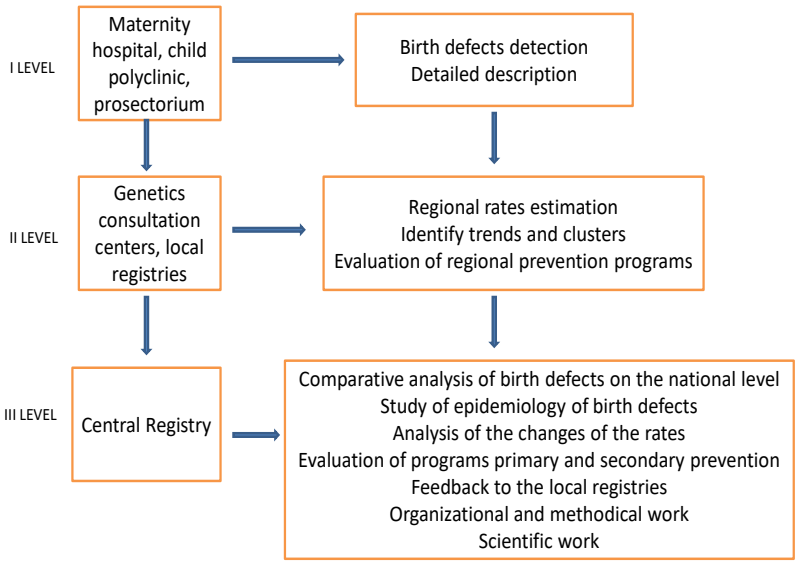

Figure 1. Overview of the Russian Birth Defects Register.

1.5 Registries operating in the Murmansk region, Northwest Russia

1.5.1 Kola Birth Registry

The Kola Birth Registry (KBR) was initiated during 1996-1997 in the towns of Nikel and Zapolyarniy and the city of Monchegorsk (32). It was established as a response to a report by Chashschin et al. (32) about possible increases in spontaneous abortions and congenital malformations among infants born to nickel-exposed mothers (33). That report was the only published paper at that time about adverse effects on pregnancy outcomes of nickel exposure, and the worrying findings prompted further investigation.

At the outset, data for the KBR were collected from the three towns Nikel, Zapoljarnyj and Monchegorsk, as all featured nickel refining operations (34). For sample-size reasons, retroactive data collection was required, and this focused on the largest of these communities, namely the city of Monchegorsk. Data collection was started with the year 1973, and all live births as well as stillbirths from 28 weeks of pregnancy were included (34).

The KBR database contains information about the following: nationality of parents, age and occupation of parents, previous pregnancies, abortions, diseases before and during pregnancy, prenatal screening data, complications during delivery and in labour, detailed information about the newborn (weight, height, sex, Apgar score, neonatal and perinatal conditions and diagnoses, birth defects).

The validity and quality of the data in the KBR has been deemed suitable for scientific research (34, 35). By 2005, about 26 841 newborns were registered in the database (36). Many studies have been carried out using data from the KBR. Most of them have focused on delivery outcomes and mother's life style factors. Results show that unmarried mothers were at higher risk of delivering preterm infants compared to those who were married (37). Furthermore, in Monchegorsk there was a negative association between a mother's exposure to nickel and the number of small gestational age babies (38), while higher prevalences for this outcome were observed for smoking mothers, mothers who abused alcohol and/or were exposed to solvents. Compared to Norway, women in Monchegorsk had a lower prevalence of obesity, diabetes and heavy smoking (32). No significant associations were found between nickel exposure during early pregnancy and genital (39) and musculoskeletal (40) birth defects. Mothers who had undergone at least one ultrasound examination during pregnancy had a decreased risk of having a newborn die during the perinatal period [adjusted OR = 0.49 (95% CI = 0.27-0.89)]. The overall prenatal detection rate was 34.9%, with the highest rate for malformations of the nervous system (41).

The KBR was discontinued in 2005 due to lack of local resources. At the same time, at the end of 2005, a prospective medical birth registry project was initiated for the whole of Murmansk County. This new project was funded by UiT The Arctic University of Norway and the Arctic Monitoring and Assessment Programme (AMAP).

1.5.2 Murmansk County Birth Registry

The Murmansk County Birth Registry (MCBR) was modelled after the MBRN with adaptations to the Russian health care system. It was planned in early spring 2005 and organized in late Autumn of 2005 (42). Early in 2012, the MCBR included more than 52 000

deliveries (31). The information recorded on the registry form came from four different sources: medical history files, obstetric journals, newborns' delivery records and results of interviews with mothers carried out by medical staff (midwife or physician). A two-page birth registry form comprising 54 major fields contained detailed medical and personal information about the mother, her baby/babies and the father (43).

The MCBR includes information about the parents (age, residence and occupation), maternal characteristics such as smoking, alcohol consumption, drug use during pregnancy, multivitamins and folic acid intake before and during pregnancy, induced and spontaneous abortions, and previous pregnancies and their outcomes. Information is also provided on diseases prior to and during pregnancy and also pregnancy complications. Furthermore, details are found on prenatal screening results, complications during delivery, and detailed newborn data (sex, weight, length, head circumference, Apgar score at 1-st and 5-th minute, neonatal and perinatal diagnosis as well as birth defects) (43). An assessment of the quality and completeness of the MCBR has been published earlier and was satisfactory (42). A major limitation for the MCBR, in comparison with Nordic birth registries, is that induced and spontaneous abortions less 22 weeks are not included (31).

Numerous studies based on the MCBR have been published. The pertinent publications show that Murmansk County had a higher proportion of preterm deliveries (8.7%) compared to Northern Norway (6.6%). While the odds ratio of the risk of perinatal mortality (Northern Norway as the reference group) was higher for all gestational ages in Murmansk County, the largest risk difference occurred among term deliveries (OR 2.45, 95% CI 1.45, 4.14) (44). The observed prevalence of preterm births (6.9%) in Murmansk County was comparable with data on live preterm births from European countries. Adverse prior pregnancy outcomes, low maternal educational level, unmarried status, alcohol abuse, and diabetes mellitus or gestational diabetes were the most common risk factors for preterm birth (45). Underweight, overweight and obesity in early pregnancy associated with both preterm and very preterm births (46).

About 25.0% of smoking women in Murmansk County quit smoking after becoming aware

of their pregnancy, and one-third of them reduced the number of smoked cigarettes while pregnant (47). Interestingly women with higher education, are married, and/or are primiparous were more likely to quit smoking during pregnancy. Maternal age and number of children were also indicators that influenced the reduction in smoking during pregnancy (47). However, smoking reduction during pregnancy relative to its pre-gestation level did not seem to influence the odds of adverse birth outcomes (48). Maternal smoking was inversely associated with preeclampsia/eclampsia. Moreover, an increase in the number of daily smoked cigarettes during pregnancy decreased the odds of preeclampsia/eclampsia (49).

The overall four-fold increase in occurrence of urinary malformations in Murmansk County during 2006-2011 showed little annual dependence. During pregnancy, use of medications, infections, pre-existing diabetes mellitus, or gestational diabetes associated with increased risk of these anomalies, as did conception during summer (50).

Murmansk County Birth Registry was actively operating during 2006 to 2012, being the only such birth registry in the Russian Federation. Data from the complete database is available for 2006-2011 and account for 52 806 deliveries in Murmansk County. In the middle of 2012, the funding for this project ended and the birth registry was permanently closed.

1.5.3 Murmansk Regional Congenital Defects Registry

The Murmansk Regional Congenital Defects Registry (MRCDR) was established in 1996 as a local registry (Alexandr Voitov, personal communication). At this juncture, registration of birth defects was not obligatory in Russia. Since 1999, the MRCDR has been involved in the Russian Birth Defects Monitoring program (see Section 1.4.3). The following data are registered for each child with a congenital birth defect: birth date, weight, alive/not alive, whether multiple delivery, diagnosis, gender, gestational age, place of delivery, mother's age, parity, and mother's place of residence at the time of delivery.

The MRCDR collects information on all congenital birth defects of which 21 selected defects (major defects) are included in the mandatory MRCDR annual report, which is sent to the health authorities in Moscow (51). The MRCDR includes information on congenital birth

defects diagnosed between birth (from week 22 of pregnancy, birth weight > 500 grams) and 16 years of age. The main sources for the registry are maternity hospitals, children's polyclinics and hospitals, pathology departments, as well as other medical institutions. When a congenital birth defect is diagnosed, the doctor fills in a special notice form and sends it to the Medical Analytic Information Center where it is registered. Notification forms from maternity hospitals are registered, but they are not entered into the MRCDR database until they are confirmed by another medical institution. Notice forms from children's policlinics and hospitals are registered by the Medical Analytic Information Center and need not to be confirmed before they are entered into the MRCDR.

Annual reports generated by the Medical Analytic Information Center include incidence/prevalence rates of all birth defects detected during the past year and grouped according to ICD 10 codes divided by territory (towns). As an option, 3-year incidence/prevalence time trends are also included in the report. To our knowledge, scientific investigations based solely on MRCDR data have never been conducted due to lack of information about possible risk factors in this database. In Table 2, an overview of birth/congenital defects registries in the Kola Peninsula is presented.

Table 2. Overview of birth/congenital defects registries in the Kola Peninsula

Name	Period of BD registration	BD in stillbirths	Therapeutic /spontaneous abortions	Membership in surveillance programs	Data sources
Kola Birth Register (KBR)	Until hospital discharge	Yes, ≥28 weeks	yes	-	Birth and prenatal records
Murmansk County Birth Registry (MCBR)	Until hospital discharge	Yes ≥ 22 weeks	Yes, ≥ 22 weeks	-	Birth records
Murmansk Regional Congenital Defects Registry (MRCDR)	Up to 16 years	Yes ≥ 22 weeks (since 2011)	Yes, ≥ 22 weeks (since 2011)	-	Records from any medical institution

2. AIMS OF THE THESIS

The overall aim of this thesis was to investigate the epidemiology and selected risk factors for congenital malformations by linking a medical birth registry and a congenital defects registry in Northwest Russia.

Specifically, I wanted to:

- Combine the MCBR and MRCDR to identify possible under-reporting of birth defects and compare the prevalences of birth defects in Murmansk County with those of Norway and Archangelsk County (Paper I).
- Explore potential risk factors that may help explain the high occurrence of hypospadias in Murmansk County (Paper II).
- Identify maternal risk factors for the most frequent cardiovascular malformations, namely ventricular septal heart defects (Paper III).

3. MATERIAL AND METHODS

3.1 Study setting

Murmansk County was established on 28 May 1938. Its territory covers the Kola Peninsula, which is surrounded by the Barents and White Seas. The region has an area of approximately 145 000 km^2 and borders on both Finland and Norway (52). Murmansk County experiences a moderate Arctic sea climate that is influenced by the Gulf Stream. Significant stocks of bio-resources are found in its fresh water resources as well as in the Barents and White Seas. The Kola Peninsula is characterized by diverse landscapes and unique ecosystems which includes areas that are virtually unaffected by economic development (the eastern part of the region) (53).

According to the census of 2010, the population of Murmansk County was 795 409, which is 6.2% of the population of Northwest Russia and 0.6% of Russia. Among ethnic groups, Russians constitute 89.0%, Ukrainians, 4.8%, Belarusians, 1.7%, Tatars, 0.8% and Azeris, 0.5% (52). The port of Murmansk is the only non-freezing, deep port that has direct access to the ocean routes of the maritime European part of Russia. Important strategic installations are located in the territory of the region such as Russia's Northern Fleet naval base (at Severomorsk) and the Kola Nuclear Power Station (at Polyarnie Zori) (53). The Arctic shipping sea route constitutes a strategic transport route and provides access to the natural resources of the Far North, Siberia and the Far East, as well as enabling transit from the Atlantic to the Pacific Ocean. In addition, the Russian Nuclear Icebreaker Fleet is based in the Port of Murmansk.

The economic specialization of the Murmansk region includes extraction and processing of mineral resources, industrial production of copper, nickel, cobalt, semi-precious metals, primary aluminium, electricity and chemical products, as well as fishing and fish-processing (54).

Figure 2. Murmansk County

3.2 Overview of data sources and study design

About 9 000 births are registered each year in Murmansk County. Primary data sources for the research presented in this thesis were the aforementioned MCBR and MRCDR databases (see Section 1.5.2 and 1.5.3). Pertinent data from them were combined to enhance the power of all three registry-based studies (Papers I-III).

The procedure of linkage of the registries was one of the aims of Paper I, namely: all cases from the MRCDR with major birth defects for babies born between 1 January 2006 and 31 December 2009 were selected. The MRCDR electronic platforms changed during the study period from Medmonitor to Microsoft Excel, and subsequently to Microsoft Access. Consequently the available data were fragmentised. Only paper printouts could be obtained from The Ministry of Health Care located in Murmansk City and, consequently, the linking of the MCBR and the MRCDR was done manually. Based on the place of delivery, date of

birth of the mother and hospital ID file number for major birth defect cases in the MCBR, we requested all original medical files (n = 210) from the maternity hospitals. Similarly for cases in the MRCDR, we requested 195 original medical files from the appropriate maternity hospitals. After receiving these original files, I checked whether a case with a major birth defect had been registered in the MCBR, the MRCDR or in both. The 64 cases registered only in the MRCDR were combined with those in the MCBR using a manual (but direct) linkage algorithm, based on the original medical file and hospital ID number of the participant in the MCBR and the mother's birthdate. Thus, the combined registry included 274 cases of major birth defects with the corresponding ICD-10 code and date of diagnosis. This linked registry was then used as the data source for Papers II and III.

Details on the study populations and data sources are depicted in Figure 3.

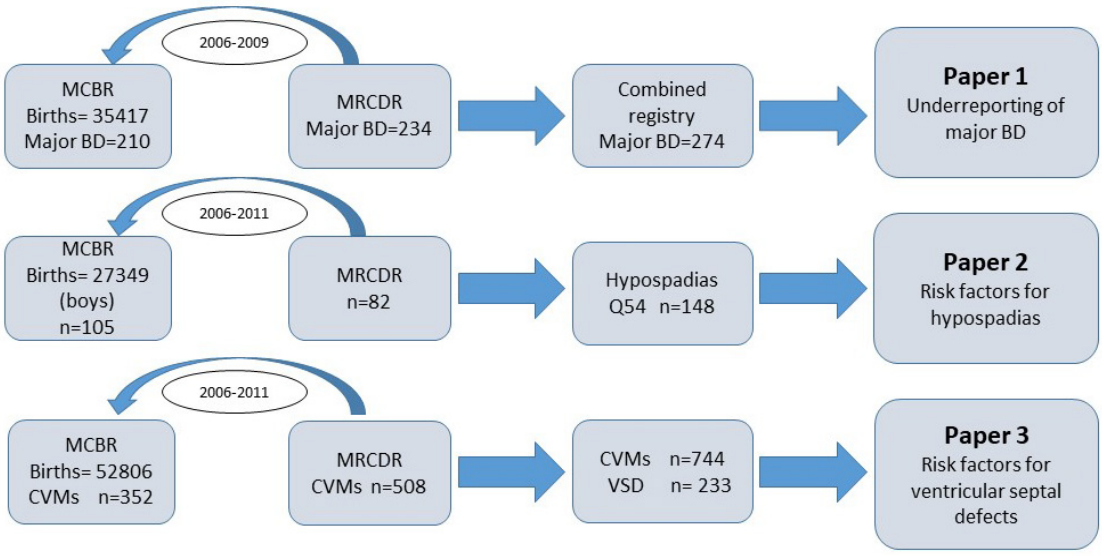

Figure 3. Study populations and sources of data

The initial study population described in this thesis included all newborns registered in the MCBR (n = 35 417) and MRCDR from 1 January 2006 to 31 December 31, 2009. This period applies to Paper I. Two additional years were subsequently added for use in Papers II and III, which increased the cohort to 52 806 and covered the period 2006-2011.

3.2.1 Paper I: Underreporting of major birth defects in Northwest Russia: a registry-based study

As indicated above, detailed information was obtained from the MCBR for mothers and their newly born babies, as well as for diagnosed birth defects (including all livebirths, stillbirths and terminations) during the perinatal period (specifically, from ≥22 weeks of gestation to the hospital discharge generally 7–12 days post-partum). Comparable details were taken from the MRCDR, which included information on all birth defects diagnosed between birth (≥22 weeks of gestation and birth weight >500 grams) up to 16 years of age.

All those born within the study period 1 January 2006 to 31 December 2009 constituted the study cohort. Of the 234 neonates registered in the MRCDR as having major birth defects, 17 were double entries, 6 triple and 10 were from outside the Murmansk region. After exclusion of these cases, there were 195 children with major birth defects. Thus based on both registries, there were 274 cases of major birth defects with assigned ICD-10 codes and dates of diagnosis.

3.2.2 Paper II: Risk Factors for Hypospadias in North West Russia: a Murmansk County Birth Registry Study

All male infants registered in the MCBR and MRCDR between 1 January 2006 and 31 December 2011 were included. A diagnosis of hypospadias (ICD 10 code Q54) depends on the location of the urinary opening (meatus). In Paper II, due to a potential lack of power, hypospadias cases were not investigated separately by severity but all cases were treated as one group. Information from the MBCR (105 babies) and MRCDR (82 babies) were combined and duplicate records removed which gave a final study sample of 48 cases. The manual merging of the data from the two registries was by the mother's hospital ID number and birthdate as well as the birthdate of the baby. Only singleton deliveries were considered. After registry linkage, entries in the MCBR with missing information or erroneous coding (n = 1 874) for selected variables (gestational age, BMI, mother's age, birth weight and others) were excluded from the study. This resulted in a final sample of 25 475 male infants for the regression analysis.

3.2.3 Paper III: Risk Factors for Ventricular Septal Defects in Murmansk County, Russia: A Registry-Based Study

The study population consisted of all singleton deliveries registered in the MCBR and MRCDR between 1 January 2006 and 31 December 2011 (n = 52 253). Cases of septal heart defects (n = 492) followed by ventricular septal heart defects (n = 233) were selected from this population by linking information in the MCRBR and the MRCDR for up to 2 years after birth. Twelve cases of septal heart defects registered in the MCDR were not included in the study cohort because these were born outside Murmansk County, or constituted duplicate entries.

Information on the infant characteristics, i.e., birth weight, sex, and gestational age were extracted from the MCBR, as were the following maternal characteristics at delivery: BMI at the first antenatal visit, smoking, alcohol and drug abuse, folic acid and multivitamin intake during pregnancy, and the occurrence of maternal diabetes mellitus type 1 and 2. Smoking, alcohol and drug abuse refer to any usage during pregnancy and were coded as yes/no.
A final sample size of 233 cases of ventricular septal defects was included in subsequent statistical analyses.

