Research protocol

Title: Drug transporter protein -mediated drug interactions during pregnancy and offspring outcome; with special emphasis on second-generation antipsychotics and SSRIs

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List of abbreviations

ATC = Anatomic Therapeutic Classification

BCRP= breast cancer resistant protein

ETOPFA = Elective Termination of Pregnancy for Fetal Anomaly

Kela = Social Insurance Institution in Finland

MRP= Multidrug resistance-associated protein

P-gp = P-glycoprotein

SGA= Second Generation Antipsychotic drug

THL = National Institute for Health and Welfare

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Research synopsis

Background. Drug transporter proteins play an important role in the bioavailability and toxicity of drugs. P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are the two important efflux transporter proteins in the human placenta. These proteins function as a blood-placental barrier by preventing drugs from entering the fetal circulation and protecting the fetus from exogenous chemicals (Figure 1). While concomitant use of transporter substrates may result in inhibition of function and increase fetal exposure to drugs, research in this field is only starting to emerge. It is not known if drug transporter protein -mediated drug interactions account for the previously reported inconsistent findings related to possible teratogenicity of second-generation antipsychotics (SGAs) and SSRIs, or if such interactions can also predispose to neonatal drug toxicity.

Objectives. To investigate if concomitant use of two or more drug transporter substrates or a substrate and an inhibitor during first trimester is associated with an increased risk of offspring major congenital malformations. Specifically, we will assess the risk of overall malformations in offspring of women using SGAs, and the risk of cardiac malformations in offspring of women using SSRIs or bupropion. We will also investigate if concomitant use of SGAs or SSRIs together with a drug transporter substrate or inhibitor during the third trimester is associated with an increased risk of severe or prolonged neonatal adaptation problems.

Methods. This is a population-based cohort study based on the Drugs and Pregnancy project database in Finland. Data are derived from national health registers: the Medical Birth Register, the Register on Induced Abortions, the Malformation Register (all maintained by the National Institute for Health and Welfare), and the Prescription Register and Special Refund Entitlement Register (both maintained by the Social Insurance Institution). Data in these registers have been collected during Jan 1st 1996 - Dec 31st 2011 and include all births (live and still births), pregnancy terminations due to major congenital malformation, and information on drug purchases during

pregnancy and 3 months before pregnancy. To this database we will further link data on individual drugs and their relation (substrate, inhibitor) to P-gp and BCRP from the University of Washington Metabolism and Transport Drug Interaction Database (DIDB). Offspring of women with concomitant use of two or more drug transporter substrates, or a combination of a substrate and an inhibitor, are compared to offspring of women using only one drug transporter specific substrate, and to unexposed.

Timelines. Linkage of the drug transporter substrate database data to the Drugs and Pregnancy database will start in May 2016. Final results with manuscript submission are expected in spring 2017.

Background and significance

Drug use during pregnancy is common: in Finland, more than half of pregnant women use prescription drugs, and one out of four use two or more prescription drugs (THL 2014). A recent study from the U.S. reported that nearly 8% of pregnant women use more than four drugs during the first trimester (Mitchell et al. 2013).

Use of the SGAs has increased during the last decade. This tendency is evident not only on population level but also within the pregnant population in Finland; in 2006, 0.2% of pregnant women used SGA drugs and the use increased up to 0.8 % in 2012, while during the same period the use of first generation antipsychotics remained relatively stable, 0.1 % (THL 2014). The increased use of SGAs may to some extent be related to the argued but not uniformly proven better tolerability, and a more favorable side-effect profile when compared to the first generation antipsychotics (Tandon *et al.* 2011). Further, off-label use, including use as hypnotics and sedatives, may also play a role. There is limited experience of use of the individual SGAs use during pregnancy (Ennis and Damkier 2014; Kulkarni et al. 2014), with individual studies observing no increased risk of malformations (Cohen et al. 2015) and some reporting a two-fold increased risk (Terrana et al. 2015). There are no studies assessing the risks of polytherapy - yet, 80% of pregnant women using SGAs have been reported to use additional psychotropic medication (Cohen et al. 2015). Further, little is known about the possible adverse effects on neonatal adaptation.