3.3. Sources of outcome and independent variables

As mentioned earlier in this thesis (Section 1.4.3), the MRCDR is a comparatively simple database which does not include potential risk factors except mother's age and number of previous pregnancies. Although the MRCDR contains ICD-10 codes, it provides written descriptions of the birth defects, which render the diagnoses more precise. All independent variables used in Papers II and III were taken from MCBR, as the MRCDR does not provide this information.

The set of exposure variables varied in Papers II and III. Common variables for both papers were the categorical variables: maternal age (<18, 18–34, ≥35 years); birthweight (<2 500, 2 500-4 000, >4 000 g), cigarette smoking and evidence of alcohol and drug abuse during pregnancy (yes/no), folic acid and multivitamins intake before and during pregnancy

(yes/no). The WHO classification was used to define four groupings of maternal BMI: underweight (BMI < 18.5 kg/m^2); normal weight (BMI=18.5-24.9 kg/m^2); overweight (BMI=25-29.9 kg/m^2); and obese (BMI ≥ 30.0 kg/m^2). In Paper II, previous spontaneous and induced abortions, parity, education (≥11 years), preeclampsia, cervical erosion, HBsAg carrier were treated as dichotomous variables. In Paper III, diabetes mellitus (type 1 or 2) was used as a dichotomous variables (coded as yes/no).

3.4. Statistical analyses

In Paper I, the statistical package SPSS version 21.0 (IBM Corporation, Armonk, NY, USA, 2012) was used generate descriptive statistics. We calculated confidence intervals based on the Wilson procedure without correction for continuity. Prevalence rates of birth defects were calculated separately for the MCBR, MRCDR and the combined registry.

In Papers II-III, Chi-squared tests were initially used to assess differences in distribution of selected risk factors between birth groups, with and without a birth deficiency. The selection from a set of maternal characteristics (parity, previous and spontaneous abortions, education among some others) differed somewhat for Papers II and III, and depended on the aim of each individual paper. Binary logistic regression was used to estimate the effect of the risk factors on the prevalence of the birth defect examined. Possible associations between selected characteristics and the hypospadias/ventricular septal defects were investigated further by multivariable logistic regression. Crude and adjusted odds ratios (ORs) with 95% confidence intervals were calculated for the studied risk factors.

The final regression model for Paper II included the following independent variables: maternal age, birthweight, smoking during pregnancy, folic acid intake during pregnancy, HBsAg positive, preeclampsia (all grades) and cervical erosion. In Paper III, the final model was established by including the following independent variables: maternal age, maternal body-mass index; multivitamin intake, folic acid intake during pregnancy, cigarette smoking, evidence of alcohol abuse, drug abuse during pregnancy, diabetes mellitus type 1 or 2 and sex of the baby (male). All statistical analyses in Papers II and III were performed using

SPSS Statistics, Versions 24.0 (IBM Corporation, Armonk, NY, USA, 2016).

3.5. Ethical considerations

This thesis contains register-based research which may provide ethical challenges such as a requirement for privacy and data protection. Before this research work was initiated, permission to access and use the data was sought from the register holders of the MCBR and MRCDR. After the aims of the thesis had been formulated, I submitted a request to Alexander Voitov, leader/coordinator of the MCBR, for accessing and using the data. The same request was also submitted to the Ministry of Health Care of Murmansk County, who was the main holder of the MRCDR. Permission to use the data for my thesis work was granted by both.

The MCBR registration forms do not contain personal identifiers such as names, surnames, addresses, and phone numbers and it is therefore not possible to link the data to individual women and thus protected their privacy. Additionally, the health information in the MCBR remained confidential and therefore no personal consent was required to conduct the research described in this thesis and the published papers. Furthermore, all patient-related data from the MRCDR were anonymized for comparative and statistical purposes.

All data were stored in two fire-resistant safety cabinets in the central MCBR office. One box was used to keep the paper forms with a flash-disc with electronic back-up data, and the second one was used for safe keeping of the laptop with the MCBR database. The keys for both repositories were shared between me and two individuals working in the central office. In addition, the original MCBR database had been saved in a separate folder on the laptop, which was hidden to avoid someone making changes in the original. This was done to prevent the introduction of errors/changes in the database, such as unexpected deletions of records. Furthermore, the laptop containing the MCBR data had no internet access to avoid external entry. As new births were added, a new back-up was generated on a separate flash disc every few days and was stored in the fire-resistant safe. Taken together, these actions addressed and fulfilled the ethical requirements pertinent for data protection. As this thesis

used registry-based data as primary sources, no harm or risks for the participants were expected. Indeed, and speaking generally, some potential benefits of our research for women in Murmansk County includes the generation of new knowledge about the prevention of selected birth defects that is now publically available through multiple publications based on the MCBR over the past few years. As a result, the new knowledge generated is available for medical doctors/specialists which can help improve health care for pregnant women, especially those in high risks groups.

There was also no discrimination regarding who was included in the registries as in Murmansk County, a special legislation was passed in 2005 by the Regional Government to make registration of births in the Murmansk County Birth Registry mandatory for all delivering women.

In summary, the work in this thesis followed the codes of conduct in the Declaration of Helsinki (55). Ethical approval was obtained in Russia from the Regional Health Administration of Murmansk County, the Ethics Committee of the Gynaecology-Obstetrician Association Group (2013/14) as well as Murmansk County. In Norway, ethical approval was obtained from the Regional Committees for Medical and Health Research Ethics; REC North (2013/2146).

4. MAIN RESULTS

Based on the three individual papers, the key results of the research presented in this thesis are summarized in this section. For a more detailed description, please refer to the individual papers provided at the end of this thesis.

4.1 Paper I: Underreporting of major birth defects in Northwest Russia: a registry-based study.

This study has two parts: i) linkage of the MCBR and MRCDR medical registries to obtain more accurate prevalence estimates for 21 types of major birth defects, and to discover possible under or over-reporting based on an assessment of the agreement between them; ii) based on the observed prevalences, conduct a comparison of data with those available for Norway and Arkhangelsk County (Northwest Russia).

We found 210 cases of major birth defects in the MCBR, compared to 195 in the MRCDR for the period January 1, 2006-December 31, 2009. Data linkage between registries increased the overall prevalence of major birth defects from 55 to 77 per 10 000, which corresponds to an increase of 40% due to underreporting in both data bases.

Among the 35 417 deliveries registered in the MCBR, 297 were multiple (0.8%); maternal age was lower than paternal age at the time of delivery (average age 26.5 and 29.5 years, respectively); at delivery, more than 80% of mothers were in the age range of 21-35 years old; the average gestational age was 39 weeks; the average birthweight of the babies was 3 340 g; and 11.7% of women had previously experienced one or more spontaneous abortions.

Of the 210 MCBR cases, 79 were not included in the MRCDR; conversely, 64 of the 195 cases in the MRCDR were not in the MCBR. After linkage, there were 274 cases of major birth defects in the combined registry. The percentage of agreement (i.e., the cases registered in both registries) was 47.8%. Both registries demonstrated identical prevalences for seven out of the 21 major birth defects, namely: anencephaly, encephalocele, micro-anophthalmos, hypoplastic left heart syndrome, oesophageal atresia, exstrophy of the bladder and

gastroschisis. For five major birth defects, the prevalences were comparable, namely: micro-anotia, ano-rectal atresia, renal agenesis and dysgenesis, diaphragmatic hernia and Down syndrome. Those for the remaining nine birth defects were more dissimilar, namely: hypospadias, epispadias, spina bifida, congenital hydrocephalus, transposition of great vessels, cleft palate, cleft lip with or without cleft palate, limb reductions defects, and omphalocele.

In order to compare the prevalence data for 21 types of major birth defects with Norway, we removed abortion data before 22 weeks of gestation from the Norwegian dataset to reflect the absence of such data in the Murmansk and Archangelsk Counties registries. Compared with Murmansk County, Arkhangelsk County had higher prevalences of birth defects of the nervous system, namely: anencephaly (0.6 *versus* 6.9, respectively), spina bifida (1.1 *versus* 9.5) and encephalocele (0 *versus* 1.9). The corresponding values in Norway for these birth defects were more comparable to those in Murmansk County (0.4, 1.9 and 0.4, respectively). Furthermore, the prevalences of oesophagus atresia (2.3, 2.4, and 2.4) and ano-rectal atresia (1.4, 1.5, and 2.5) were almost identical to those in Norway, Murmansk County and Archangelsk County. In Murmansk County, the prevalences of reduction defects of the limbs (9.6) and hypospadias (25.7) were much higher than in Arkhangelsk County (respectively 1.7 and 4.1) and Norway (3.1 and 13.0). Among the three study sites, Murmansk County had the highest prevalence of cleft palate (8.5), and the lowest prevalence of cleft palate and lip combined (4.0).

4.2. Paper II: Risk Factors for Hypospadias in Northwest Russia: a Murmansk County Birth Registry Study.

Based on Paper I, the prevalence of such major birth defect as hypospadias appeared high, and also observed that low birth weight, cervical erosion and preeclampsia (all grades) were associated with the risk of hypospadias.

The EUROCAT prevalence range for hypospadias was 1.3-39.4 per 10 000 newborns for the 2012-2016 time frame (56) while in Murmansk county it was 25.7 per 10 000 for the 1 January 1 2006 to 31 December 2011 study period. The MCBR registered 105 cases of hypospadias while MRCDR contained 82 cases. After combining data from the two registries and removing duplicates, there were 148 cases of hypospadias. Not all of the 105 hypospadias cases in MCBR were reported to MRCDR, which confirmed the presence of underreporting. Of the 148 cases from the combined registry, only 110 cases were diagnosed during the perinatal period and the remaining 38 within the 3 months after birth. Based on the ICD-10 classification of hypospadias and severity proportion, 84 cases (56.8%) belonged to the mild form, 29 cases (19.6%) were moderate, with 7 (4.8%) cases severe and 28 (18.8%) remained unspecified.

The mean birthweight was 3 291.0 g, which was significantly lower ($p<0.01$) in the group with hypospadias. In contrast, maternal age, the gestational age distribution, parity, as well as previously induced and spontaneous abortions were comparable between both groups. There was also no significant difference among multivitamin and folic acid intakes during pregnancy between the two groups, while preeclampsia and cervical erosion were higher among women those who had delivered a baby with hypospadias ($p = 0.03$ and $p<0.01$, respectively).

Both crude and the adjusted ORs for the variables included in the logistic regression analysis did not differ substantially between babies born with or without hypospadias. Low infant birthweight and cervical erosion were associated with a two-fold elevation of hypospadias risk in both the unadjusted and adjusted model; and for preeclampsia, the increase was somewhat lower (OR 1.67 and 1.66, respectively). Other potential risk factors investigated in

such as smoking during pregnancy, folic acid intake during pregnancy, HBsAg positivity did not influence the risk of hypospadias. The influence of progesterone-containing drugs intake during pregnancy (namely Progesteron, Utrogestan, Duphaston and others) was examined, and no association with the risk of hypospadias was evident.

4.3. Paper III: Risk Factors for Ventricular Septal Defects in Murmansk County, Russia: A Registry-Based Study.

This study was conducted for two reasons. First, a 2014 study of risk factors for cardiovascular malformations (CVM) in the city of Monchegorsk (Murmansk County) was published (35) as the first of its kind in Russia. However, it had some limitations because it was based on 92 cases of CVMs diagnosed either during the perinatal period or before birth and the risk factors were analyzed only for the whole CVM group. Since CVMs constitute a leading cause of perinatal and infant mortality, a more detailed analysis was warranted.

Taking into account that most of CVMs are usually diagnosed after birth, our linkage of the MCBR and MRCDR made it possible to assess cases up to two years after birth. The sample size of 744 CVMs identified in Murmansk County enabled us to analyze ventricular septal heart defects separately as it is the most common CVM.

Based on regression modelling, we found that smoking, alcohol abuse, and maternal diabetes were risk factors for VSDs. During the study period, 52 253 eligible births were recorded in the MCBR and included 352 cases of CVM. By comparison, 508 CVM cases were noted in the MRCDR. After combining and removing duplicates, 744 cases of CVMs remained, which corresponds to a prevalence of 14.2 per 1000 newborns. Isolated SHDs accounted for 492 (66.1%) of all CVM cases. Among all septal defects, Q21.0 (VSD) was the most common (233 cases, 47.4%), with Q21.1 (ASD; 22.8%) and Q21.9 (unspecified; 23.8%) as major contributors.

Although lower birth weight was observed for VSD cases, it likely shares a common risk factor with other cardiovascular malformations. For this reason, low birthweight was not included in the regression analysis. Significant increase in risk for having a baby with a ventricular septal defect was found for women who had diabetes type 1 or 2 (OR=8.72) and for those who abused alcohol during pregnancy (OR = 4.83). Maternal smoking as a risk factor also reached statistical significance (OR = 1.35), while male gender of the baby was protective (OR = 0.67) for developing VSD. Maternal age at delivery, BMI, drug abuse during pregnancy, folic acid and multivitamins intake during pregnancy were not associated

VSD risk. We also conducted a separate multiple logistic regression analysis for ASD cases (n = 112) using the same potential risk variables. In this case, only male sex of the baby was statistically significant (OR = 1.52).

5. DISCUSSION

This thesis constitutes the first attempt to combine a birth registry and a regional birth defects registry in Russia with the intent of revealing a more accurate prevalence of birth defects. Based on the linkage of MCBR and MRCDR data, the research presented in this thesis shows that systematic under-reporting of birth defects exists in Murmansk County. Since the hypospadias prevalence was found to be comparatively high, this warranted further investigation of its risk factors. Finally, the thesis research also focused on cardiovascular malformations which are known to be the leading cause of perinatal and infant mortality.

5.1 Registered-based research and linking databases as a tool for disease surveillance

Data collected in both clinical and population registries are helpful for a wide range of purposes including disease surveillance, health systems management, scientific research and strategic planning. The use of registries can be further optimised by linkage between them. Preparation of a linked data set involves identifying the sources and quality of the required data elements as well as establishing a method of actually combining the data. The linked data set will then yield a more complete picture than could be obtained from any single data source, as it results in a single population with duplicates and mismatches removed. Data linkage requires not only a thorough understanding of the databases to be linked, but also expertise in statistics and programming in order to establish a methodology for identifying matches between files, while minimizing errors.

Linkage of data is simplified when all of the data sources use a common unique key to identify individual subjects. Such an ideal identifier is unique, permanent, and applicable to the entire population of interest. Unique identifiers assigned at birth exist in a number of countries, including Sweden, Norway, Denmark and Israel. By 1997, there were more than twenty different registries in the Nordic countries that could be linked to national birth registries (3). These registries are linkable at the individual level because of the unique identification number given to all residents in the Nordic countries. This ensures the correct identification of a person and makes it possible to collect information on the same person in

different registries (57), and thereby facilitates the use of the data in statistical analyses.

In practice, numbering systems are not universal and not even within health systems. Therefore other identifying information ─ such as name, birth date, gender and residence─ may need to be taken into consideration to identify matching records. In Russia, the use of unique identifiers is not common, nor is the linkage between registries. Most registries in Russia include passport data, as well as names and surnames and date of birth (which are not unique). However, to date the registration of a medical insurance number and/or a taxpayer identification number (TIN) is becoming obligatory especially in health care systems. This means that it will be possible in the future to perform more linkage between registries.

5.2 Methods for linking databases

Two basic methods exist for linkage of disparate datasets, namely deterministic and probabilistic (58, 59). Deterministic linkage requires an exact match between linkage variables (identity number, last name/first name, etc.). If for example data entry errors or name changes have occurred, there will be a differences between linkage variables in the two files. This will lead to either the incorrect coding of an identity number or, for example, the appearance of a maiden name in one file and a married name in the other, thereby circumventing true matches between records. By contrast, in probabilistic linkage less than an exact match may be acceptable. This approach is based on a predetermined method that assigns a score to the level of a match. The level of acceptable error depends on how crucial the identification of a specific person is. Different fields may be given different weight. For example, a matched birth date may be more important than matching spelling of the last name.

In terms of the MCBR and MRCDR, a direct link between these registries was unavailable due to the absence of unique personal identification numbers. Potentially either a deterministic or probabilistic approach could be used for linkage, but the MRCDR data were provided by the Ministry of Health Care of Murmansk County only in printout form. Consequently the official medical documents were requested to validate the data and to conduct the manual linkage of the MCBR and MRCDR. The procedure of linkage has been

described in detail is Section 3.2.

5.3 Linking birth registries with birth defect registries

5.3.1 Combining a birth registry and a birth defect registry in Russia

To our knowledge, the research described in this thesis constitutes a first attempt in Russia to combine a birth and a birth defects registry with the intent of obtaining a more accurate estimate of prevalence values.

As already mentioned (see Section 4.1), we found that for the 210 cases of the 21 major birth defects that are obligatory for surveillance in Russia and registered in the MCBR, only 131 (63%) were actually registered in the MRCDR. Ideally, all MCBR cases should have been reported to MRCDR as it focused on the period 22 weeks of pregnancy until a child is 16 years old. Of course, some cases were also missing from the MCBR. We have illustrated a 40% increase in the overall prevalence of major defects after combining the two registries. The wider coverage period of the MRCDR is a major advantage over the MCBR in that the observation period is much longer.

The use of indirect identifiers for linking large datasets has been described previously in adult populations (60, 61) and is usually successful as long as the identifiers overlap sufficiently (62).

5.3.2 Advantages of data linking

The research described in this thesis is an example of how useful data linkage can be. Before 2006, there were no adequate mechanisms to estimate the completeness of the MRCDR and therefore no reports were available regarding its quality. Clearly the linkage efforts described in this thesis have revealed some under-reporting in the official data on major birth defects in Murmansk County.

Table 3. Prevalences of 21 types of BD per 10 000 newborns (obligatory for reporting) in Russia based on regional congenital defects registries.

Region	2006-2009 years
Moscow	56
Saint-Petersburg	43
Archangelsk	67
Krasnodar	67
Stavropol	47
Other 46 regions	Range from 25 to 82
Murmansk MRCDR	55
Murmansk MRCDR+MCBR	77

It is evident from the data in Table 3 that the linking of the registries in Murmansk County afforded a more accurate estimate of the prevalence of 21 types of major birth defects. The combined prevalence of 77 per 10 000 newborns observed is close to be the highest values in Russia. Another advantage of data linkage is that it provides follow-up possibilities (Figure 4).

Figure 4. Number of defects detected among babies born in 2006 (MCBR) with 4 years of follow-up through the MRCDR.

With reference to Figure 4, 8 399 newborns were registered in the MCBR in 2006. Among them, 184 had birth defects that were identified at birth, which corresponds to a 2.2 % increase. Using the data available in the MRCDR, after 4 years of follow-up the total number of defects increased almost 3-fold [from 184 (2.2 %) to 508 (6 %)].

It is likely that the official prevalence data from Russia for the most severe defects (reporting of which is mandatory) are comparable with EUROCAT data for the same defects for live-born and stillborn (with exclusion of TOPFAs). The reason being that these birth defects 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 Russian national guidelines that define the phenotypes for all registered malformations, nor is there a list of minor malformations that are not reportable; neither should the latter be included in the calculation of prevalence values. It is therefore likely that both under- and overestimation of prevalence occurs and that misclassification of defects exists in data provided by national statistics.

5.4 Birth defect: Hypospadias

5.4.1 Reports on risk factors and prevalence

In 1994, Chashchin et al. published the first report about increased risk of structural malformations in newborns among female nickel-refinery workers in Murmansk County (33). That investigation did not address specific malformations, and thus warranted closer attention. A retrospective study published in 2006 by Vaktskjold et al. [37] was the first attempt to investigate possible risk factors for genital malformations in Murmansk County. It reported no negative effect of maternal exposure to water-soluble nickel compounds in terms of the risk of genital malformations in the offspring of pregnant women (including nickel refinery workers) in the town of Monchegorsk (39).

The availability of registry data on hypospadias and related publication are of fundamental importance. It raises awareness among all relevant healthcare providers and among the

general public about the importance of such a common congenital condition (63). In Russia, hypospadias is included in the 21 types of major birth defects that are obligatory for registering and reporting. Relatively speaking, the overall observed prevalence of hypospadias in Murmansk county may be considered to be high, namely 25.7 per 10 000 newborns (Paper I). Interestingly, worldwide trends in this birth defect are contradictory. Stable time trends for hypospadias have been reported in Russia, 21 European regions (combined data) and California (USA). By contrast, increasing trends have been observed in China, South Korea, Sweden and Atlanta (USA). In Table 4, selected worldwide changes in prevalence of hypospadias are summarized.

Table 4. Worldwide changes in prevalence of hypospadias.

Country	Year	Study population	Time period	Prevalence per 10 000 births	Trend
Russia (64)	2015	4 676 605	2006-2012	12.1	stable
23 European regions (65) (EUROCAT)	2015	5 871 855	2001-2010	18.6	stable
Sweden (66)	2014	1 948 591	1973-2009	22.5-40	increasing
China, Chengdu (67)	2012	3 793 988	1996-2008	0.7-4.5	increasing
South Korea (68)	2011	8 929 033	2000-2004	1.4 -3.3	increasing
California, USA (69)	2011	5 974 154 *(males only)*	1985-2006	42*	stable
Finland (70)	2003	2 164 720	1970-1986	10.7-16	variable
Atlanta (71)	1997	18 291 500	1970-1993	17-50	increasing

* Corresponds to prevalence among newborn males

Overall, it is unclear whether hypospadias prevalence is rising. Early studies report increasing trends (72-74), while more recently either increasing (75-78), stable, or decreasing prevalences (79-81) are reported. Varying prevalences and trends therein may well have genetic and environmental risk factors that differ between geographical regions. However,

another possible explanation pertains to methodological differences between studies because the ascertainment of hypospadias cases may vary. Exclusions of mild forms of hypospadias and hypospadias with known aetiology might well explain the lower prevalences observed for some regions. Moreover, data on the severity of hypospadias cases are often not provided.

Any rising trend could be due to an increased awareness of hypospadias among examiners, a more frequent or early diagnosis of mild hypospadias, a tendency to surgically correct mild forms, and the reporting of minor defects that were previously neglected or disregarded (82). Minor hypospadias can contribute up to 75% of the cases, and the effect of over- or under-reporting remains a major concern.

In Paper I it is illustrated that during the period 2006-2009, the prevalence of hypospadias in the MCBR, MRCDR and the combined registry were 22.3, 15 and 25.7 respectively. During the same period in Norway, the MBRN reported a hypospadias prevalence of 13.0 per 10 000 births (TOPFA excluded) although in the MBRN's report to EUROCAT for the period 2006-2009 it was 20.3 (TOPFA excluded) per 10 000 newborns (56). It is an example that data sources and period of observation are highly important and should be taken into account. Furthermore, these data reflect that 36% of babies with hypospadias in Norway were diagnosed after the neonatal period.

5.4.2. Hypospadias is a public health problem

To limit psychological stress and possible behavioural problems, surgery is recommended when a patient is between 6 and 18 months old (83). Even when surgery is conducted during the first two years of life, severe medical, social and sexual problems later in life might be encountered (84). Indeed, a 10-year follow-up of patients with mainly mild forms of hypospadias who underwent a stage-1 repair showed different rates of complications in up to 50% of the patients (85). Although most studies conclude that psychosocial development of a patient is not seriously altered, some do suffer from negative genital appraisal, sexual inhibition, as well as erection and ejaculation problems (86, 87).

5.4.3 Limited studies on risk factors for hypospadias in Russia

In Russia, to date there is a lack of studies that address risk factors for hypospadias. In most cases, hypospadias has an unknown etiology, but is probably a mix of genetic and environmental factors. Among the factors associated with risk and that are frequently investigated are: low birth weight, being small for gestational age, maternal hypertension, preeclampsia and high maternal BMI (84). Factors that do not associate with hypospadias in most studies include: maternal alcohol consumption, maternal smoking, paternal age, folic acid intake and gestational diabetes (84).

Due to small sample size, it was only possible to investigate a limited number of risk factors out of those mentioned above. We found that low infant birthweight, preeclampsia, and cervical erosion were risk factors for hypospadias in Murmansk County. In agreement with previous studies in the USA, Sweden and Denmark (77, 88, 89), we found no associations with hypospadias for maternal alcohol consumption and smoking, nor with multivitamin and folic acid intakes during pregnancy or maternal age. Paper II summarizes the first investigation of risk factors for hypospadias in Northwest Russia; it includes the entire population of Murmansk County (i.e., the Kola Peninsula).

5.5 Birth defect: Cardiovascular malformations

5.5.1 Reports on risk factors and prevalence

CVMs are of public health concern given that they occur in approximately 1% of all live births (90, 91) and constitute the leading cause of infant and perinatal mortality (92, 93). Most CVMs are thought to be multifactorial in origin, involving both genetic and environmental factors (94-97).

In Russia, among all CVMs, only hypoplastic of the left heart (ICD-10 Q23.4) and transposition of great vessels (ICD-10 code Q20.3) are included in the 21 types of major birth defects that are subject to annual reporting to the Central Registry in Moscow. Federal monitoring in Russia for other CVM types does not exist. However, local congenital defects registries collect information about all types of CVMs, and some of the local reports have been published (30, 98-100). By comparison with the Russian data, prevalences of

hypoplastic left heart and transposition of great vessels based on EUROCAT data (56) are summarized in Table 5.

Table 5. Prevalence of the two major birth defects of the heart that are obligatory for reporting in Russia (calculated per 10 000 births in 2006-2011 years)

Country	Hypoplastic left heart		Transposition of great vessels	
	LB+FD	***TOPFA***	***LB+FD***	***TOPFA***
Russia	1.1	-	1.8	-
Finland	1.1	0.9	3.5	0.6
Sweden	0.9	1.4	2.7	0.2
Norway	1.8	1.6	3.9	0.6
Poland	1.6	-	2.1	-

Information about termination of pregnancy due to foetal anomaly are not available to date for Russia and Poland. Prevalences of hypoplastic left heart (LB+FD) are comparable in Russia, Finland and Sweden, while those in Norway are somewhat higher by comparison (Table 4). The reported prevalence for transposition of great vessels (LB+FD) was the lowest in Russia.

To our knowledge, the first attempt to investigate risk factors of CVMs in the city of Monchegorsk based on local registry data was published in 2014 by Postoev et al. (101). That study was limited to the neonatal period and included 86 babies with CVMs. Due to the relatively small sample size, individual subcategories of CVMs were not assessed. The adjusted odds ratio between maternal smoking during pregnancy and CVM was 4.09 (101).

5.5.2 Septal heart defects; the most prevalent of cardiovascular malformations

Paper III focused on the most prevalent group of CVMs, namely septal heart defects. Atrial and ventricular septal defects are common cardiovascular malformations and are found in around 0.5% of newborns. Due to the success of current paediatric cardiac care as well as

improvements in case ascertainment and reporting, the number of adult patients with atrial septal defects and ventricular septal defects is increasing. The prevalence of ventricular septal defects and atrial septal defects identified at birth for different countries are presented in Table 6.

Table 6. Prevalence of Ventricular Septal Defects (VSD) and Atrial Septal Defects (ASD) calculated per 10 000 births in 2006-2011 based on EUROCAT data.

Country	**VSD**		**ASD**	
	LB+FD	**TOPFA**	**VB+FD**	**TOPFA**
Murmansk (Russia)	44.1	-	21.2	-
Finland	126.9	4.8	29.2	1.7
Sweden	41.6	1.3	17.9	0.2
Norway	44.0	3.4	23.9	0.8
Poland	25.3	-	16.0	-

The prevalences of ventricular septal defects and atrial septal defects in newly born babies is similar in Sweden, Norway and Murmansk County. Surprisingly, Finland has around a three-fold higher prevalence. The pan-European analysis indicates that the prevalence of ventricular septal defects at birth increased on average 0.7% per year during 2006-2015 in six registries of Europe, namely Basque Country, Zagreb, Antwerp, Isle de Reunion, Ukraine and Tuscany (102). Due to the absence of federal monitoring of ventricular septal and atrial septal defects in Russia, corresponding data there are unavailable.

5.5.3 Investigating risk factors for cardiovascular malformations via register-based data

To date our analysis of risk factors for ventricular septal defects is the only study in Russia that is based on data from population registries. Worldwide numerous studies have been published on etiological factors involved in the formation of cardiovascular malformations, including septal defects. Many of these are retrospective case-control studies with exposure

information obtained from maternal interviews or questionnaires (103-106). They carry a risk of recall bias and some have additional worrisome issues such as a high rate of non-responders. Other studies are cohort studies which analyse the occurrence of such defects in a defined cohort of women with a certain exposure, but often are of limited size and have low statistical power (95).

By contrast to case-control and cohort studies, those based on health registers usually have information for a large number of cases, and the exposure data are obtained prospectively in relation to the outcome (107, 108). A large Swedish study based on data from three national registries─namely the Medical Birth Register, the Birth Defect Register, and the Hospital Discharge Register─ involved more than 7 300 babies diagnosed with ventricular septal and atrial septal defects during 1998-2010 shows a set of interesting associations (109). For example, maternal age and parity had weak effects on the risk for septal defects, and this was similar for ventricular and atrial septal defects. Maternal smoking in early pregnancy was associated with an increased risk for ventricular septal defects, whereas maternal obesity or being overweight were associated with an increased risk for atrial but not for ventricular septal defects. Maternal pre-existing diabetes was a strong factor with a three-fold increase in risk for any septal defect, with the highest impact for the combination of ventricular and atrial septal defects. Children with a septal defect are born preterm more often, and the highest odds ratio for preterm birth were seen for the atrial septal defect. Female newborns seemed to be more susceptible to these defects, and this appears the most pronounced for the combination of the ventricular and septal defects (109).

We found that an increased risk of ventricular septal defects among infants born to mothers who abused alcohol [OR = 4.83; 95% CI 1.88–12.41] or smoked during pregnancy [OR = 1.35; 95% CI 1.02–1.80]. Maternal diabetes mellitus was also a significant risk factor [OR = 8.72; 95% CI 3.16–24.07], while maternal age, body mass index, folic acid and multivitamin intake were not associated with increased risk. Overall risks of ventricular septal defects for male babies were lower [OR = 0.67; 95% CI 0.52–0.88]. Our findings correspond largely to the Swedish study described above (c.f., (109)).

5.5.4 Treatment for cardiovascular malformations in Russia

In 2014, the Federal Russian Statistics Service (Rosstat) estimated the infant mortality resulting from CVM to be 1.5 per 1000 infants. Up to 75% of Russian babies who need life-saving surgical treatment do not receive it due to a lack of specialized regional centres.
In terms of current treatment, atrial septal percutaneous closure is mainly indicated for ostium secundum defects, although other types can also be treated percutaneously. In contrast, percutaneous treatment is not widely used for ventricular septal defects. Post-myocardial infarction ventricular septal defects have a very high surgical risk, and certain cases of perimembranous ventricular septal defects are the ones treated more commonly. Percutaneous closure of ventricular septal defects is a safe and suitable procedure, although small residual left-to-right shunts occur in a relatively high percentage of patients. The endovascular surgery department in Murmansk Regional Clinical Hospital can handle such treatment, although most young patients undergo treatment at the central facilities in Moscow and Saint-Petersburg.

5.6 Methodological discussion

Based on published findings, we judge the validity of the MCBR to be satisfactory for epidemiological research (42). Consequently, the results and conclusions made on the basis of data from the linked database may be deemed to be of good-to-high generalizability. It is more difficult to judge about causality from ethical and epidemiological points of view because unidentified confounders may have influenced any of the cause-and-effect relationship reported (110, 111) .

5.6.1 Internal Validity

Validity is closely related to an absence of bias in any measured variable (112). In this context, exposures, outcomes, co-variables and confounders are considered to be of concern in clinical and epidemiological studies. Internal validity is the extent to which systematic errors are minimised during all stages of data collection (112, 113).

5.6.1.1 Systematic error

Systematic error, also known as bias, can affect internal and external validity of studies. By

definition, it is any systematic error in design, data gathering, analysis, interpretation and dissemination of results that finally leads to an under- or over-estimation of effects of a given exposure on a specific outcome. There are different kinds of systematic errors in medical research that are not fully controllable or removable, but awareness of such errors can lead to more reliable reports and conclusions (114-116). Systematic errors can be generally divided into two categories, namely selection bias and information bias (114, 116-118). Selection bias occurs when the selected sample is not representative of the reference population. Information bias arises when gathered information about exposure, outcome or both are subject to an error in measurement (114, 118-120). Both types of bias could lead to an erroneous correlation, namely one that is not real but yet is constructed based on the available data (116, 117).

Selection bias did not directly apply to the MCBR as the registry covered about 98.8% of the annual deliveries in Murmansk County (42). Nevertheless, it is likely that 1% of unregistered pregnancies had different characteristics or outcomes compared to those registered, although it was not possible to verify this. The reason for not having been registered (missing) could be the withdrawal of paper-based medical documents (e.g., both maternal and infant medical histories) by official institutions such as the prosecutor's office, the Bureau of Forensic Medicine, and/or the Ministry of Health. Most of these withdrawals are explained by the necessity of conducting detailed analyses of any adverse pregnancy outcomes such as stillbirth, maternal death or complaints by the mother about the poor quality of service provided by the maternity hospital. Information about such possibilities was not available.

A main source of information bias was the difference in codes used between hospitals in Murmansk County. To minimize this, doctors and midwifes responsible for data collection/recording for the MCBR were regularly trained to make coding practices more uniform. Furthermore, since maternal smoking was self-reported by the mothers underreporting was a possible. Alcohol and drug consumption were not self-reported, but were noted by a doctor when signs of alcohol or drug abuse were evident or provided in primary medical documentation (43). In general, information biases when present would lead to the misclassification of an exposure and would most likely influence the estimated risk.

5.6.1.2 Measurement errors

Measurements errors may also have occurred in estimating the gestational ages recorded in the registries. Various steps were taken to minimize misclassification bias. To make the definition of gestational age uniform, we used gestational age defined by the first day of last menstrual period. To avoid birthweight measurement errors, 15 digital calibrated scales were provided to each maternity hospital. Body mass index was used at the first visit to the gynaecologist, which normally occurred before week 12. Fattah et al. (121) have demonstrated that BMI does not change much during the first 14 weeks of pregnancy and therefore accurate early pregnancy measurements are recommended as preferable compared to data based on self-reports or pre-pregnancy measurements.

5.6.1.3 Random errors

Random errors constitute a variability in the data that cannot be readily explained (122). It causes inaccurate measures of association (113). Rothman states that if a study is large, the estimation process would be comparatively precise and there would be little random error in any estimates (122). In Papers I-III, the relatively large sample size minimized the sources of random error and thereby increased the accuracy. Additionally, the results are given as 95% confidence interval or a p-value is reported to indicate the degree of random error. As p-values were calculated in relation to the null hypothesis (assumes there is no true association between variables). A p-value of ≤ 0.05 therefore indicates that the data were not consistent with the null hypothesis.

5.6.1.4 Confounding

Confounding was controlled at the statistical analysis stage. The investigation of associations between risk factors during pregnancy and the occurrence of hypospadias (Paper II) and of ventricular heart defects (Paper III) were potentially subject to bias from confounding. Adjustment for potential confounders was the primary tool for addressing this bias source. As a first step in the estimation of birth defects risk factors, univariate analysis identified any variables that potentially could be associated with selected malformations (Papers II and III). The next step was the use of multivariate logistic regression. Inclusion of all independent variables as categorical in the model could potentially lead to imperfect adjustment (123),

and thereby introduce bias due to residual confounding. We therefore employed stratification with more than two categories for age, body mass index, gestational age and birthweight. 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 that up to 5% of the data was missing for some of these variables.

5.6.2 External validity

Internal validity is necessary for external validity, but does not guarantee the latter. External validity or generalizability is the extent to which the results of a study apply to people not in it (113). Thus external validity identifies the accuracy of research findings, by exploring its applicability from one setting to another (124). It requires quality control of measurements and observations in order to extrapolate any finding. As mentioned earlier in this thesis, quality controls established that the proportion of error in the MCBR was less than 1 % (42). Moreover, since our studies only included women giving birth at the maternity clinics, the results may not be generalizable to those who gave birth outside such facility. However, the number of births registered in the MCBR comprised 98.8% of the official number of births recorded by the Health Department in Murmansk County (42).

5.7 Ethical considerations when using data from MCBR and MRCDR

5.7.1 Ethical approval for the work in this thesis

The creation of the MRCDR in 1998 was associated with approval by the Murmansk County Committee for Research Ethics (Murmansk, Russia). Since the setting up of the MCBR was a Norwegian-Russian cooperative project, it also required approval by both the Murmansk County Committee for Research Ethics and the REK Regional Committee for Health and Research Ethics, Northern Norway (Tromsø, Norway).