During the last two decades the use of antidepressants has also been steadily increasing and up to 4-10 % of women use antidepressants during some stage of pregnancy (Malm et al. 2012; Cooper et al. 2007). Given that 6% of the pregnant population in the U.S. and 4% of the pregnant population in Finland receive SSRIs, the question of safety of SSRIs during pregnancy is a question of major importance to patients and clinicians. While most studies have not observed an increased risk of malformations, several studies have observed an association between SSRI use and specific cardiac defects (Reefhuis et al. 2015; Wemakor et al. 2015; Malm et al. 2011; Bakker et al. 2010; Alan et

al. 2007; Louik et al. 2007). A recent, population-based register study from the five Nordic countries including more than 2 million pregnant women could not rule out an association between individual SSRIs and an increased risk of some specific cardiac malformations, even if the overall increased rate of cardiac malformations associated with SSRI use could largely be explained by familial factors rather than SSRI exposure (Furu et al. 2015). Another recent study suggested that the increased rate of cardiac malformations is likely due to other factors, including maternal age, chronic diseases and alcohol or illicit drug use rather than SSRIs (Petersen et al 2016). For bupropion, published research has also been conflicting, suggesting an increased risk for cardiac malformations in some (Thyagarajang et al. 2012; Alwan et al. 2010; Cole et al. 2007) but not in all (Louik et al. 2014) studies. Further, while neonatal adaptation symptoms after prenatal exposure to SSRIs are usually short-lived, recent findings suggest that in some cases the symptoms may be more severe and even if subtle, more prolonged after polytherapy (Salisbury et al. 2016; Källen et al. 2012; Oberlander et al. 2004). Given that one out of five pregnant women using SSRIs also use other psychotropic drugs (Malm et al. 2015) limited data exist if concomitant use of psychiatric or other drugs may increase the risk of cardiac malformations or exacerbate the neonatal symptoms.

Drug transporter proteins play an important role in the bioavailability and toxicity of drugs. P-glycoprotein, P-gp and the breast cancer resistance protein, BCRP, both belonging to the ATP-binding cassette (ABC) transporters, are expressed in several human tissues, and are considered the two most important transporter proteins in the human placenta (Iqbal et al. 2012). The placenta is the organ with the highest known expression of both P-gp and BCRP. These proteins are efflux transporters and they are expressed in the maternal blood-facing surface of the syncytiotrophoblast of placenta. Both P-gp and BCRP actively transport their substrates out of the syntiotrophoblast back into the maternal circulation and prevents them from reaching the fetus. Both transporters are also involved in the regulation of several endogenous compounds to the fetal circulation. Their

presence in the placenta suggests an important barrier-role of the placenta in preventing drugs from entering the fetal circulation and accordingly, protecting the fetus from exogenous chemicals. Both P-gp and BCRP are present in first trimester placental tissue. The expression of P-gp is high in the first trimester and decreases with advancing gestation (Sun et al, 2006, Lye et al, 2013). BCRP is found in placental tissue throughout pregnancy, but it is unclear how the different stages of pregnancy affect its expression. The expression of P-gp and BCRP may be changed by different pathological states like diabetes (Anger et al, 2012), inflammation (Mason et al, 2011), hypoxia (Lye et al, 2013) and obesity (Wang et al, 2015). Inflammation itself influences the expression of drug transporters. Inflammation is associated not only with diabetes and obesity but also pre-eclampsia. It is therefore possible that pre-eclampsia may influence the expression of these transporters similarly to diabetes and obesity.

P-gp has a broad substrate specificity, including several individual drugs in the calcium channel inhibitor, macrolide, opioid, SSRI and SGA drug groups. Several of these substrates may also inhibit the function of this transporter. BCRP has many substrates overlapping with the P-gp, the individual substrates having different affinities to the transporters. Simultaneous use of several substrates or a substrate together with an inhibitor may consequently affect the placental barrier function and alter the degree of fetal exposure to the specific substrate. As teratogenesis is a dose-response phenomenon, higher exposure to a harmful agent would be expected to result in an increased risk of fetal adverse effects, including congenital malformations. Research in this field is only starting to emerge. It is not known if drug transporter protein -mediated drug interactions account for the previously reported inconsistent findings related to possible teratogenicity of SGAs and SSRIs, or if such interactions can also predispose to neonatal drug toxicity.

Objectives

The objectives of the study are 1) to investigate if concomitant use of two or more drug transporter substrates during first trimester is associated with an increased risk of offspring major congenital malformations. 2) Specifically, we will assess the risk of i) overall malformations in offspring of women using SGAs, and ii) the risk of cardiac malformations in offspring of women using SSRIs or bupropion. 3) We will also investigate if concomitant use of SGAs or SSRIs together with a drug transporter substrate or inhibitor during the third trimester is associated with an increased risk of severe or prolonged neonatal adaptation problems.

Methods

The data for this study are extracted from the existing database of 'Drugs and Pregnancy' project in Finland (Lahesmaa-Korpinen *et al*. 2014). This project has been established by three governmental organizations: The National Institute for Health and Welfare (THL), the Social Insurance Institution in Finland (Kela) and the Finnish National Medicines Agency (Fimea). The objective of the project is continuing surveillance of drug-related safety during pregnancy. Several studies on drug use and safety have already been carried out using this continuously growing project material (Artama et al. 2013; Kieler *et al.* 2012, Artama *et al.* 2011, Malm *et al.* 2011, Malm *et al.* 2005). Data from births and terminations of pregnancy have been gathered since Jan 1st 1996 and are currently available until Dec 31st 2012 for study purposes, apart from congenital malformations, for which information is available until 2011. In that project, the Medical Birth Register, the Abortion Register, the National Register of Congenital Malformations, and the Prescription Register, including also the Special Refund Entitlement Register, have been linked by the personal identification number (PIN) assigned to all citizens and permanent residents (Artama *et al*. 2011). In this study we use a cohort study design and include i) births (the Medical Birth Register and the National Register of Congenital Malformations), and ii) fetuses from elective terminations of pregnancy for fetal anomaly (ETOPFA) (the National Register of Congenital Malformations). Women and their offspring exposed to drugs included in this study and non-exposed controls will be collected from

this database. To this database we will further link data on individual drugs and their relation (substrate, inhibitor) to P-gp and BCRP from the University of Washington Metabolism and Transport Drug Interaction Database (DIDB). Linkage is made using the International Anatomic-Therapeutic-Chemical (ATC) classification code for drugs.

Description of the registers included in the study

The national Medical Birth Register (MBR) was established in 1987 and is maintained by the National Institute for Health and Welfare (THL) (THL 2013*a*). This computerized register collects data on maternal demographic characteristics, medical history including reproductive history, smoking, diagnoses during pregnancy and delivery, and neonatal outcome data up to six days' age. Data in the MBR includes all live births and stillbirths with gestational age of 22 weeks or more or birth weight of 500 grams or more, and the data are collected in a standard form from all maternity hospitals and include all births, including the occasional homebirths. All infants are examined in the hospital by a paediatrician. The register data are confirmed and complemented from the maternity hospital records in cases of conflicting or missing information. The definitions and variables included in this registry are based on established international concepts and use the 10th version of the WHO International Classification of Diseases (ICD) since 1996. Extensive review of the data, including cross-checking with the data from the Finnish Population Register and Cause-of-Death Register at Statistics Finland indicate that the data are virtually complete (THL 2013a; Gissler and Shelley 2002, Teperi 1993).

The national Register of Congenital Malformations, maintained by THL, receives comprehensive data on MCAs including live births, stillbirths and ETOPFAs, all with at least one detected major congenital anomalies including major structural malformations, chromosomal defects, teratomas and congenital hypothyroidism, classified and coded according to the extended 9th version of the

ICD classification. Minor anomalies are excluded principally according to the exclusion list of the European Surveillance of Congenital Anomalies, EUROCAT (www.eurocat-network.eu). Data are collected from hospitals, health-care professionals and cytogenetic laboratories as well as from the Medical Birth Register, the Register of Induced Abortions, the Register of Visual Impairment and the Care Register for Health Care (including Information on Outpatient Services in Specialised Health Care), all maintained by THL, as well as from the National Supervisory Authority for Welfare and Health (Valvira) and from the Cause of Death Statistics maintained by Statistics Finland. Diagnoses obtained from these data sources are confirmed by contacting the hospitals concerned. Although the register mainly collects data from the first year of the child's life, it also includes subsequently detected congenital malformations. The validity of the RCM is considered good and has been ascertained in several studies (Leoncini *et al.* 2010, Pakkasjärvi *et al.* 2006, THL 2013*b*).