Indeed, one ethical issue is the approval of the research conducted in Russia by a Norwegian Committee. In general, it is surprising that REK in Norway is involved in approving research outside Norway with participants who are not citizens of Norway. On the other hand, most of the researchers that have been involved in research with MCBR and MRCDR are affiliated to Norwegian universities which could be a possible explanation for the current procedures

surrounding the ethical approval.

5.7.2 Data collection and consent

In case of both MCBR and MRCDR, the Health Authority and Administration of Murmansk Region passed legislation which made it mandatory to collect data on birth registration and medical information including data of birth defects. Hence, it is mandatory for delivering women to be registered in both registries, and no written consent was therefore obtained from the mothers before their inclusion in the registry.

5.7.3 Data storage

To protect confidentiality of the participants as well as the collected data, protective measures were implemented regarding the security of data storage. Pertinent details are provided in Section 3.5 of this thesis.

5.7.4 Privacy/Confidentiality

As indicated in Section 3.5, the MCBR did not collect any personal data (ID, name, surname and other), but nevertheless includes some specific sensitive information about smoking habits, date of birth, medicine intake during pregnancy as well as alcohol and drug abuse. Due to the fact that some information was collected during the standard mother's interview prior to delivery by the attending medical personal, the mother's oral consent is implied.

In MCBR and MRCDR the possibility of tracking individual participants is therefore limited. In 2006-2007, two extensive quality controls of the data were performed in most maternity hospitals by a central registry team using indirect identifiers, specifically the birth date of both mother and her child as well as the hospital file number. Access to hospital files in the archive room was limited as required by Russian law, and so it was not possible for unauthorized personnel to access these. Any release of data from MRCDR to a third party needs to be approved by the Murmansk County Health Authority. At the same time, any release of the MCBR data requires the approval of both the Russian and Norwegian institutions/organizations mentioned at the end of Section 3.5. The data when released are to be provided in such a way that it is impossible to change the data entries.

5.7.5 Withdrawing participation

Since the registration process for the MCBR and the MRCDR were mandatory, no formal consent was sought for the registered data. It seems appropriate that the use of a consent form be considered by the MRCBR, to be signed by the delivering mother about the possible use of her and her baby's data in private research and its publication.

5.8 Challenges when using data from MRCDR and MCBR to improve health care

While the MRCDR registry was implemented in 1998 in all parts of Russia, as of 2006 the MCBR was the first medical birth registry for the Murmansk region. It has been widely used by numerous researchers from different countries to gain and provide new knowledge about pregnancy outcomes and perinatal epidemiology in Northwest Russia.

To enable the improvement of the health care system in the Murmansk region, it is also important to share any new knowledge and evidence it generates with medical doctors and pregnant women through press-releases, daily newspapers, conferences etc. Hopefully the results described in this thesis and the three individual papers, as well as other publications based upon the MCBR (e.g., 30, 35, 40, 45, 47-50), may serve an important role in formulating prevention strategies for birth defects and, at the organizational level, devising possible improvements in the health care system.

The MCBR and MRCDR have some obstacles in the context of the distributive justice principle. Since the MCBR was established in cooperation with the University of Tromsø, initially nearly all studies based on it have been carried out by Norwegian researchers, and even now most related published articles have been written in English. This development has limited the access of the published results by Russian health care professionals. Moreover, to date there has been no overall plan for the dissemination of results through general communication channels, such as those mentioned above.

5.9 Future perspectives

The MCBR only covers the complete years of 2006 to 2011and, as mentioned earlier, is the only such birth registry in the Russian Federation. Unfortunately, in June of 2012, the funding for this project ended and therefore the birth registry was permanently closed.

Interestingly, the Arkhangelsk County Birth Registry (ACBR) was launched on 1 January 2012. It was modelled after the MCBR in terms of the paper form and the manner the database was compiled were identical. Unfortunately, the ACBR stopped operating after a few years in 2015 due to lack of ongoing financial support from abroad (Anna Usynina, personal communication). By 2015, more than 45 000 deliveries had been registered in the ACBR.

Both MCBR and ACBR depended on Norwegian financial support, while the Russian Government did not pay sufficient attention to such potentially important projects. Among possible reasons for this includes the mentioned lack of publications in Russian journals, as well as insufficient sharing of data with Russian health care professionals and the Ministry of Health Care of the involved regions. Furthermore, the challenge in obtaining financial support in Russia for medical research and medicine in general makes it difficult to obtain funding for birth registries and similar projects.

To increase the knowledge about the importance of birth registries, it is my hope that the published papers and the thesis summary in Russian may be distributed widely among health care professionals in Russia to show the increasing need and value of continuing both the MCBR and ACBR. Furthermore, the work described in this thesis will hopefully serve to demonstrate how necessary it is to create a national birth registry in Russia. In the meantime, it is possible and relatively easy to connect the MCBR and ACBR databases as they have identical structures. Together this would provide a database for a total of over 98 000 deliveries. This would constitute an important instrument for future research on risk factors for adverse pregnancy outcomes including birth defects etc. Another promising future prospective is to link the already collected data in the MCBR and ACBR with other databases such as other regional cancer registries, death records, hospital discharge

databases, among others.

5.10 Recommendations

Based on the findings presented in this thesis, below are practical recommendations which could increase the validity of MCBR and MRCDR data.

- Mandatory registration of termination of pregnancy at any gestational age due to foetal anomaly.

- A unique identifier common to all data sources would provide the simplest solution to linkage of files from multiple sources; in the absence of such an identifier, probabilistic linkage methods strategies must be developed.

- Creation of electronic submission forms, which would help to avoid missing information.

- A common coding system for use by registries and other medical sources for diagnoses, treatments, pharmaceuticals (continuously updated dictionaries).

- Document all birth defects, including minor defects and those which are not obligatory for reporting.

- To accompany each ICD-10 code from the range of Q00-Q99 with extra fields with detailed text description of the defect.
- Medications used in pregnancy should only involve international non-proprietary names (not tradenames). To date there are only four fields in the MCBR in terms of medicines used during pregnancy; all should be mentioned in any primary medical documentation.

- It is common that pregnant women undergo an ultrasound examination three or more times during pregnancy. Currently only one investigation (specifically the first) can be recorded in the MCBR. Not recording all ultrasound examinations might hide some indication of a diagnosis found later.

- To our knowledge, only two quality controls were of the MCBR were conducted in 2006-2007, while no such controls have been done for the MRCDR. Implementing systematic reviews seem mandatory. Ongoing/compulsory validation of birth defects databases is also recommended.

6. CONCLUDING REMARKS

It is clear that MCBR and MRCDR were useful tools for birth defects surveillance and related research. Based on the work in this thesis, it is evident that:

- Routine under-reporting of major birth defects to the MRCDR of 40% cases occurred in Murmansk County for the 2006-2011 period;

- Linkage of the two registries allowed better prevalence estimates for 21 types of major defects obligatory for registering and reporting. Due to this, the prevalence of major birth defects increased from 50 to 77 per 10 000 newborns after registry linkage;

- Hypospadias cases were the most prevalent birth defect in Murmansk County with a prevalence 25.7 per 10 000 newborns;

- Hypospadias was associated with cervical erosion, low infant birthweight and preeclampsia. Maternal hormone imbalance and placental insufficiency may be factors associated with the occurrence of hypospadias;

- Alcohol abuse during pregnancy, as well as maternal diabetes mellitus were risk factors for delivering infants with ventricular septal defects. The effect of smoking during pregnancy was marginal. Male sex was a protective factor that reduced the risk to be born with a ventricular septal defect;

- The research presented in this thesis demonstrates that linking the MCBR and MRCDR data improved case ascertainment and official prevalence assessments, and reduced the potential of under-reporting by physicians. Our findings have a direct implication for improving perinatal care in Murmansk County. Potentially numerous cases of hypospadias and ventricular septal defects are preventable in Russia if health policy makers were to give more attention to established risks.

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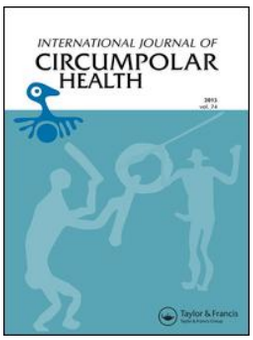
Paper I

Under-reporting of major birth defects in Northwest Russia: a registry-based study

Anton A. Kovalenko, Tormod Brenn, Jon Øyvind Odland, Evert Nieboer, Alexandra Krettek and Erik Eik Anda



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RESEARCH ARTICLE

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Under-reporting of major birth defects in Northwest Russia: a registry-based study

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ABSTRACT

The objective was to assess the prevalence of selected major birth defects, based on data from two medical registries in Murmansk County, and compare the observed rates with those available for Norway and Arkhangelsk County, Northwest Russia. It included all newborns (≥22 completed weeks of gestation) registered in the Murmansk County Birth Registry (MCBR) and born between 1 January 2006 and 31 December 2009 (n=35,417). The infants were followed-up post-partum for 2 years through direct linkage to the Murmansk Regional Congenital Defects Registry (MRCDR). Birth defects identified and confirmed in both registries constituted the "cases" and corresponded to one or more of the 21 birth defect types reportable to health authorities in Moscow. The overall prevalence of major birth defects recorded in the MRCDR was 50/10,000 before linkage and 77/10,000 after linkage with the MCBR. Routine under-reporting to the MRCDR of 40% cases was evident. This study demonstrates that birth registry data improved case ascertainment and official prevalence assessments and reduced the potential of under-reporting by physicians. The direct linkage of the two registries revealed that hypospadias cases were the most prevalent among the major birth defects in Murmansk County.

Abbreviations: ICD-10, International Classification of Diseases, 10th revision; MCBR, Murmansk County Birth Registry; MRCDR, Murmansk Regional Congenital Defects Registry; MGC, Murmansk Genetics Center

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KEYWORDS
Birth defect; birth registry; linkage; under-reporting

Background

Congenital anomalies (also known as birth defects) are structural or functional anomalies that exist at or before birth, although some become evident during infancy. Based on EUROCAT data, the total prevalence of all birth defects diagnosed at birth in Europe is about 2.5% [1] and its temporal prevalence is stable. Even so, congenital anomalies have become the main cause of perinatal mortality as other causes of death have declined [2]. Each year an estimated 7.9 million babies are born with serious birth defects and approximately 50% of all congenital malformations do not have an identified cause. Genetic factors, exposure to viruses or bacteria, maternal diseases and exposure to chemicals have been associated with increased risk [3]. Although some congenital birth defects are treatable (surgically or otherwise), annual estimates indicate that 3.2 million children are handicapped for life [4]. These children often need special medical treatment and may suffer from long-term effects, as well as socially [4]. Birth defects not only affect the child, but also the child's family and society as a whole [5]. Because of the serious public health significance, understanding the causes of birth defects constitutes a growing priority, as do the development, implementation and evaluation of preventive programmes [6,7].

Acquisition of data from population-based registries of birth defects constitutes an important information source [8]. Since not all birth defects are detectable at delivery or even during the neonatal period, some defects, such as hearing defects or mental disorders, remain under-reported. Another deficiency is incomplete or incorrect recording by physicians [9].

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The Murmansk County Birth Registry (MCBR) is based on the format used in the Nordic countries and was established in 2006. Pertinent information was systematically and routinely collected from the 15 county maternity clinics, each of which deliver 1–4 neonates per day (in total ~9000 deliveries annually). In 2010, it was the only operational birth registry in Russia [10]. The MCBR records information on birth defects in newly born babies with 22 completed weeks of gestation and diagnosed between birth and hospital discharge. In 1996, the Murmansk Regional Congenital Defects Registry (MRCDR) was established to collect information on all birth defects diagnosed in children from birth to 16 years of age. Mandatory reporting of 21 birth defect types to the National Birth Defects Surveillance Monitoring Programme has been in place since 1999. However, only 54 regions of 83 in Russia participated in this federal monitoring programme in 2011 [11]. There are several publications based on data from local Russian registries of birth defects. They focus on prevalence rates and time trends, but it is difficult to conduct a systematic scientific investigation (e.g. of case control design) of risk factors due to a lack of information in such registries [12,13]. In addition, there is no experience in Russia at the local or national level of linking such data with birth registries.

Recent studies demonstrate the effectiveness of using secondary databases to improve the quality of registry data [14]. One study in particular that combined hospital discharge data and cancer registry data reports that hospital discharge data added between 12% and 21% more cases [15]. In this context, we examined information from the MCBR and the MRCDR, with the overall objective of obtaining more reliable prevalence estimates of birth defects in Northwest Russia. To achieve this we (i) combined the results of these two registries; (ii) identified possible under-reporting; and (iii) compared the prevalences of birth defects in Murmansk County with those of Norway and Archangelsk County. The latter is located in the northern region of European Russia, and lies on the banks of the Northern Dvina River, near its exit into the White Sea.

Materials and methods

According to the 2010 Census, Murmansk County in Northwest Russia had 795,409 inhabitants, with a population density of 6.2 per square kilometre [16,17]. The City of Murmansk is a port and the administrative centre of Murmansk County and is located not far from Russia's borders with Norway and Finland. In 2010, the population of Murmansk City was 307,257 inhabitants [16]. Even though it has declined rapidly from 442,000 in 1989, it remains the largest city above the Arctic Circle. As already mentioned, the average annual number of deliveries in the region is around 9000. The study population consisted of all neonates registered in the MCBR between 1 January 2006 and 31 December 2009. Both singleton and multiple deliveries were included.

The Murmansk county birth registry

We obtained detailed information on mothers and their newly born babies from the MCBR, as well as for birth defects diagnosed (included all livebirths, stillbirths and terminations) during the perinatal period, namely from ≥22 weeks of gestation to the hospital discharge 7–12 days post-partum, as appropriate for the type of delivery (normal or caesarean section) or any complications. The data in the MCBR derived from the mothers' medical and obstetric records, the neonatal delivery records and from interviews with the mothers. The same physician or midwife who gathered the required information from medical and obstetric records conducted the interview and completed a two-page birth registry form comprised of 54 major fields of detailed medical and personal information about the mother and her baby/babies and father as well [10].

The Murmansk regional congenital defects registry

We extracted details about cases of major birth defects from the MRCDR, which included information on all birth defects diagnosed between birth (≥22 weeks of gestation and birth weight >500 grams) up to 2 years of age. The MCBR was a passive registry with its main sources of information being the maternity hospitals, children's polyclinics (primary care), children's hospitals and pathology departments and other medical institutions. On diagnosis of a birth defect, the physician completed a notice form and submitted it to the local Medical Analytic Information Centre for registration. The pertinent information was recorded in the MRCDR only after its confirmation by a medical institution. One exception were the notice forms issued by children's polyclinics, which were exempt from the confirmation requirement. The MRCDR includes information on birth date, weight, vital status, whether multiple delivery, birth defect diagnosis, gender, gestational age, place of delivery, mother's age, mother's parity and mother's place of residence at the time of delivery. Subsequently we selected all cases born within the study period 1 January 2006 to 31 December 2009. During the study period, 234 neonates registered in the MRCDR had major birth defects (see Figure 1). Of these, 17 cases were double entries, 6 triple and 10 were from outside of the

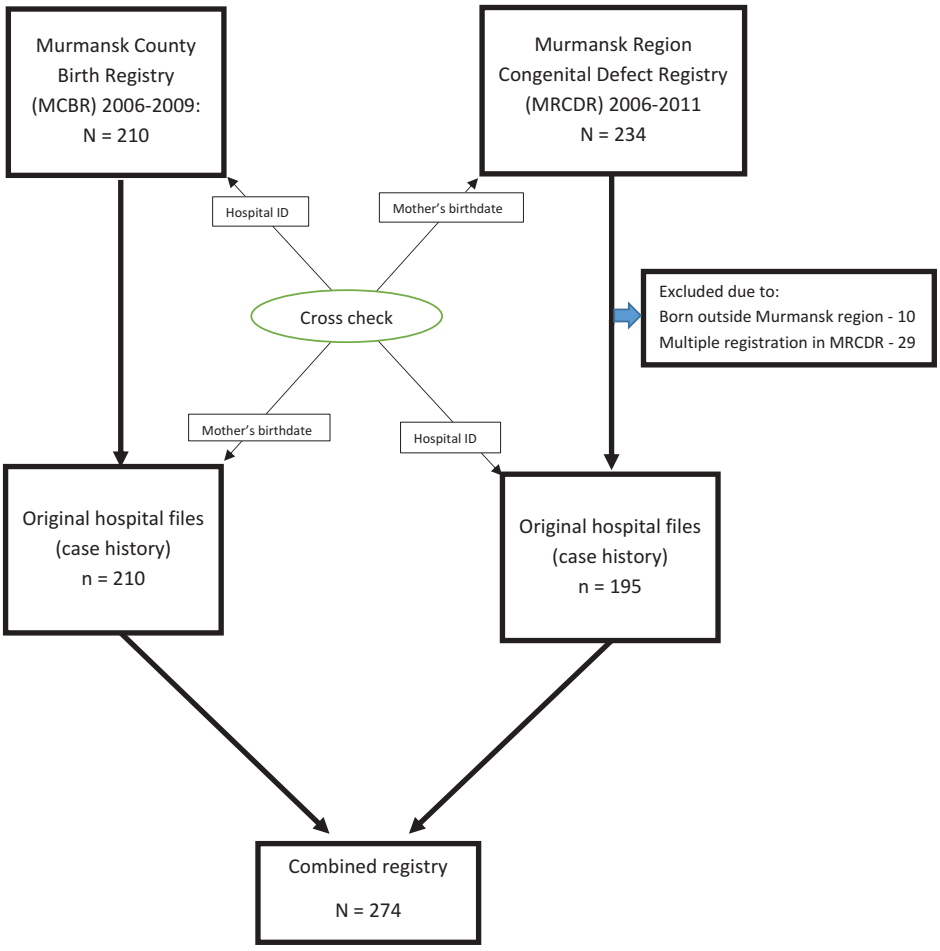

Figure 1. Number of major birth defect cases, exclusions and the manual linkage procedure of the Murmansk County Birth Registry (MCBR) and the Murmansk Regional Congenital Defects Registry (MRCDR). Note that, after the linkage procedure was completed, 64 new cases were added to the MCBR based on the MRCDR data and 79 to the latter from the former (includes cases up to age 2). Babies with multiple birth defects were excluded.

Murmansk region; these cases were excluded automatically, leaving 195 children with major birth defects.