The Prescription Register is maintained by the Social Insurance Institution in Finland (Kela) since 1995. The register contains data on 99% of reimbursed prescription drug purchases (Finnish Statistics on Medicines, 2010). Prescription-only medicines deemed necessary for the treatment of an illness are reimbursed under the Social Insurance System which covers all permanent residents in Finland. Drug purchases are reimbursed concomitantly upon purchase at pharmacies and drugs are supplied to the patient for a maximum of three months at a time. Data in the register include the date of the purchase, the ATC classification code indicating the generic name of the drug, and the dose prescribed. Over-the-counter drugs or medications given to institutionalized persons are not included in the register (Kela 2012). Kela also maintains the Special Refund Entitlement Register since 1964 with data on patients holding entitlement for higher reimbursement for several chronic illnesses requiring continuous drug treatment. The entitlement for special reimbursement has to be

shown by doctor's certificate and the register includes information about indications for prescription.

With the annual rate of 55,000 - 60,000 births and the average annual rate of 260 ETOPFAs during years 1996-2012, the total Drugs and Pregnancy database counts up to nearly 1 mill. births and 4,000 ETOPFAs.

The Metabolism and Transport Drug Interaction Database™ (DIDB™) and the Pharmacogenetics Database (e-PKGene™) are part of a knowledge base ("DIDB Platform™") designed for scientists and clinicians working in the field of drug development, drug disposition and drug-drug interactions. The DIDB Platform was developed at the University of Washington's Department of Pharmaceutics, School of Pharmacy with input from pre-clinical and clinical pharmaceutical scientists. The DIDB was first licensed in 2002 and is currently used by a large number of pharmaceutical companies, regulatory agencies, contract research organizations and academic institutions worldwide (www.druginteractioninfo.org). The updated version of the DIBD (Oct. 2015) is used to identify drugs which are P-gp or BCRP transporter substrates or inhibitors and these are linked by ATC code in the Drugs and Pregnancy project database.

Definition of exposed and unexposed cohorts

1. *General exposure group.* Pregnant women who have purchased during the first trimester two or more drugs that are P-gp or BCRP transporter substrates or inhibitors. As 50% of pregnant women use prescription drugs, and of them, about one half use two or more different drugs (Lahesmaa-Korpinen et al. 2014). By estimating that 10% of these are transporter substrates or inhibitors, we expect to include appr. 25,000 pregnant women to have at least two such drug purchases, and further, half of these purchases occurring during one month before pregnancy or first trimester (expected n= 12,000).

2. *Exposed to second generation antipsychotics.* Women who have purchases of SGAs (4th level ATC code N05AE, N05AH and N05AX) which are P-gp or BCRP transporter substrates or inhibitors (Table 1) during one month before pregnancy or during pregnancy. In Finland, 0.3 % of pregnant women have a diagnosis of psychosis as a chronic disease (Lahesmaa-Korpinen et al. 2014). Several of the SGAs have only been introduced recently to the market and we expect to include approx. 2,000 pregnancies exposed to SGAs. We expect that approx. half of these women have been exposed to other transporter-specific substrates. This assumption is crude and based on the fact that nearly 80% of pregnant women using SGAs have been reported to use also other psychotropic drugs (Cohen et al. 2015). Accordingly, the SGA exposure groups will include an estimated 1,000 pregnancies exposed to SGAs only, and 1,000 pregnancies exposed to SGAs together with a transporter substrate. Major congenital malformations will be analyzed in the cohort with SGA purchase(s) during one month prior to pregnancy or during the first trimester. Neonatal adaptation problems will be analyzed including SGA purchases during the 3rd trimester.

3. *Exposed to SSRIs or bupropion.* Women who have purchased SSRIs (4th level ATC code N06AB) which are P-gp or BCRP transporter substrates or inhibitors (Table 1) or bupropion (N06AX12) during one month before pregnancy or during pregnancy.

   We expect to include a total of 20,000 pregnancies exposed to SSRIs or bupropion. Of SSRIs, citalopram is a P-gp substrate, citalopram, sertraline and fluoxetine are P-gp inhibitors, and paroxetine is BCRP substrate. According to the THL statistics, citalopram is the most commonly used antidepressant among pregnant women In Finland, and we expect to include appr. 14,000 pregnancies exposed to these

particular SSRIs or bupropion. Further, we calculate that approximately 10% of these women have also been exposed to other transporter-specific substrates, including proton pump inhibitors (PPIs), calcium channel blockers, antipsychotics, corticosteroids, or macrolide antibiotics, among others. This assumption is crude and based on the fact that 65% of women who use SSRIs during pregnancy have been reported to use other prescription drugs during pregnancy (Malm et al. 2011). Accordingly, the SSRI exposure groups will include an estimated 12,000 pregnancies exposed to SSRIs or bupropion only, and 1,400 pregnancies exposed to SSRIs or bupropion together with a transporter substrate.

The beginning of pregnancy has been calculated from the best clinical estimation of gestational age at birth (primarily based on ultrasound) as registered in the MBR. Timing of exposure is defined by trimesters. The length of pregnancy is divided into first (days 0 - 84 after last menstrual period), second (days 85 - 182), and third trimester (days 183 until birth). Major congenital cardiac malformations will be analyzed in the cohort with SSRI and bupropion purchase(s) during one month prior to pregnancy or during the first trimester. Neonatal adaptation problems will be analyzed including SSRI purchases during the 3rd trimester. The use of registers and study methods are illustrated in Figure 2.

4. *Unexposed controls*, with no drug purchases during one month prior to pregnancy or during pregnancy. Women in this group are matched for year of birth of child or pregnancy termination (+/- 1month) and will be randomly selected as 5 referents for one exposed (5:1).

Offspring of women with concomitant use of two or more drug transporter substrates, or a combination of a substrate and an inhibitor, are compared to offspring of women using only one drug transporter substrate, and to unexposed.

Definition of outcomes

1. Major congenital malformations and major cardiac malformations, according to EUROCAT coding (www.eurocat-network.eu). These analyses include all pregnancies ending in birth or ETOPFA and are restricted to exposure during one month before pregnancy until the end of first trimester.
2. Neonatal outcomes are analysed in singleton, full-term live born infants and are restricted to exposure during the third trimester, and include
    - Apgar score <7
    - need for respirator treatment
    - need for treatment in neonatal (intensive) care unit
    - need for care outside home at the age of one week.

Covariates and possible confounders to be considered for adjustment in the analyses are presented in Table 3. Alcohol use is not routinely collected in any of the registers and data on alcohol use are only available occasionally and therefore cannot be included in analyses. Data on alcohol exposure are available in the Register of Congenital Malformations for all cases with a diagnosis of fetal alcohol spectrum defects.

Statistical analyses

All data are anonymized and coded prior to statistical analysis. The prevalence of specific outcomes is compared between the different exposure groups of pregnant women and their offspring. Crude and

adjusted odds ratios (cOR and aOR) and 95% confidence intervals (CI) were calculated. Statistical significance was set at a *P* value of less than 0.05.

Univariate analyses are used to study demographic differences between the study cohorts. Univariate and logistic regression are used to calculate crude and adjusted odds ratios (cOR and aOR), and 95% confidence intervals (CI) and to assess the association between exposures during pregnancy and major congenital malformations and other perinatal outcomes. Covariates will be tested using a *P* -value of < 0.1 to detect associations with exposure and outcome. If associated with both exposure and outcome, the covariate will be included as a true confounder in the analysis. Missing information for categorized variables are categorized as the harmless alternative (*i.e.* not exposed to tobacco). With an estimated 1,000 pregnancies exposed to SGAs monotherapy and 1,000 pregnancies exposed to SGA and substrate, the study has a 95 % power to detect a doubled relative increase (3.0 % absolute increase) in the prevalence of major congenital malformations presuming a baseline prevalence of 3% in the control cohort (alpha = 0.05, two-sided).