Creation of a "combined registry"

For the linkage procedure, we selected all cases from the MRCDR with major birth defects for babies born between 1 January 2006 and 31 December 2009. The MRCDR electronic platforms changed during the study period from Medmonitor to Microsoft Excel, and subsequently to Microsoft Access; they were thereby fragmentised. We received only paper printouts from The Ministry of Health Care located in Murmansk City and, thus, the linking of the MCBR and the MRCDR was manual.

Based on place of delivery, date of birth of the mother and hospital ID file number in the MCBR, we requested all 210 original medical files from the maternity hospitals. Similarly, based on the same variables in the MRCDR, we requested 195 original medical files from maternity hospitals. After receiving these original files, we checked whether a case with a major birth defect had been in the MCBR, the MRCDR or in both. The 64 cases registered only in the MRCDR were combined with those in the MCBR using a manual (but direct) linkage algorithm, based on the original medical file and hospital ID number of the participant from the MCBR and the mother's birthdate. Thus, the combined registry included 274 cases of major birth defects with the corresponding International Classification of Diseases, Revision 10 (ICD-10) code and date of diagnosis.

Statistical analyses

We considered data on the 21 selected birth defects (referred to in this text as major birth defects), namely those included in the mandatory MRCDR annual report

to the health authorities in Moscow. The statistical package SPSS version 21.0 (IBM Corp., 2012) was used to analyse and create descriptive statistics. We calculated confidence intervals based on the Wilson procedure, without correction for continuity.

Prevalence rates were calculated separately for the MCBR, MRCDR and the combined registry. Furthermore, we compared rates of major birth defects with those reported for Arkhangelsk County and Norway.

Ethical considerations

The Regional Health Administration of Murmansk Oblast, as well as the Ethics Committee of the Association of Gynecologists & Obstetricians of Murmansk Oblast approved this study. The Regional Ethics Committee (REK) in Norway also granted ethical approval. After linkage, all data from the MCBR and the MRCDR were de-identified. Both registries (MCBR and MRCDR) were obligatory parts of the healthcare system in the Murmansk County during the study period. All study participants signed an agreement form kept in their hospital medical files about their willingness to share future observations and possible use of personal data for further research. Within the study period, no one declined to complete the written consent form.

Results

Of the 35,417 neonates (live and stillborn) registered in the MCBR during the study period, 210 had major birth defects (see Figure 1).

The characteristics of the study population summarised in Table 1 reflect information obtained from both the MCBR and MRCDR; the latter did not yield any additional descriptive information about the mothers and children other than the birth defect diagnoses themselves. Among the 35,417 deliveries in the MCBR, 297 were multiple deliveries (0.8%). On average, maternal age was lower than paternal age at the time of delivery (26.5 and 29.5 years, respectively). At delivery, 81.2% of mothers were between 21 and 35 years of age. The average gestational age was 39.04 weeks, 3340 g was the average birth weight and 4109 women (11.7%) had previously experienced one or more spontaneous abortions. Multivitamin and folic acid intakes during pregnancy, respectively, were 91.3% and 70.7%, compared with 13.3% and 8.5% before pregnancy (Table 1).

We found 210 cases of major birth defects in the MCBR, compared to 195 in the MRCDR (Table 2). Of the 210 MCBR cases, 79 were not included in the MRCDR; conversely, 64 of the 195 cases in the MRCDR were not in the MCBR. In the combined registry, there were 274 cases of major birth defects. The updating of the MCBR dataset increased the overall prevalence of major birth defects from 55 to 77 per 10,000, which corresponds to an increase of 40%. A detailed comparison of the rates per 10,000 newborns of major birth defects in the MCBR and MRCDR is provided in Table 3. Both registries demonstrated the identical prevalence for seven out of the 21 major birth defects, namely; anencephaly, encephalocele, micro-anophthalmos, hypoplastic left heart syndrome, oesophageal atresia, exstrophy of the bladder and gastroschisis. For five major birth defects, the prevalences were comparable, namely: micro-anotia, ano-rectal atresia, renal agenesis and dysgenesis, diaphragmatic hernia and Down syndrome; and those for the remaining nine were more dissimilar (Table 3).

To the extent possible, the prevalence of major birth defects in Murmansk County were also compared with those in Arkhangelsk County [18–21] and in Norway

Table 1. Characteristics of the study population.

Variables	n=35,417
Multiple deliveries (%)	297 (0.8)
Singleton deliveries	34,820
Babies born	35,417
Boys (%)	18,219 (51.9)
Girls (%)	16,868 (48.0)
Maternal age in years, mean (SD)	26.5 (5.3)
Maternal age distribution (%), n=35,084	
<20	13.1
21–35	81.2
>35	5.7
Body mass index (BMI), mean (SD), n=34,325	23.41 (4.2)
BMI distribution, (%)	
<18.5	5.7
18.5–25.0	64.9
>25.0	26.2
Parity, n=35,101	
0	19,962 (56.9)
1	12,425 (35.4)
≥2	2,714 (7.7)
Previous spontaneous abortions (%), n=35,043	
0	30,934 (88.3)
≥1	4,109 (11.7)
Education of mother in years (%), n=34,653	
≤11	13,046 (37.7)
>11	21,607 (62.3)
Paternal age, years, mean (SD)	29.5 (6.0)
Gestational age, GA, in weeks, mean (SD)	39.04 (2.3)
GA distribution, (%), n=33,694	
22–29	1.0
30–36	7.2
37–42	89.1
>42	2.7
Birth weight in g, mean (SD)	3,340 (553)
Multivitamins taken before pregnancy (%)	13.3
Multivitamins taken during pregnancy (%)	91.3
Folic acid intake before pregnancy (%)	8.5
Folic acid intake during pregnancy (%)	70.7
Smoking before pregnancy (%)	24.3
Smoking during pregnancy (%)	18.4
Alcohol abuse during pregnancy (%)	0.6
Drugs abuse during pregnancy (%)	0.5

SD, standard deviation.

Table 2. Registration of major birth defects in Murmansk County 2006–2009.[a]

Type of defect	Cases recorded by both registries (1)	Cases recorded by MCBR only (2)	Cases recorded by MRCDR only (3)	Agreement[b] (1)/[(1)+(2)+(3)]
Anencephaly; Q00	0	1	1	0%
Spina bifida; Q05	2	2	0	50%
Encephalocele; Q01	0	0	0	100%
Congenital hydrocephalus; Q03	10	2	7	53%
Anophthalmos, microphthalmos; Q11.0, Q11.2	1	0	0	100%
Anotia, microtia; Q16.0, Q17.2	3	0	1	75%
Transposition of great vessels; Q20.3	1	2	0	33%
Hypoplastic left heart syndrome; Q23.4	1	0	0	100%
Cleft palate; Q35	13	10	7	43%
Cleft lip with or without cleft palate; Q36.0, Q36.9, Q37	6	6	2	43%
Oesophageal atresia; Q39.0-Q39.4	4	2	2	50%
Ano-rectal atresia; Q42.0–Q42.3	4	1	0	80%
Renal agenesis or dysgenesis; Q60.1, Q60.4, Q60.6	3	2	1	50%
Hypospadias; Q54.0–Q54.3, Q54.8, Q54.9	41	38	12	45%
Epispadias; Q64.0	1	0	2	33%
Bladder exstrophy; Q64.1	1	0	0	100%
Limb reduction defects; Q71–Q73	11	3	20	32%
Diaphragmatic hernia; Q79.0	4	2	0	67%
Omphalocele; Q79.2	1	2	0	33%
Gastroschisis; Q79.3	5	0	0	100%
Down syndrome; Q90.0	19	6	9	56%
Total	131	79	64	47.8%

[a] Major birth defects are those included in the mandatory MRCDR annual report. [b] Agreement refers to the percentage of total cases that are common between the two registries. MCBR, Murmansk County Birth Registry; MRCDR, Murmansk Regional Congenital Defects Registry.

Table 3. Registration of major birth defects[a]; Murmansk County 2006–2009 (n=35,417).

	MCBR		MRCDR		New combined registry	
Type of birth defect; ICD-10 code	n	rate[b]	n	rate[b]	n	rate[b]
Anencephaly; Q00	1	0.3	1	0.3	2	0.6
Spina bifida; Q05	4	1.1	2	0.6	4	1.1
Encephalocele; Q01	0	0	0	0	0	0
Congenital hydrocephalus; Q03	12	3.4	17	4.8	19	5.4
Anophthalmos, microphthalmos; Q11.0, Q11.2	1	0.3	1	0.3	1	0.3
Anotia, microtia; Q16.0, Q17.2	3	0.8	4	1.1	4	1.1
Transposition of great vessels; Q20.3	3	0.8	1	0.3	3	0.8
Hypoplastic left heart syndrome; Q23.4	1	0.3	1	0.3	1	0.3
Cleft palate; Q35	23	6.5	20	5.6	30	8.5
Cleft lip with or without cleft palate; Q36.0, Q36.9, Q37	12	3.4	8	2.3	14	4.0
Oesophageal atresia; Q39.0–Q39.4	6	1.7	6	1.7	8	2.3
Ano-rectal atresia; Q42.0–Q42.3	5	1.4	4	1.1	5	1.4
Renal agenesis or dysgenesis; Q60.1, Q60.4, Q60.6	5	1.4	4	1.1	6	1.7
Hypospadias; Q54.0–Q54.3, Q54.8, Q54.9	79	22.3	53	15	91	25.7
Epispadias; Q64.0	1	0.3	3	0.8	3	0.8
Bladder exstrophy; Q64.1	1	0.3	1	0.3	1	0.3
Limb reduction defects; Q71–Q73	14	4	31	8.8	34	9.6
Diaphragmatic hernia; Q79.0	6	1.7	4	1.1	6	1.7
Omphalocele; Q79.2	3	0.8	1	0.3	3	0.8
Gastroschisis; Q79.3	5	1.4	5	1.4	5	1.4
Down syndrome; Q90.0	25	7	28	7.9	34	9.6
Total	210	60	195	55	274	77

[a] Major birth defects are those included in the mandatory MRCDR annual report. [b] Rate per 10,000 newborns. MCBR, Murmansk County Birth Registry; MRCDR, Murmansk Regional Congenital Defects Registry

[22–25] for the years 2006–2009 (in rates per 10,000; Table 4). We decided to use the Norwegian data representing the whole country instead of different regions because of the uniform distribution of birth defects across Norway. We removed abortions data before 22 weeks of gestation from the Norwegian dataset to reflect the absence of such data in the Russian dataset. Compared with Murmansk County, Arkhangelsk County demonstrated a higher prevalence of birth defects of the nervous system, namely: anencephaly, spina bifida and encephalocele, whereas those from Norway were more comparable. The prevalence of oesophageal atresia and ano-rectal atresia were almost identical in the three areas. In Murmansk County, the prevalence of limb reduction defects and hypospadias was higher than in Arkhangelsk County and Norway. Among the

Table 4. National and international comparisons of birth defects for 2006–2009, rate per 10,000 newborns (includes livebirths, stillbirths and terminations at 22 weeks and beyond).

	Arkhangelsk County[a] (n=58,141)		Murmansk County "Combined registry" (n=35,417)		Norway[b] (n=243,231)	
Type of birth defect	n	rate (95% CI)	n	rate (95% CI)	n	rate (95% CI)
Anencephaly; Q00	40	6.9 (5–9)	2	0.6 (0–1)	9	0.4 (0–1)
Spina bifida; Q05	55	9.5 (7–12)	4	1.1 (0–2)	46	1.9 (1–2)
Encephalocele; Q01	11	1.9 (1–3)	0	0	10	0.4 (0–1)
Congenital hydrocephalus; Q03	27	4.6 (3–6)	19	5.4 (3–8)	73	3.0 (2–4)
Anophthalmos, microphthalmos; Q11.0, Q11.2	2	0.3 (0–1)	1	0.3 (0–1)	—	—
Anotia, microtia; Q16.0, Q17.2	3	0.5 (0–2)	4	1.1 (0–2)	10	0.4 (0–1)
Transposition of great vessels; Q20.3	16	2.8 (2–5)	3	0.8 (0–2)	102	4.2 (3–5)
Hypoplastic left heart syndrome; Q23.4	18	3.1 (2–5)	1	0.3 (0–1)	46	1.9 (1–2)
Cleft palate; Q35	14	2.4 (1–4)	30	8.5 (5–12)	164	6.7 (6–8)
Cleft lip with or without cleft palate; Q36.0, Q36.9, Q37	30	5.2 (3–7)	14	4.0 (2–6)	291	12.0 (11–13)
Oesophageal atresia; Q39.0–Q39.4	14	2.4 (1–4)	8	2.3 (1–4)	58	2.4 (2–3)
Ano-rectal atresia; Q42.0–Q42.3	9	1.5 (1–3)	5	1.4 (0–3)	60	2.5 (2–3)
Renal agenesis or dysgenesis; Q60.1, Q60.4, Q60.6	0	0	6	1.7 (0–3)	12	0.5 (0–1)
Hypospadias; Q54.0–Q54.3, Q54.8, Q54.9	24	4.1 (2–6)	91	25.7 (2–31)	317	13.0 (12–14)
Epispadias; Q64.0	0	0	3	0.8 (0–2)	—	—
Bladder exstrophy; Q64.1	2	0.3 (0–1)	1	0.3 (0–1)	—	—
Limb reduction defects; Q71–Q73	10	1.7 (1–3)	34	9.6 (6–13)	76	3.1 (2–4)
Diaphragmatic hernia; Q79.0	7	1.2 (0–2)	6	1.7 (0–3)	50	2.1 (1–3)
Omphalocele; Q79.2	23	4.0 (2–6)	3	0.8 (0–2)	30	1.2 (1–2)
Gastroschisis; Q79.3	17	2.9 (2–4)	5	1.4 (0–3)	79	3.2 (3–4)
Down syndrome; Q90.0	68	11.7 (9–14)	34	9.6 (6–13)	309	12.7 (11–14)
Total	390	67 (60–74)	274	77 (68–86)	1742	72 (68–75)

[a] Data from Arkhangelsk Regional Congenital Defects Registry. [b] Data from Norwegian Birth Registry. CI, confidence interval.

three locations, Murmansk County had the highest prevalence of cleft palate and the lowest prevalence of cleft palate and lip.

Discussion

To the authors' knowledge, this is the first time that a birth registry and a birth defect registry have been combined in Russia to determine the prevalence of birth defects. We found that 79 of the 210 cases of major birth defects (i.e. for the 21 birth defects included in the mandatory MRCDR annual report) registered in the MCBR were not included in the MRCDR. We, therefore, demonstrated a 40% increase in the overall prevalence of major birth defects after combining the two registries.

Before 2006, there were no adequate mechanisms to estimate the completeness of the MRCDR and, consequently, there are no published reports regarding its quality. When comparing the MCBR and the MRCDR, we found that the former had better case ascertainment. The most likely explanation for this is that the registration routines were better in the MCBR, such as regular quality controls, having only one person responsible for registration in each maternity hospital, strict delivery of birth registry forms to the central office using courier services and in general having fewer individuals involved in the data chain. In contrast, the MRCDR draws upon all health institutions and, thereby, involves more people and fewer quality control routines. Furthermore, it covers the neonatal period and includes diagnoses for the child to 16 years of age.

Our study is, therefore, an example of how useful registry linkage can be. It revealed significant under-reporting of some major birth defects in Murmansk County, which led to under-reporting of the overall rate of birth defects in this region. Our findings provide decision-makers with insight about a need for suitable and routine quality control measures to guarantee the quality of public health statistics.

Certain population characteristics may influence the prevalence of birth defects and, therefore, it is important to compare them for the same period to those of neighbouring jurisdictions such as Arkhangelsk County and Norway. The average age of mothers (at the time of delivery) in Murmansk County was 26.5 years, which is lower than that in Norway, where it was 29.6 years during study period [10]. The proportion of mothers over 35 years of age at the time of delivery in Murmansk County was 5.7%, while it was 16.7% in Norway [10]. Advanced maternal age is significantly associated with an increased risk for a variety of birth defects [26], including those of the heart and Down syndrome [27]. In our study, the prevalence of these two defects was lower in Murmansk County than in Norway, which likely reflects the lower average maternal age observed in Murmansk County.

Folic acid supplementation reduces the risks of spina bifida and some ano-rectal atresia, as well as of

selected orofacial clefts in high doses [28–31]. The use of multivitamins and folic acid during pregnancy in Murmansk County are attributable to existing programmes of the Ministry of Health Care in the region. Furthermore, these supplements are available free of charge for pregnant women. However, the pertinent studies also show that folic acid intake is most effective in preventing birth defects when taken prior to conception. In our study, only 8.5% of mothers in Murmansk County took folic acid before pregnancy, while in Norway this percentage was 27.4%. Even with higher folic acid intake by Norwegian mothers, the prevalence of neural tube defects in Murmansk County was slightly lower, although this was not statistically significant. A higher prevalence of birth defects of the nervous system (including anencephaly, spina bifida, encephalocele and hydrocephalus) occurred in Arkhangelsk County relative to Murmansk County and Norway (for which they were comparable [32]). Poverty and food insecurity during the study period were cited as potential contributing factors (including low folic acid intake before and during pregnancy). Since Arkhangelsk County is larger and more rural compared to Murmansk County, a lower availability of regular ultrasound screening might have led to later diagnoses of birth defects (i.e. after 22 weeks of gestation).

More than 90% of pregnant women in Murmansk County undergo ultrasound examinations at least three times during their pregnancy, with the first one usually at about 12 (12.4 weeks on average) weeks of gestation, as required by Federal Order № 572 from the Ministry of Health Care of the Russian Federation [33]. According to unpublished data from the Ministry of Health Care of Murmansk Oblast, thorough ultrasound observations help detect around 100 each of major and minor birth defects every year and about 50% of these women decide to continue the pregnancy, despite the presence of birth defects.

Maternal smoking is also associated with increased risk of birth defects, specifically missing or malformed limbs and facial disorders [34]. In Norway, smoking during the first trimester was associated with an increased risk of cleft lip, with or without cleft palate [35]. We observed that the prevalence of cleft lip was lower in Murmansk County compared to both Arkhangelsk County and Norway. This observation appears to be inconsistent with the high percentage of women in Murmansk County who smoked both before and during pregnancy (respectively, 24.3% and 18.4%). While the prevalence of cleft palate was the highest in Murmansk County, cleft lip with or without cleft palate was the lowest. Ethnic and racial differences, misclassification, wrong coding and/or possible under-reporting of cleft lip in Murmansk Oblast may well have contributed to this discrepancy compared to Norway.