For SSRIs, with an estimated 12,000 pregnancies exposed to monotherapy and 1,400 exposed to SSRI and substrate, the study has a 86 % power to detect a doubled relative increase (0.8 % absolute increase) in the prevalence of congenital cardiac malformations presuming a baseline prevalence of 0.8% in the control cohort.

Study timelines

This study will be registered in the ENCePP Register of Studies before data collection starts. Data extraction will start on May 2016 and end by Sept. 2016. Analyses of data will start during autumn 2016, and an interim report of preliminary results is to be expected during spring 2017. Final results and manuscript for submission in an international, peer-reviewed scientific journal are expected by end of 2017.

Approval

The utilization of sensitive health register data for scientific research and the data linkages in the 'Medicines and Pregnancy' -project has been approved by the register administrators and the national data protection authority. Since the study subjects are not contacted, according to the Finnish legislation informed consent is not required.

Implications of the study

Using national, population-based register data for 16 years enables us to have a large enough material to obtain a reasonable number of exposed pregnancies for studying rare outcomes, such as major congenital malformations. The quality and coverage of the registers included in the study material are considered excellent and information bias is therefore unlikely. Register-based studies are free of recall bias but limitations include to possible bias of drug compliance. However, non-compliance is likely to occur with short-term drug therapies and for fear of teratogenicity, while drug therapies for treating chronic diseases, including antipsychotics and antidepressants, are usually not given up during pregnancy (Malm *et al.* 2003). This study will provide novel epidemiologic evidence on the safety of SSRIs and SGAs on pregnancy outcome, focusing on transporter protein -mediated drug interactions. As concomitant use of drugs is common and use SGAs and SSRIs has been steadily increasing, the results will have important implications for pregnant women with psychiatric disorders needing drug treatment, and for prescribing practices for clinicians who treat these pregnant women.

Data protection and storage

The Drugs and Pregnancy database contains anonymized data, maintained in the THL in locked-up location and accessible only to researchers with permission and guarded by institutional and

personal passwords. The research data extracted from this database are similarly secured and accessible only for persons with researcher status in the THL. The research data will be stored in this location for 10 years.

Possible amendments and deviations

Thorough reasons will be given for possible amendments and deviations from the research protocol and, if realized, will be documented and made publicly available in the ENCePP forum.

Independent review of study results

According to the national data protection legislation, the research data are available only for those researchers who have applied for and granted permission to data access. In case of a justified reason for outside review, permission to check the data can be applied from the National Institute for Health and Welfare.

Communication of results to regulatory authorities

The study results are communicated at each phase of analyses directly to the representative of the Finnish National Medicines Agency.

Author contribution

All authors have contributed substantially to the planning and writing of the study protocol.

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Table 1. Second-generation antipsychotics and SSRIs and bupropion included in drug-specific analyses.

P-gp substrate	**P-gp inhibitor**	**BCRP substrate**	**BCRP inhibitor**
SGAs			
paliperidone	aripiprazole		aripiprazole
risperidone	clozapine		
	loxapine		
	paliperidone		
	quetiapine		
	sertindole		
	ziprasidone		
SSRIs			
citalopram	citalopram	paroxetine	
	fluvoxamine		
	sertraline		
Bupropion		bupropion	

Table 2. Covariates to be tested

Covariate	Availability in register data
Year of birth of child	Virtually complete
Maternal age at the end of pregnancy 25-29 (ref) <25 or >=30	Virtually complete
Parity one or more previous deliveries (ref) no previous deliveries	Virtually complete
Marital status married or co-habiting (ref) single	95%
Smoking no (ref) yes	97%
Socio-economic status based on maternal occupation at birth upper white collar = ref lower white collar blue collar other	82%
Exposure to other psychiatric drugs (ATC codes N05B, N05C, N06A, N06B, N06C, N07B) any time during pregnancy or one month prior to pregnancy	Virtually complete
Exposure to lithium (N05AN01) any time during pregnancy or one month prior to pregnancy	
Exposure to antiepileptic drugs (N03) any time during pregnancy or one month prior to pregnancy	
Exposure to any of the other suspected or established teratogens any time during pregnancy or one month prior to pregnancy: Warfarin (B01AA03) Drugs acting on the renin-angiotensin system (C09) Isotretinoin (D10BA01) Acitretin (D05BB02) Alitretinoin (D11AH04) Carbimazole (H03BB01) Antineoplastic agents (L01)	