Generally speaking and based on the combined Murmansk County registries, the overall prevalence of major birth defects of 77 per 10,000 compared well with the 67 in Arkhangelsk County and 72 in Norway. Without linking the two registries, Murmansk County would have exhibited the lowest prevalence (55 per 10,000).

For oesophageal atresia and ano-rectal atresia, the prevalence ranged from 1.5–2.5 per 10,000 in all three locations and was, thus, too rare to allow adequate comparisons. These two defects are easily recognisable at birth and require urgent surgical treatment.

In Murmansk County, the prevalence of limb reduction defects was unexpectedly high (9.9), while in Arkhangelsk County it was 1.7 and in Norway 3.1 per 10,000. Detailed analysis revealed that 10 such cases were recorded with the same ICD-10 code and were all diagnosed in the military town of Gadzhiyevo, which has a population of about 11,000 and around 250 annual deliveries [16]. All 10 cases recorded in the MRCDR database were reported for the same children's polyclinic, where a single doctor was responsible for regular infant check-ups. The description of all 10 of these cases in the MRCDR database was "developmental hypoplasia of the hip", but the code used was Q71. Incorrect coding here is partly responsible for the overall high prevalence of limb reduction defects in the County. Clearly, this needs further confirmation and follow-up. The prevalence of hypospadias was high in Murmansk County (25.4) and Norway (13.0), but low in Arkhangelsk County (4.1). Even though 70% of hypospadias cases in Murmansk County were identified during the perinatal period, the remainder occurred between the neonatal and infant periods. Our detailed analysis revealed an even distribution throughout Murmansk County in relation to population size. This suggests that no systematic error was present, but this requires closer examination. Another possibility is that mild forms of hypospadias in Arkhangelsk County were not registered.

Strengths of the study

We describe a successful linkage of records from a birth defects registry with those of a medical birth registry, based on original hospital data, hospital ID number and the last name of the mother. The established satisfactory quality of the MCBR constitutes a strength [10]. Although federal law dictates that neonatal data be collected from week 22 of

gestation on, the MRCDR does not contain data on infants below 970 grams (which equates to approximately 27–28 weeks). This is a remnant of the earlier Russian system before 2012 that considered that termination of a pregnancy at 22–27 weeks was a spontaneous/induced abortion, not a pre-term delivery. Potential under-reporting of birth defects might have occurred because women at 22–27 weeks of pregnancy gave birth in a hospital gynaecology department. Fortunately, the MCBR covered this period.

Limitations of the study

The dependence on the experience of the medical doctors to detect and correctly diagnose birth defects, especially in remote areas, may cause systematic errors such as under-reporting, over-reporting and misclassification. Another limitation is that elective abortions due to birth defects (<22 weeks of gestation) were not included in the Murmansk County and Arkhangelsk County registries. This hindered our attempts to acquire more accurate prevalence estimates. Moreover, differences in pre-natal diagnostics algorithms of birth defects and early terminations may also have contributed to rate differences in the regions compared. Information from the Murmansk Genetics Centre (MGC) could potentially include pregnancy terminations due to birth defects diagnosed pre-natally by the MGC. Although these data were available, they were not included in the MCBR. Another limitation is that some selected defects were so rare (as might be expected) that comparisons of rates lacked statistical power.

Conclusions

A number of studies have indicated substantial under-reporting of birth defects based on statutory notifications of births compared with hospital records and this was the case in Murmansk County. A surveillance system solely based on notifications of births is not advocated [36]. Under-reporting of prevalence like that found in our study hides the extent to which birth defects affect a population. When such information is part of the planning or evaluation of prevention strategies it can lead to erroneous conclusions about the effectiveness of a programme and can influence health policies and the allocation of resources [37]. Our study demonstrates that birth registry data can serve to improve existing surveillance data, increases case ascertainment and reduces the effects of possible under-reporting by physicians. This is an effective approach to enhance birth defects surveillance.

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Authors' contributions

AAK designed the study, collected the data, performed statistical analysis and wrote the manuscript. EEA participated in the design and coordination of the study, critically revised the manuscript and, together with JOO, EN and AAK, pioneered the setting up of the MCBR. TB, JOO, AK and EN helped in the drafting/editing of the manuscript. All authors read and approved the final manuscript.

Availability of supporting data

The MCBR and MRCDR databases have restricted access due to privacy issues and patient confidentiality. Permission to use data requires the submission of an application. For access to the MCBR data, permission of both the Ministry of Health Care of the Murmansk Region and the UiT Arctic University of Norway is required. For the MRCDR data, access requires permission of the Ministry of Health Care of the Murmansk Region.

Consent for publication

Not applicable.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Paper II

Risk Factors for Hypospadias in Northwest Russia: a Murmansk County Birth Registry Study

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Risk Factors for Hypospadias in Northwest Russia: a Murmansk County Birth Registry Study

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Abstract

Background

Hypospadias is the most common congenital anomaly of the penis, but its causes are mainly unknown. Of the risk factors identified, the most plausible are hormonal and genetic. The aim of this study was to identify risk factors for hypospadias in Northwest Russia based on registry data.

Methods

The study population included male infants registered in the Murmansk County Birth Registry between 1 January 2006 and 31 December 2011 (n = 25 475). These infants were followed-up for 2 years using the Murmansk Regional Congenital Defects Registry to identify cases of hypospadias not diagnosed at birth. We used logistic regression analysis to examine the contributions of hypospadias risk factors.

Results

Out of 25 475 male infants born during the study period, 148 had hypospadias. The overall prevalence rate was 54.2 (95% CI 53.6-54.8) per 10 000 male infants. Those born to mothers with cervical erosion (OR = 2.05; 95% CI 1.25-3.38), infant birthweight < 2500 g (OR = 2.02; 95% CI 1.15-3.54) and preeclampsia (OR = 1.66; 95% CI 1.04 - 2.68) exhibited increased risk for hypospadias. Maternal age, smoking during pregnancy, folic acid intake during pregnancy or hepatitis B surface antigen positivity did not associate with increased risk of hypospadias.

Conclusions

Combining data from a birth registry with those from a congenital defects registry provided optimal information about the prevalence of hypospadias and its association with cervical erosion, low infant birthweight and preeclampsia. These factors have in common changes in

hormone levels during pregnancy, which in turn may have contributed to hypospadias development.

Keywords: birth registry, Russia, hypospadias, risk factors, pregnancy

Introduction

Hypospadias is a male-specific congenital birth defect that leads to displacement of the external urethral orifice and often associates with an incomplete development of the foreskin [1]. It usually develops 8-14 weeks after conception and is one of the most common structural malformations in humans. It occurs in 18.6 per 10,000 newborn[2]. A single cause of hypospadias is still not identified [3]. Cases of this defect are usually relatively mild, but when severe may constitute a symptom of a disorder of sexual differentiation [4]. The prevalence of hypospadias increased in many countries during the 1960s to early 1990s [5]. This trend could be due to an actual increase of hypospadias' events or improved diagnostic practices [5] Recent reports show that the prevalence in most countries has not continued to rise since the mid-1980s [6] and has been stable from 2001 to 2010 in 23 EUROCAT (European network of population-based registries for epidemiologic surveillance of congenital anomalies) registries [2].

Over the past 30 years male reproductive health has changed; specifically, sperm counts have decreased and the number of cases of undescended testes and testicular cancer have increased [7]. This has prompted scientists to investigate the possible role of environmental contaminants, especially those with endocrine-disruption capabilities [8, 9]. The cause of most hypospadias cases remains unknown, including the potential impact of genetic and environmental factors. Nevertheless, several plausible associations have been suggested

[10]. Among these are advanced maternal age, increased body mass index (BMI) of the mother, preexisting diabetes, cervical erosion, preeclampsia during pregnancy, smoking, phytoestrogens intake during pregnancy, exposure to different chemicals, and some infectious diseases such as hepatitis [11-16].

A retrospective study published in 2006 was the first to investigate possible risk factors for hypospadias in the Murmansk Region. It reported no negative effect of maternal exposure to water-soluble nickel compounds on the risk of genital malformations in the offspring of pregnant women in the town of Monchegorsk [17]. This cohort included women who worked in the local nickel refinery complex. The prevalence rate of hypospadias in Murmansk County has remained unusually high at 25.7 per 10,000 newborns during 2006-2011, compared with those for Arkhangelsk County (4.1 per 10,000 newborns) and Norway (13.0 per 10,000 newborns) during the same period [18]. We here combined information from the Murmansk County Birth Registry (MCBR) and the Murmansk Regional Congenital Defects Registry (MRCDR) to explore potential risk factors that may help explain the high occurrence of hypospadias in Northwest Russia.

Materials and methods

Study population

We included all male infants registered in the MCBR and MRCDR between 1 January 2006 and 31 December 2011. A detailed description of the MCBR has been published earlier and includes details about its implementation and quality control exercises [19]. The MRCDR has been in effect since January 1996 and includes data from week 28 of pregnancy to age 16. A diagnosis of hypospadias (International Classification of Diseases Revision 10 code Q54)

depends on the location of the urinary opening (meatus). We combined information from the MBCR and MRCDR and removed duplicate records to obtain the final study sample. The manual merging of the data from the two registries was by the mother's hospital ID number and birthdate, and the birthdate of the baby. Detailed descriptions of MCBR and MRCDR as well as the linkage procedure have been published recently [18]. We included only singleton deliveries. After registry linkage, entries in the MCBR with missing information or erroneous coding (N = 1874) for selected variables were excluded from the study, which resulted in a final sample of 25 475 male infants (Figure 1).

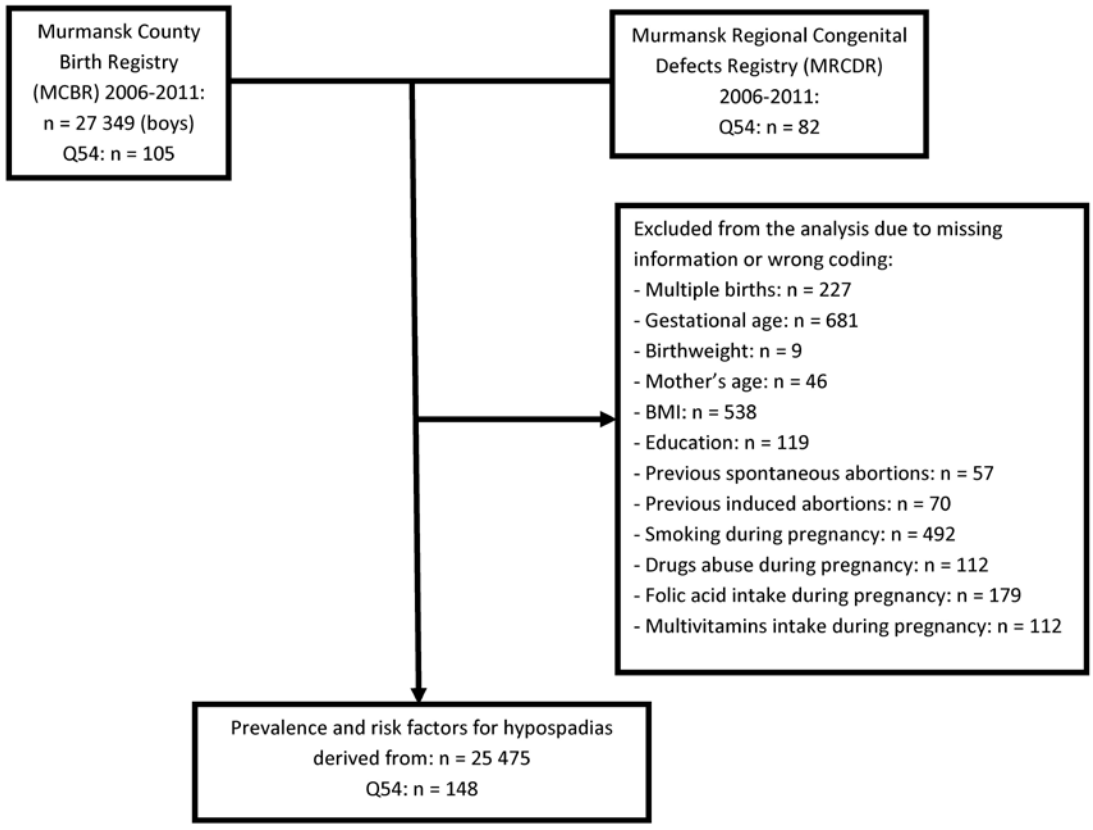

Figure1. Number of births and exclusions for the combined Murmansk County Birth Registry and the Murmansk Regional Congenital Defects Registry (2006-2011). The individual numbers add up to more than the total number excluded due to missing information on two or more variables.

Statistical analyses

We used Chi-square statistics to compare rates and the independent sample t-test for differences in mean values. Statistical significance was set at $p \leq 0.05$. Logistic regression analysis was applied to identify risk factors associated with hypospadias, including neonatal birthweight and gestational age and the following maternal issues: residence, age at delivery, education, body-mass index at the first antenatal visit, parity, number of previous spontaneous and induced abortions, intake during pregnancy of progesterone-containing drugs, folic acid, multivitamins (not containing folic acid), hepatitis-B surface antigen (HBsAg) positivity, preeclampsia, cervical erosion (ICD-10 code N86) and alcohol/drug abuse.

Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CI) were calculated. Variables that reached significance in the univariate analyses (namely, infant birthweight, preeclampsia, and cervical erosion) were included in the final multivariable logistic regression model. Cases of mild, moderate and severe preeclampsia constituted one group. In the final model, we included previously reported risk and protective factors for hypospadias (namely, maternal age at delivery, smoking during pregnancy, folic acid intake during pregnancy, and HBsAg positivity [20], and adjusted for gestational age. Statistical package IBM SPSS v.24.0 (IBM Corp., Armonk, NY, USA, 2016) was used for data analyses.

Ethical considerations

Ethical approval was obtained from The Regional Health Administration of Murmansk County, the Ethics Committee of Gynecology-Obstetrician Association Group (reference number:

2013/14), Murmansk County, Russia, and the Norwegian Regional Committee for Medical and Health Research Ethics (ethical code reference number: 2013/2146). All data from the two registries were anonymized.

Results

One hundred and five cases of hypospadias were registered in the MCBR and 82 in the MRCDR. After combining data from the two registries and removing duplicates, there were 148 cases of hypospadias, corresponding to a total prevalence of 54.2 per 10,000 male births. Of the 148 only 110 cases were diagnosed during the perinatal period and the remainder within 3 months after birth. In terms of the ICD-10 classification of hypospadias and severity proportion, 84 cases (56.8%) belonged to the distal type of hypospadias (considered a mild form), 29 cases (19.6%) were of the midshaft type (moderate form), with 7 (4.8%) in the proximal group (a severe form) and 28 (18.8%) unspecified cases. The mean birthweight was significantly lower ($p < 0.01$) in the group with hypospadias, while maternal age, the gestational age distribution, parity, previous induced and spontaneous abortions were comparable in both groups (Table 1). Multivitamin and folic acid intake were not significantly different in the two groups, while preeclampsia and cervical erosion were higher among the cases (respectively, $p = 0.03$ and < 0.01). Additional details about the mothers and infants are provided in Table 1.

Table 1. Characteristics of cases and non-cases of hypospadias (Q54). Data shown constitute a combined set for the Murmansk County Birth Registry and the Murmansk Regional Congenital Defects Registry during the period 2006-2011.

	Cases N = 148[a]		**Non-cases** N = 25 327[a]		
Variables	**Value** or N[b]	**SD** *or* %[c]	**Value** or N[b]	**SD** *or* %[c]	p-value[d]
Infant Characteristics					
Birth weight (g), mean ± SD	**3291.0**	**540.7**	**3421.0**	**580.1**	<0.01
< 2500	14	9.5	1160	4.6	
2500-3999	121	81.7	20 899	82.5	
≥ 4000	13	8.8	3268	12.9	
Maternal Characteristics					
Age at delivery (years), mean ± SD	**26.94**	**4.99**	**26.83**	**5.27**	0.79
< 18	2	1.4	343	1.4	
18-35	137	92.5	23 395	92.3	
> 35	9	6.1	1589	6.3	
Gestational age (weeks), mean ± SD	**39.5**	**1.9**	**39.4**	**2.2**	0.59
BMI (kg/cm^2), mean ± SD	**23.62**	**3.60**	**23.49**	**4.27**	0.72
< 18.5	11	7.4	1573	6.2	
18.5-24.9	92	62.2	16 567	65.4	
> 25	45	30.4	7187	28.4	
Parity					
0	93	62.8	14 040	55.4	0.16
1	48	32.4	9438	37.3	
≥2	7	4.7	1849	7.3	
Previous induced abortions					
0	93	62.8	14 609	57.7	0.20
≥1	55	37.2	10 718	42.3	
Previous spontaneous abortions					0.53
0	133	89.9	22 325	88.2	
≥1	15	10.1	2992	11.8	
Education, years					0.53
≤11	55	37.2	8781	34.7	
>11	93	62.8	16 546	65.3	
Smoking during pregnancy	36	24.3	6264	24.7	0.91
Alcohol abuse during pregnancy	1	0.7	75	0.3	0.36
Drug abuse during pregnancy	0	0	85	0.3	0.61
Folic acid intake during pregnancy	108	73.0	18 832	74.4	0.70

Multivitamin intake during pregnancy	136	91.9	23 479	92.7	0.71
HBsAg positive	3	2.8	471	1.9	0.76
Preeclampsia	20	12.7	2171	8.6	0.03
Cervical erosion	18	9.5	1619	6.4	<0.01

[a] Number of cases and non-cases are less than the entire study population due to missing values for some independent variables.

[b] Means or numbers

[c] Standard deviation (SD**)** or percentages

[d] t-Test, Chi-square test or Fisher's exact test

The crude and the adjusted ORs for the variables included in the logistic regression analysis did not differ substantially between cases and non-cases. Low infant birthweight and cervical erosion were associated with a two-fold elevation of hypospadias risk in both the unadjusted and adjusted models (Table 2); and for preeclampsia, the increase was somewhat lower (OR values of 1.67 and 1.66, respectively). Smoking during pregnancy, folic acid intake during pregnancy, progesterone-containing drugs intake during pregnancy (data not shown) and HBsAg positivity did not influence the risk of hypospadias.

Table 2. Crude and adjusted odds ratio (OR) with 95 % confidence interval (CI) of hypospadias[a]. Data shown constitute a combined set for the Murmansk County Birth Registry and the Murmansk Regional Congenital Defects Registry during the period 2006-2011.

	Crude		Adjusted[b]	
Variables	OR	95 % CI	OR	95 % CI
Birthweight (g)				
< 2500	2.09	1.20-3.64	2.02	1.15-3.54
2500-3999	1.00	Reference	1.00	Reference
> 4000	0.69	0.38-1.22	0.68	0.39-1.21
Age at delivery (years)				
< 18	0.99	0.25-4.03	0.97	0.24-3.96
18-35	1.00	Reference	1.00	Reference
> 35	0.97	0.49-1.90	0.93	0.47-1.84
Smoking during pregnancy	0.98	0.67-1.42	0.96	0.65-1.40
Folic acid intake during pregnancy	0.93	0.65-1.34	0.88	0.61-1.27

HBsAg positive	1.09	0.35-3.44	1.05	0.33-3.33
Preeclampsia	1.67	1.04-2.68	1.66	1.04-2.68
Cervical erosion	2.03	1.24-3.33	2.05	1.25-3.38

[a] Number of cases is 148 with 25 327 non-cases.

[b] Each variable is adjusted for the others listed.

Discussion

We found that low infant birthweight, preeclampsia, and cervical erosion were risk factors for hypospadias in Murmansk County which suggest a linkage to changes in maternal hormone levels during early pregnancy. In agreement with our findings, previous reports suggest that alcohol consumption during pregnancy is not associated with the development of hypospadias [11, 21]. Similarly, the lack of an observed association between hypospadias and smoking during pregnancy has been reported [21-23]. Although high maternal age at delivery is suggested as a risk factor for hypospadias [24], most studies do not report such an association [25-28]. Our findings concur with the latter, and further illustrate that young maternal age at delivery does not influence the risk of having a son with hypospadias. Therapeutic drugs such as corticosteroid hormones, antibiotics, or antifungal medications, are reported not to associate with hypospadias [29, 30], while the reported influence of progesterone-containing drugs varies [31]. Although oral contraceptives may cause high estrogen levels, limited association has been found between hypospadias and oral contraceptive use during pregnancy [32]. However, an experimental study in mice shows that high doses of synthetic estrogen during pregnancy induces hypospadias in 50% of male fetuses [33]. In humans, neither folate [34] nor iron supplementation [35]influence hypospadias risk [35, 36]. Although we did not have information on the use of all drugs and supplements taken during pregnancy, our logistic analyses indicate that folic acid intake and

progesterone-containing drugs (data not shown) were not associated with the risk of hypospadias.

Maternal hypertension during pregnancy and preeclampsia may associate with placental dysfunction, possibly by compromising utero-placental perfusion [36]. Weak spiral artery invasion of the placenta disturbs utero-placental perfusion during early gestation in women with gestational hypertension or preeclampsia [36]. Placental insufficiency may also affect fetal somatic and urethral development, and an association between hypospadias and low placental weight has been observed [37]. Since human chorionic gonadotropin (hCG) is a hormone produced by the placenta following implantation and placental hCG stimulates fetal testicular steroidogenesis, placental insufficiency may result in inadequate fetal hCG provision that leads to intrauterine growth retardation [38]. This may explain the association between hypospadias and low infant birthweight we and other researchers [39, 40] have observed.

Our observation that cervical erosion associates with higher risk of hypospadias is consistent with other reports [41-43]. Cervical erosion is cervical ectopy because the cells at the os of the cervix change from squamous to columnar type – this pathological condition gives it a red and eroded appearance. There does not seem to be a direct link between cervical erosion and urethra development, but there may be an indirect effect through high estrogen levels in the blood, which is common in women during pregnancy. Perhaps women with a genetic predilection of changes in estrogen-receptor sensitivity during pregnancy are predisposed to more severe effects of high estrogen levels.

Strengths and limitations of the study

The high quality of data in the MCBR is a strength of this study. By combining MBCR and MRCDR, we can follow children up to 16 years of age, which helps identify more cases of hypospadias and other congenital malformations not diagnosed at birth.

This study may be limited through the inexperience of medical doctors to detect and correctly diagnose hypospadias, especially in remote areas of Murmansk County. This may contribute to systematic errors such as under reporting, over reporting, and misclassification of cases. A second limitation is that abortions before 22 weeks of gestation are not included in registries in Russia, and this hindered more accurate prevalence estimates. Our data on smoking, alcohol abuse, and drug abuse are in part self-reported, which may have led to underreporting. Another potential limitation is that all three degrees of preeclampsia constituted a single variable. Finally, not all possible maternal, perinatal, and environmental risk factors were included in the analysis due to the relatively small sample size.

Conclusion

Our Russian registry-based data showed that hypospadias was associated with cervical erosion, low infant birthweight and preeclampsia in Murmansk County, Northwest Russia. Cervical erosion (through changes in estrogen hormone levels) may have contributed to hormone imbalance, which is one of the risk factors of hypospadias. The consistent association between hypospadias and low infant birthweight and preeclampsia suggests placental insufficiency.

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Availability of supporting data

The MCBR and MRCDR databases have restricted access due to privacy issues and patient confidentiality. Permission to use data requires the submission of applications as follows. For access to the MCBR data, permission of both the Ministry of Health Care of the Murmansk Region and the UiT the Arctic University of Norway is required. For the MRCDR data, access requires permission of the Ministry of Health Care of the Murmansk Region.

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Paper III

Risk Factors for Ventricular Septal Defects in Murmansk County, Russia: A Registry-Based Study

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Risk Factors for Ventricular Septal Defects in Murmansk County, Russia: A Registry-Based Study

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Abstract: Cardiovascular malformations are one of the most common birth defects among newborns and constitute a leading cause of perinatal and infant mortality. Although some risk factors are recognized, the causes of cardiovascular malformations (CVMs) remain largely unknown. In this study, we aim to identify risk factors for ventricular septal defects (VSDs) in Northwest Russia. The study population included singleton births registered in the Murmansk County Birth Registry (MCBR) between 1 January 2006 and 31 December 2011. Infants with a diagnosis of VSD in the MCBR and/or in the Murmansk Regional Congenital Defects Registry (up to two years post-delivery) constituted the study sample. Among the 52,253 infants born during the study period there were 744 cases of septal heart defects (SHDs), which corresponds to a prevalence of 14.2 [95% confidence interval (CI) of 13.2–15.3] per 1000 infants. Logistic regression analyses were carried out to identify VSD risk factors. Increased risk of VSDs was observed among infants born to mothers who abused alcohol [OR = 4.83; 95% CI 1.88–12.41], or smoked during pregnancy [OR = 1.35; 95% CI 1.02–1.80]. Maternal diabetes mellitus was also a significant risk factor [OR = 8.72; 95% CI 3.16–24.07], while maternal age, body mass index, folic acid and multivitamin intake were not associated with increased risk. Overall risks of VSDs for male babies were lower [OR = 0.67; 95% CI 0.52–0.88].

Keywords: registry; risk factors; ventricular septal defects

1. Introduction

Cardiovascular malformations (CVMs) constitute one of the most common birth defects in newborns [1], and are a leading cause of perinatal and infant mortality [2]. The prevalence of CVMs ranges from three to 12 per 1000 infants and depends on case ascertainment, inclusion criteria, and duration of post birth follow-up [3–5]. The etiology of most CVMs is unknown, but possibly up to 30% are attributable to modifiable factors [6]. Genetic causes are estimated to account for <20% of CVMs [7]. Approximately 5–10% of cases are associated with a chromosomal abnormality, 3–5% are related to defects in single genes, and around 2% to environmental factors. Causes of CVMs can also be multifactorial such as an interaction between several genetic and other factors [8]. At present,

there is little information on potentially modifiable risk factors, which has made it difficult to develop population-based CVM prevention strategies [9].

The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) classifies a range of CVMs (ICD-10 codes Q20–Q28). ICD-10 code Q21 represents septal heart defects and includes, among others: atrial (ASD), ventricular, atrioventricular septal (AVSD), tetralogy of Fallot, and aorto-pulmonary defects—conditions that range from relatively mild to fatal. Ventricular septal defects (VSDs) are the most common form of cardiovascular malformations. A VSD can occur as an isolated anomaly or in conjunction with other cardiac malformations and/or genetic conditions [10]. Depending on their location in the interventricular septum, septal defects are described as perimembranous, muscular, subarterial, and inflow [11]. Echocardiography is the main imaging modality for the diagnosis and follow-up of VSDs [12]. Children with a VSD are at risk of endocarditis, pulmonary infection, ventricular arrhythmias, and death from heart failure or pulmonary hypertension [13–15].

Risk factors for VSDs and ASDs may differ. For example, the effects of maternal alcohol abuse, being overweight and obese are related to VSDs but not ASDs. Conversely, the influence of maternal body mass index (BMI) is evident for ASDs only [16]. High maternal age ($\geq$35) is one of the maternal characteristics known to associate with the risk of septal heart defects (SHDs), and appears to affect both VSDs and ASDs. Smoking, drug abuse, diabetes mellitus, and some infections during pregnancy also appear to be risk factors [17–19].

The European Surveillance of Congenital Anomalies and the International Clearinghouse for Birth Defects Surveillance and Research are well-known birth defect monitoring systems [20,21]. Birth defect surveillance in Russia reflects the principles and experiences of these systems, with certain adaptations to the Russian health care system. The registration of congenital defects in regional registries, such as in the Murmansk Regional Congenital Defects Registry (MRCDR), was implemented in 1998. These registries ideally record all birth defects, but currently only 21 are subject to annual reporting including two types of CVMs, specifically hypoplasia of the left heart (ICD-10 Q23.4) and transposition of great vessels (ICD-10 code Q20.3). By contrast, the Murmansk County Birth Registry (MCBR) records and reports on all types of birth defects.

More than 10,000 babies are born with different types of CVM in Russia annually [22]. In 2014, the Federal Russian Statistics Service (Rosstat) estimated the infant mortality resulting from CVM to be 1.5 per 1000 infants. Up to 75% of Russian babies who need life-saving surgical treatment do not receive it. By contrast, in North America modern surgical techniques allow 96–98% of babies with CVM who receive such treatment to survive and live longer [23]. On the basis of the Rosstat data, the prevalence of CVM in Russia ranges from 2.4 to 14.4 per 1000 infants, depending on the region; in Murmansk County, it was 10.9 per 1000 infants in 2010.

The aim of the current study was to identify maternal risk factors for the most frequent CVM, namely ventricular septal heart defects. Our findings constitute a first report on VSDs in Russia.

2. Materials and Methods

2.1. Data

The study population consisted of all singleton deliveries registered in the MCBR between 1 January 2006 and 31 December 2011 (n = 52,253). We searched for cases of SHD followed by VSD within this population by linking information in the MCBR, and in the MRCDR for up to 2 years after birth. We applied a manual linkage procedure based on the maternal hospital ID number and the birth dates of the mother and child. Detailed description of the MCBR and MRCDR establishment and linkage procedure have been published previously [24]. Twelve cases of SHD registered in the MRCDR were not included in the study cohort because they were born outside Murmansk County, or constituted duplicate entries. Supporting data are available upon request.

2.2. Ethical Considerations

The study received approval from by the Regional Health Administration of Murmansk County, as well as by the Ethics Committee of Gynecology–Obstetrician Association Group, Murmansk, Russia, and the Regional Ethics Committee, Tromsø, Norway. Ethical code is (reference number): 2013/2146.

2.3. Variables

Information on the infant characteristics: birth weight, sex, and gestational age were extracted from the MCBR, as were the following maternal characteristics at delivery: BMI at the first antenatal visit, smoking, alcohol and drug abuse, folic acid and multivitamin intake during pregnancy, and the occurrence of maternal diabetes mellitus type 1 and 2. Smoking, alcohol and drug abuse refer to any usage during pregnancy and were coded as yes/no.

2.4. Statistical Analyses

Comparisons of maternal characteristics for groups with VSDs and without any CVMs (control-group) involved chi-square statistics and the two-sample *t*-test for cases and non-cases; the accepted statistical significance level was set at $p \leq 0.05$. We applied logistic regression to identify factors associated with VSDs. In the latter analysis, the risk and preventive factors considered linked to this birth defect in the literature and those found in the current study to do so. Cases with at least one missing variable were excluded, leaving 49,463 infants for the statistical analyses (Figure 1). A multivariable logistic regression model was used and crude and adjusted odds ratio with 95% confidence intervals (CIs) were calculated. We used the statistical package SPSS v.24.0 (IBM Corp., Armonk, NY, USA, 2016).

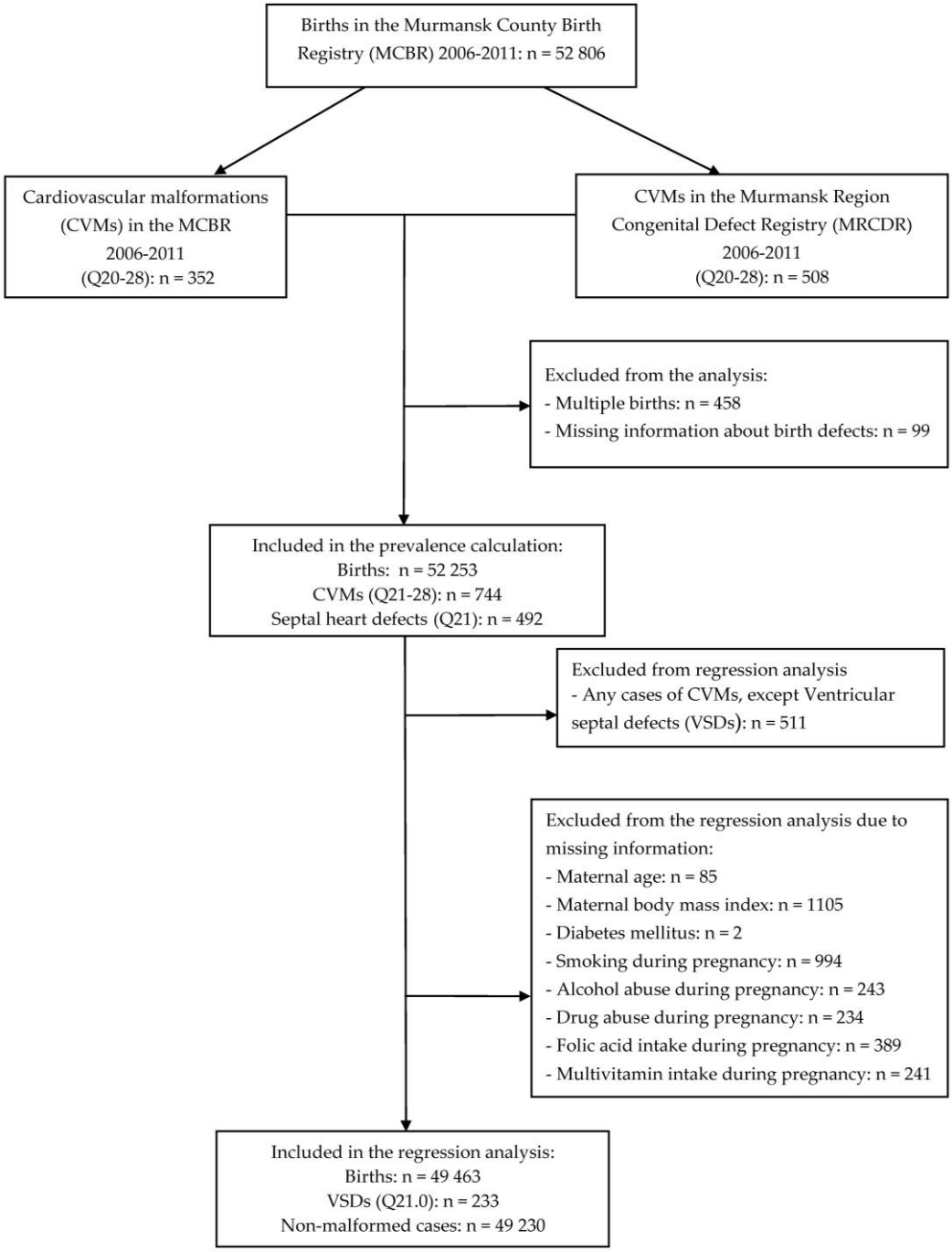

Figure 1. Number of births and exclusions for the combined Murmansk County Birth Registry and the Murmansk Regional Congenital Defects Registry 2006–2011 data. The individual numbers add up to more than the total number excluded because of missing information on two or more variables.

3. Results

During the study period, 52,253 eligible births were recorded in the MCBR and included 352 cases of CVM; by comparison, 508 CVM cases were noted in the MRCDR. After combining and removing duplicates, 744 cases (ICD-10 code Q20–Q28) remained. The latter correspond to a total prevalence of CVM of 14.2 per 1000. One hundred and sixteen cases of CVM were present in both registries, while 236 appeared only in the MCBR and 392 only in the MRCDR. Isolated SHDs accounted for 492 (66.1%) of all cases of CVM (Table 1).

Table 1. Incidence and prevalence [a] of cardiovascular malformations (CVMs) for the combined data set of newborns registered in the Murmansk County Birth Registry (MCBR) and the Murmansk Regional Congenital Defects Registry (MRCDR) during the period 2006–2011.

ICD-10 Code [b]	CVM	Cases		Prevalence [c]
		n	%	
Q20	Congenital malformations of cardiac chambers and connections	14	1.9	0.27 (0.2–0.5)
Q21	Septal defects	492	66.1	9.4 (8.6–10.3)
Q22–23	Valves defects	32	4.3	0.6 (0.4–0.9)
Q24	Other congenital malformations of the heart	51	6.9	1.0 (0.8–1.3)
Q25–27	Vessels anomalies	88	11.8	1.7 (1.4–2.1)
Q28	Other congenital malformations of the circulatory system	2	0.3	0.038 (0.037–0.040)
Multiple	Two or more	65	8.7	1.2 (1.0–1.7)
Q20–28	All	744	100	14.2 (13.2–15.3)

[a] Among all 52,253 study-period newborn. [b] ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision. [c] Prevalence per 1000 infants with 95% confidence interval.

The subdivision of the observed septal defects by ICD-10 codes was as follows: Q21.0 (VSD) was the most common defect (47.4%), with Q21.1 (ASD; 22.8%) and Q21.9 (unspecified; 23.8%) as secondary major contributors (Table 2).

Table 2. Distribution of septal heart defects (SHDs) for the combined data set of newborns registered in the MCBR and the MRCDR during the period 2006–2011.