Mychophenolate (L04AA06)
Leflunomide (L04AA13)
Thalidomide (L04AX02)
Methotrexate (L04AX03)
Lenalidomide (L04AX04)
Misoprostol (A02BB01) and (M01AB55)
Ergotamine (N02CA52)

Entitlement to special reimbursement due to pre-pregnancy diabetes

Entitlement to special reimbursement due to other chronic diseases than psychosis or pre-pregnancy diabetes

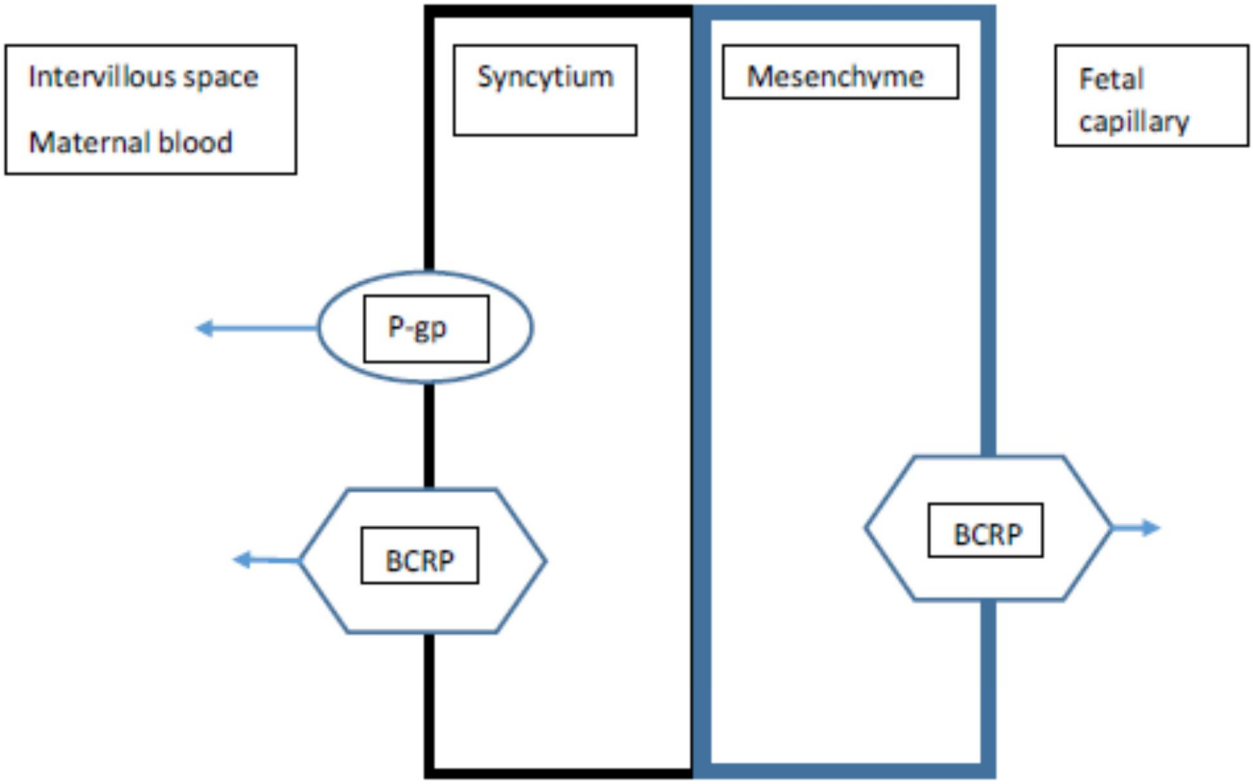

Figure 1. P-gp and BCRP localization and function in the placenta.