ICD-10 Code [a]	CVM	Cases	
		n	%
Q21.0	Ventricular septal defects	233	47.4
Q21.1	Atrial septal defects	112	22.8
Q21.2	Atrio-ventricular septal defects	10	2.0
Q21.3	Tetralogy of Fallot	6	1.2
Q21.4	Aorto-pulmonary septal defects	9	1.8
Q21.8	Other	5	1.0
Q21.9	Unspecified	117	23.8
Q21	All	492	100

[a] ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

The mean birth weight (3244.4 g) and gestational age (39.2 weeks) were significantly lower in the group with VSD (Table 3). The proportion of mothers who smoked, abused drugs or abused alcohol during pregnancy was also higher in this group. Multivitamin and folic acid intake were not significantly different in the compared groups.

Although lower birth weight was observed for VSD cases (Table 3), it likely shares a common risk factor with other cardiovascular malformations. For this reason it was not included in the regression analysis. After adjustment, the entry-method regression modelling results (see Table 4) suggest that smoking, alcohol abuse, and maternal diabetes constituted predictors.

Note the significant increases in risk for having a baby with a ventricular septal defect for the following factors were: 8.72 (evidence of maternal diabetes mellitus type 1 and 2); 4.83 (alcohol abuse). Maternal smoking also reached statistical significance (OR = 1.35), while male gender of the baby was protective (OR = 0.67). In a separate multiple logistic regression analysis for ASDs that included the same variables as indicated in Table 4, only male sex of the baby was statistically significant (data not shown).

Table 3. Characteristics of the groups with ventricular septal defects (VSDs) and those without any CVMs (Q21) for the combined data set of newborns registered in the MCBR and the MRCDR during the period 2006–2011.

Variables	Cases, n = 233 [a]		Non-Cases, n = 49,230 [a]		p-Value [b]
	X	SD or %	X	SD or %	
Infant characteristics					
Birth weight (g), mean ± SD	3244.4	677.6	3377.2	546.5	<0.001
<2500	30	12.9	2211	4.5	
2500–3999	179	76.8	41,958	85.2	
≥4000	24	10.3	5061	10.3	
Sex, male	98	42.1	25,571	52.0	0.003
Maternal characteristics					
Age at delivery (years), mean ± SD	26.06	5.44	26.79	5.27	0.43
<18	3	1.3	727	1.5	
18–35	209	89.7	45,429	92.3	
>35	21	9.0	3074	6.2	
Gestational age (weeks), mean ± SD	39.2	2.3	39.5	2.2	0.05
BMI (kg/cm^2), mean ± SD	23.37	4.57	23.49	4.28	0.67
<18.5	16	6.9	3103	6.3	
18.5–24.9	157	67.4	32,325	65.7	
25.0–29.9	40	17.2	9712	19.7	
30.0–34.9	15	6.4	3084	6.3	
35.0–39.9	3	1.3	782	1.6	
≥40	2	0.9	224	0.5	
Smoking during pregnancy	74	31.8	12,234	24.9	0.02
Alcohol abuse during pregnancy	6	2.6	178	0.4	<0.001
Drugs abuse during pregnancy	4	1.7	173	0.4	0.01
Folic acid intake during pregnancy	175	75.1	36,545	74.2	0.76
Multivitamins intake during pregnancy	211	90.6	45,568	92.6	0.25
Diabetes mellitus Type 1 or 2	4	1.7	94	0.2	0.001

[a] The number of cases and non-cases are less than the entire study population due to missing values of the independent variables. [b] t-test, Chi-square test, or Fisher's exact test.

Table 4. Multivariable logistic regression. Crude and adjusted odds ratio (OR) with 95% confidence interval (CI) of ventricular septal defects [a] for the combined data set of newborns registered in the MCBR and the MRCDR during the period 2006–2011.

Variables	Crude		Adjusted [b]	
	OR	95% CI	OR	95% CI
Maternal age at delivery (years)				
<18	0.90	0.29–2.81	0.84	0.27–2.65
18–35	1	Reference	1	Reference
>35	1.49	0.95–2.33	1.53	0.97–2.41
Maternal BMI (kg/cm^2) [c]				
<18.5	1.06	0.63–1.78	1.10	0.66–1.85
18.5–24.9	1	Reference	1	Reference
>25	0.90	0.66–1.21	0.86	0.63–1.16
Smoking during pregnancy	1.41	1.07–1.86	1.35	1.02–1.80
Alcohol abuse during pregnancy	7.28	3.20–16.60	4.83	1.88–12.42
Drugs abuse during pregnancy	4.95	1.82–13.46	2.39	0.77–7.44
Folic acid intake during pregnancy	1.05	0.78–1.41	1.14	0.84–1.55
Multivitamins intake during pregnancy	0.77	0.50–1.20	0.99	0.69–1.43
Diabetes mellitus type 1 or 2	9.13	3.33–25.04	8.72	3.16–24.07
Sex (male)	0.67	0.52–0.87	0.67	0.52–0.88

[a] There were 233 cases and 49,230 non-cases. [b] Each variable is adjusted for the other listed variables. [c] BMI: body mass index.

4. Discussion

4.1. Selected Risk Factors

4.1.1. Smoking during Pregnancy

Recent epidemiologic studies have demonstrated associations between certain maternal lifestyle factors and the risk of CVMs in offspring including smoking, alcohol abuse, drug abuse, BMI, and psychological factors [9,25–27]. Three meta-analyses involving more than 30 studies have investigated the association between maternal smoking during pregnancy and CVMs [28–30]. Most feature a positive association between maternal smoking and all CVMs combined. In studies with more detailed analyses, the highest risk (OR = 1.27) occurred for VSDs in a light smokers group [30]. Dose-dependent effects have been reported for atrial septum defects [16]. With reference to Table 4, women who smoked during pregnancy were approximately 35% more likely to have a child with VSD compared with women who did not do so.

Cardiac morphogenesis is complex and risk factors can potentially affect the development of multiple components of the heart. For this reason, the current study focused on ventricular septal defects. The exact mechanisms by which maternal smoking may lead to ventricular septal defects is still unknown. Findings show that maternal smoking has adverse effects on the developing fetus, including hypoxia caused by carbon monoxide, nicotine absorption and toxicity, and reduction in the supply of essential nutrients to the embryonic tissue [30–32]. Smoking prevalence is high among women of reproductive age in Russia, which has public health consequences [33]. Even though the adverse effects of smoking on reproductive health are well known, young women continue to smoke, and more than 75% of those who smoked before pregnancy continued to do so throughout their pregnancy [34]. From 2006 to 2011, the prevalence of smoking during pregnancy in Murmansk County increased from 23.8% to 27.9% according to the MCBR statistics.

4.1.2. Sex of the Baby

In our study, male infants were less likely to have VSDs compared with females. Many congenital defects do have a dependence on sex and ethnicity, although no explanation for such deviations has been forthcoming [35]. Within the field of cardiology, the issue of gender differences has received attention because it is recognized that risk factors for cardiovascular defects are unevenly distributed by sex [36]. Possibly, genetic, morphological, and neuro-hormonal factors all contribute towards determining sex-dependent differences in such prevalence [37].

4.1.3. Alcohol Abuse during Pregnancy

Our observation that alcohol abuse during pregnancy is robustly associated with the risk of VSDs is not surprising. Alcohol use by mothers during pregnancy has indeed been observed to associate with different types of CVM in children [38]. The adverse effects of alcohol on the developing fetus comprise a spectrum of structural anomalies and behavioral disabilities and lead to an increased number of newborns with fetal alcohol syndrome [39,40]. The mechanisms by which alcohol consumption during pregnancy results in such heart defects have yet to be determined. In this context, a wide range of teratogenic effects have been documented and suggest that ethanol may produce fetal tissue edema and affect the turgor of the primitive cardiac loop [9]. Furthermore, the signaling systems that allow normal gene activation and cardiogenesis may be affected [41]. Moreover, cell death is an hypothesized mechanism for muscle formation, and alcohol exposure can result in abnormal cell development and cell death [42]. Alcohol-related studies are complicated because of the underreporting of its consumption during pregnancy. Our modelling showed that alcohol-consuming mothers had a 4.83-fold or more increased risk of having a baby with a VSD, although only six mothers of infants with VSDs reported doing so.

4.1.4. Drug Abuse During Pregnancy

Illicit uses by mothers of marijuana, cocaine, heroin or methadone were noted in the MCBR. To date, few studies have addressed drug abuse during pregnancy, and those that do focus on one specific medication or substance. The vasoconstrictors cocaine and marijuana are potential teratogens because exposure to them may result in vascular disruptions and hypoperfusion. A case-control study from Atlanta (USA) showed that maternal cannabis use, according to self- and proxy-reports, was associated with a two-fold increased risk of septal heart defects including VSDs [19]. On the basis of our multivariable logistic regression findings a near two-and-a-half-fold increase in risk was evident for drug abuse, although statistical significance was not reached [OR = 2.39; 95% CI 0.77–7.44].

4.1.5. Diabetes

We found that diabetes mellitus was associated with an eight- to nine-fold increased risk of ventricular septal heart defects in our study. The increasing prevalence of diabetes type 2 among women of childbearing age in Russia makes identifying and implementing effective prevention strategies a high priority [43]. Diabetes mellitus is an important pathogenetic factor that is associated with a wide spectrum of CVMs, including VSDs [12]. Although the mechanisms underlying the association between diabetes and VSDs are not well known, hyperglycemia may play a critical role [44]. Strict glycemic control before conception and during pregnancy appears to reduce risk levels, but achieving and maintaining euglycemia early in pregnancy constitutes a challenge because many diabetic women do not plan their pregnancies [45].

In our study, only diabetes Type 1 and 2 were included. Gestational diabetes, which usually develops at the end of the second trimester was not considered a risk factor because VSDs develop earlier in the pregnancy. Removal of maternal age from the final regression model (see Table 4) changed the OR of diabetes minimally, specifically from 8.72 to 8.93; as did the omission of the BMI variable (to 8.50), and of both BMI and age (8.71). This highlights the importance of diabetes as a risk factor.

4.1.6. Folic Acid and Multivitamins

One of the most important recent discoveries is that periconceptional intake of folic acid may reduce the risk of different types of septal heart defects in offspring, as it does for neural tube defects. This was first identified in an Hungarian study [46]. Findings from subsequent case-control studies have generally been supportive, but not conclusive. In addition, other studies among high-risk groups present ancillary evidence that support a protective effect of folic acid supplements [47,48]. For example, one study showed that women who used medications that are folic acid antagonists exhibited an increased risk of having babies with CVMs, and that this risk was reduced among women who also took multivitamin supplements containing folic acid [49]. In our study, we did not have information on intake of all types of supplements during pregnancy. Nevertheless, in our logistic regression analyses multivitamin and folic acid intake were not associated with any change in the risk of ventricular septal defects.

4.2. Strengths and Limitations of the Study

The high quality of the MCBR data is considered a strength of our study [50]. Abortions that occur before 22 weeks of gestation were not included in our study, and this may constitute a limitation in the generalization of our findings. Russia has an active screening regime during pregnancy, and we suspect that some birth defect findings resulted in pregnancy terminations. Our data on smoking, alcohol abuse, and drug abuse are based on clinical evidence and self-reported information and thus may have been underestimated. The power of the current study was limited by the relatively small number of cases and this restricted the number of variables that could be considered in our modelling.

5. Conclusions

We showed that alcohol abuse during pregnancy, as well as maternal diabetes mellitus were risk factors for delivering infants with ventricular septal defects. The effects of smoking during pregnancy were marginal. Male offspring were somewhat less susceptible. Potentially numerous cases of VSDs are preventable in Russia if health policy makers were to pay more attention to established risks.

Author Contributions: A.A.K. designed the study, collected the data, performed statistical analysis, and wrote the manuscript. E.E.A. participated in the design and coordination of the study, critically revised the manuscript and together with J.O.O., E.N. and A.A.K. pioneered the setting up of the MCBR. T.B., J.Ø.O., E.N. and A.K. helped in the drafting/editing of the manuscript. All authors read and approved the final manuscript.

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Appendix A

Notification about newborn with congenital birth defects (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

Murmansk County Birth Registry notification form (in Russian)

А – Персональные данные матери и отца

1. Название роддома

2. Роды вне роддома

☐ Дома ☐ Другое место
☐ Во время перевозки

3. Год (0000) и номер медицинского файла

_____

4. Год рождения последнего живого ребенка (0000)

Если дата не введена → клетка 4.1

4.1 Нет даты, так как:
☐ Ранее не было живого ребенка
☐ Нет информации

4.2 Год последнего аборта (0000)

Если дата не введена → клетка 4.3

4.3 Нет даты, так как:
☐ Ранее не было абортов
☐ Нет информации

5. Дата рождения матери (день/месяц/год, 00.00.00)

6. Этническая принадлежность
☐ Саами
☐ Русская
☐ Азербайджанка
☐ Другая (уточните)
_____

7. Место жительства (Район)

7.1 Город/поселок/село

8. Менялся ли официальный адрес матери во время беременности?
☐ Нет
☐ Да (если «Да», то откуда ->)

8.1 Область/Район

8.2 Город/поселок/село

9. Семейное положение
Замужем:
☐ Да ☐ Гражданский брак
☐ Нет ☐ Другое

10. Образование, закончен.
☐ Никакого
☐ Начальное (1-9 класс)
☐ Среднее (10-11 класс)
☐ Среднее специальное
☐ Высшее

11. Профессия матери

11.1 Место работы матери

11.2 Цех, где она работает

Информация об отце

12. Возраст отца

13. Профессия отца

13.1 1 Место работы отца

13.2 Цех, где он работает

14. Этнич. принадлежность
☐ Саами
☐ Русский
☐ Азербайджанец
☐ Другая (уточните)
_____

В – О беременности и здоровье матери

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

16. Рост (в см)

17. Вес (при первой явке) (в кг)

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

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

B1. МКБ-10 код(ы)

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

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

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

B2. МКБ-10 код(ы)

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

21.1
Рождение живого ребенка _____
Мертворождения >= 22 недель _____
Рожден живым, умер в течение 7 дней _____

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

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

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

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

21.5 Медицинские аборты с
(заполните 21.6)
13 недель _____

21.6
Социальные причины _____
Медицинские причины _____

22 Витамины/алкоголь/ наркотики

24. Признаки злоупотребления алкоголем
☐ Нет
☐ Да

25. Признаки употребления наркотиков
☐ Нет
☐ Да

22.1 Прием витаминов перед беременностью
Поливитамины
☐ нет ☐ да
Таблетки фолиевой к-ты
☐ нет ☐ да

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

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

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

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

2. Название
С даты (д/м)

3. Название
С даты (д/м)

26. Болезни до беремен-ности
☐ Ничего особенного
☐ Хронич.инфекция мочеполового тракта
☐ Хронич. инфекц. заболевание почек
☐ Астма
☐ Хроническая гипертония
☐ Ревматоидный артрит
☐ Сердеч. забол.
☐ Эпилепсия
☐ Диабет, тип 1
☐ Диабет, тип 2
☐ Гепатит В
☐ Гепатит С
☐ другое (уточните в B4)

B4. Уточните МКБ-10 код (ы)

27. Болезни во время беремен-сти (включая несчастные случаи)
☐ Ничего особенного
☐ Кровотечение< 13 нед.
☐ Кровотечение13-28нед.
☐ Кровотечение> 28 нед.
☐ Диабет беременной
☐ Тромбоз
☐ Легкая преэклампсия
☐ Тяжелая преэклампсия
☐ эклампсия беременной
☐ HELLP- синдром (гемолитич. ....)
☐ Легкая анемия
☐ Умеренная анемия
☐ Тяжелая анем.
☐ Hb> 135 г/л
☐ Угроза прерывания (O20.0)
☐ инфекции (B5)
☐ другое (B5)
☐ лекарства (B6)

B5. Уточните МКБ-10 код (ы)

C – О родах

28. Платила ли мать за улучшение условий содержания в родильном отделении?
☐Нет ☐Да

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

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

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

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

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

C1. МКБ-10 код (ы)

C2. МКБ-10 код (ы)

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

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

C3. Препарат

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

C4. МКБ-10 код (ы)

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

38. Осложнения у матери после родов
☐Ничего особенного
☐ Температура > 38.5°C
☐ Сепсис
☐ Тромбоз
☐ Эклампсия послеродовая
☐ Интенсивная терапия
☐ Другое, запишите в C5
☐ Переведена
Мать переведена в (название больницы) _____

C5. МКБ-10 код (ы)

D - О новорожденном

39. Дата родов (д/м/г)

40. Время родов (час, мин.)

41. Многоплодные роды
Если многоплодные:
No. ___ ребенка из ___ (общее количество) детей

42. Пол
☐Мужской
☐Женский
☐Неизвестно

43. Вес ребенка (в граммах)

44. Рост (в см)

45. Окружность головы (в см)

46. По шкале Апгар
1 мин.
5 мин.

47. Ребенок родился:
☐ живым
☐ мертвым (47.1)
☐Выкидыш
Подтвердите причину смерти в D1

47.1 Для мертворожденного:
☐Смерть до начала родов
☐Смерть во время родов
☐Время смерти неизвестно

48. Родился живым, но умер в течение 24 часов
Время смерти (Час, мин.): ____ ____

49. Ребенок умер позднее:
Число (день/мес.) ____ ____
Время(час, мин.) ____ ____

50. Ребенок умер в больнице?
☐Да
☐Нет

D1. МКБ-10 код (ы)

51. Диагноз новорожденного
☐ Ничего особенного
☐Гипогликемия <50 мг/дл)
☐Врожд. анемия(hb<13.5)
☐Дисплазия тазобед.сустава
☐Транзиторн.частое дыхание
☐Дыхат. дистресс-синдром
☐ Аспирационный синдром
☐Интракраниальное кровотеч.
☐Церебральное раздражение
☐Церебральная депрессия
☐Абстиненция
☐Конъюнктивиты
☐Неонат. судороги
☐Инфекция пупка/кожи
☐Перинат.инфекции, уточните в D3
☐Другие инфекции (D2)
☐Другое, уточните в (D3)

D2. МКБ-10 код (ы)

☐Перелом ключицы
☐Перелом конечностей
☐Лицевой парез
☐Повреждение сплетения
☐Другое, включая травмы (D4)

52. Виды лечений:
☐Сист.антибиотики
☐ ИВЛ
☐Глазные капли

Леченная желтуха:
☐ УФ светолечение
☐Переливание крови

Причина:
☐Несовместимость по системе АВО
☐Резус-иммунизация
☐Физиологическая

D3. МКБ-10 код (ы)

53. Врожденные дефекты
☐Да ☐Нет

Описание повреждений, неонатального диагноза и врожденных дефектов
МКБ-10 код Другое:
МКБ-10 код

D4. МКБ-10 код (ы)

54. Даты выписки
Мать выписана
Ребенок выписан / переведен
Переведен в _____

Номер истории болезни