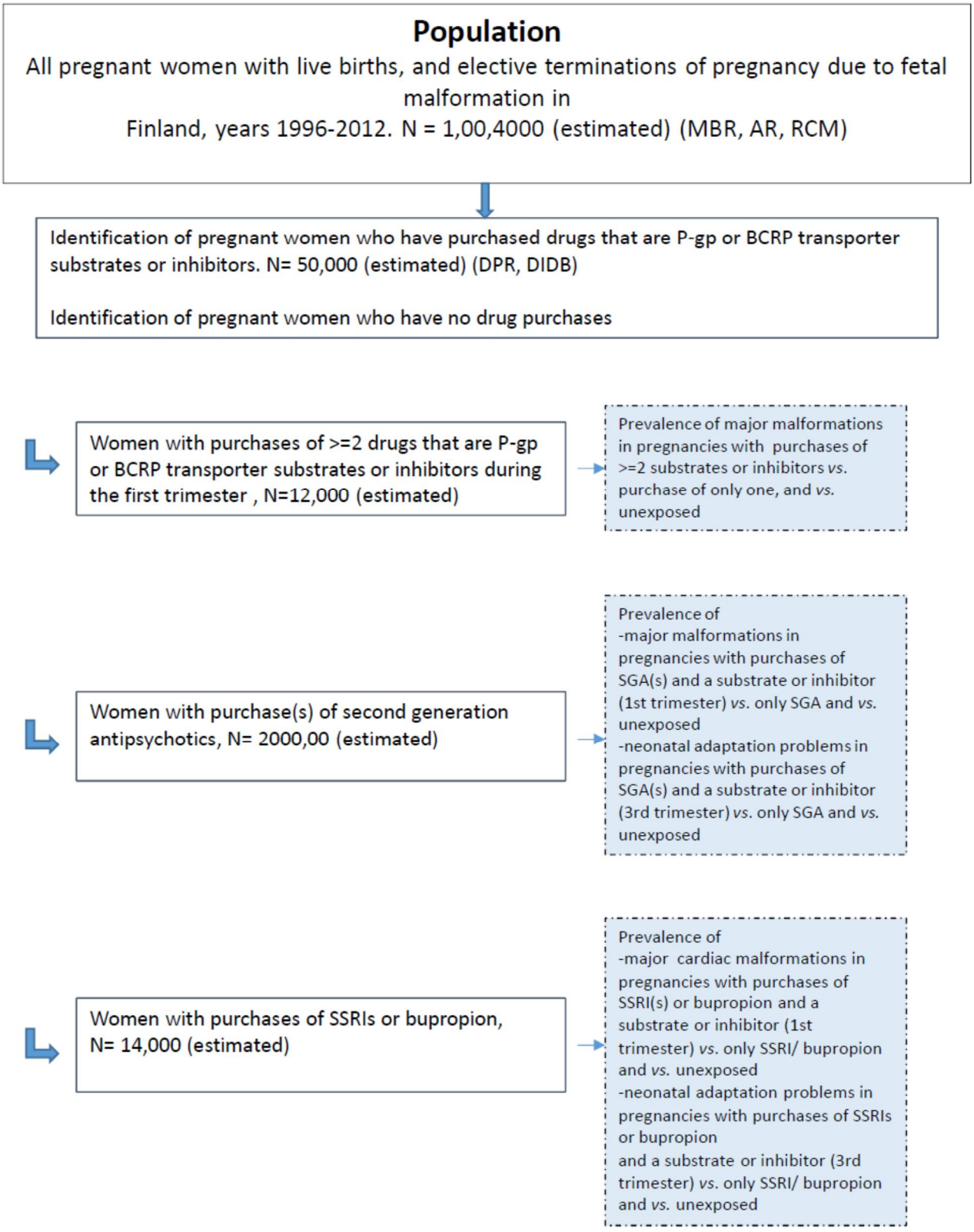

Figure 2. Flow chart of register data included in the study and comparisons of outcomes between different exposure groups.
MBR, Medical Birth Register; AR, Abortion Register; RCM, Register of Congenital Malformations; DPR, Drug Reimbursement Register; DIDB, Drug Interaction Database; SGA, Second Generation Antipsychotic; SSRI, Selective Serotonin Reuptake Inhibitor